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RESEARCH**

*APPLICATION NUMBER:*

**50-818**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review #2

<b>Date</b>	February 5, 2009
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review #2
<b>NDA/BLA #</b>	50-818
<b>Supplement#</b>	
<b>Applicant</b>	Alcon, Inc.
<b>Date of Submissions</b>	6/10/08, 8/14/08, 9/8/08
<b>PDUFA Goal Date</b>	2/13/09
<b>Proprietary Name / Established (USAN) names</b>	Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%
<b>Dosage forms / Strength</b>	ophthalmic suspension
<b>Proposed Indication(s)</b>	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists
<b>Recommended:</b>	Approval

### 1. Introduction

The combination corticosteroid/anti-infective agent, tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension (TOBRADEX) was approved in the U.S. in 1988 (NDA 50-592) for the indication: steroid responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

The submitted 505(b)(2) application proposes to market Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% using the same active ingredients and preservative as TOBRADEX and for the same indication. Tobradex ST has a lower concentration of dexamethasone (0.05%) and a retention-enhancing vehicle (xanthan gum), which is theorized by Alcon to allow the new formulation to provide similar efficacy as TOBRADEX. The concentration of tobramycin (0.3%) is unchanged.

The selection of 0.05% dexamethasone was based on the results of a bioavailability study (C-05-43) and a bioequivalence study (C-05-23). Alcon conducted a phase 3 bioequivalence study (C-06-37) and two *in vitro* microbial kill rate studies (N-06-015, N-07-040) to demonstrate the equivalence of Tobradex ST to the reference product, TOBRADEX. The goal of this program was to demonstrate that the new formulation and the reference product,

TOBRADEX, are equivalent in their ability to deliver dexamethasone to the expected site of action (aqueous humor) and kill superficial bacteria thought to be susceptible to tobramycin.

In a previous review cycle, Alcon received an approvable letter dated April 15, 2008, which stated it would be necessary for the following to be submitted:

1. Data to support your stated conclusion that neither the dexamethasone nor any other component in the tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05% will interfere with the capability of tobramycin in the drug product to effectively kill superficial bacteria in the eye. If an *in vitro* model is used to support this conclusion, the model should mimic the conditions in the eye as closely as possible including but not necessarily limited to the pH, pH buffering capacity, temperature and cation concentration. Testing should include all microorganisms listed in the package insert for tobramycin ophthalmic solution and all organisms included in the USP Preservative Effectiveness Test Monograph. Products tested in this model should include the formulation proposed for marketing, the currently approved formulation of Tobradex, tobramycin ophthalmic solution and a negative control solution.
2. A commitment to lower the currently proposed endotoxin limit for the final drug product and a timetable for the revision of your drug product specifications in which the endotoxin limit will be  $\frac{1}{1}$

b(4)

In an August 14, 2008, submission, Alcon satisfactorily addressed item #1 above. In the report 08-058 (Results of Tobradex ST Kinetics of Kill Study) it was shown that all three solutions (Tobrex, TOBRADEX, and Tobradex ST) were able to achieve 99.9% kill for all bacteria tested in at least two of the three tests. From an *in vitro* time kill perspective the TobraDex ST was shown to be equivalent to both the TOBRADEX and Tobrex solutions in respect to its performance in the "Kinetics of Kill" study.

In June 10, 2008, and September 8, 2008, submission, Alcon lowered the final drug product endotoxin limit to LT — No timetable is applicable as the change will become effective with the approval of this New Drug Application. In order to achieve this endotoxin reduction a process modification was needed.

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With the adequate resolution of items cited in the previous approvable letter, NDA 50-818 is recommended for approval for the indication steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The application has demonstrated that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

## 2. Background

A Pre-Investigational New Drug Application (PIND 72,063) meeting was conducted on August 19, 2005, to discuss Alcon's planned product development of an alternative formulation of its approved and marketed product, TOBRADEX (tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension), with a lower concentration of dexamethasone and proposed to demonstrate its equivalence to Tobradex. Alcon was advised that in order to develop the proposed drug product for the same indication and dosing regimen as TOBRADEX, it was acceptable to conduct a bioequivalence clinical pharmacokinetic study comparing the concentration of dexamethasone between the proposed drug product and TOBRADEX. In addition, Alcon was advised to conduct an *in vitro* "microbial kill rate" study comparing tobramycin to the proposed alternative formulation.

Original IND 72,063 was submitted on October 7, 2007. A protocol for a pilot aqueous humor bioavailability study (C-05-43) was submitted with the IND. The study compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of two alternative formulations of Tobradex (tobramycin 0.3%/dexamethasone 0.025% and tobramycin 0.3%/dexamethasone 0.05%) to TOBRADEX.

A special protocol assessment request was submitted to the IND on December 12, 2005, for a phase 3 aqueous humor bioequivalence study (C-05-23) that compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of alternative formulation, tobramycin 0.3%/dexamethasone 0.033% to TOBRADEX. Results from study C-05-23 showed that AUC and  $C_{max}$  for this alternative formulation were below that of Tobradex and did not meet the bioequivalence limits requirement.

Alcon then conducted a second phase 3 aqueous humor bioequivalence study (C-06-37) that compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of alternative formulation, tobramycin 0.3%/dexamethasone 0.05% to TOBRADEX.

## 3. CMC

### DRUG SUBSTANCE:

**Dexamethasone:** Dexamethasone is a corticosteroid drug primarily used for its anti-inflammatory and anti-allergic activities. Clinically, it has been demonstrated that anti-inflammatory activity of corticosteroids correlates well with mineral corticoid activity, i.e., sodium retention activity, e.g., dexamethasone and betamethasone compared to other corticosteroids have highest anti-inflammatory activities and neither compound cause sodium retention in body fluids.

Dexamethasone has been approved for oral, injectable and topical drug products. Dexamethasone and combination with tobramycin were previously approved in ophthalmic drug products (TOBRADEX). Dexamethasone solubility in water at 25°C is approximately 8-10 mg /100 mL (slightly soluble per USP). The concentration in the proposed drug product is

0.05%, i.e., 0.5 mg/mL as a suspension. Although, dexamethasone is available in several morphic forms, only one form exists in the drug product. The drug substance is  before combining with other excipients during manufacturing the drug product.

b(4)

Tobramycin: Tobramycin is an aminoglycoside antibiotic, exhibits bactericidal activity against a broad spectrum of bacteria. It inhibits bacterial protein synthesis. The drug substance is prepared by  Tobramycin is freely soluble in water (1 in 1.5 parts) and the pH of the aqueous solution is 9-11. Tobramycin in aqueous solution is stable at a controlled pH and temperature. Several drug products of tobramycin solution have been approved as injectable and inhalation solution.

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**DRUG PRODUCT:**

The drug product contains 0.3% tobramycin and 0.05% dexamethasone in aqueous suspension. Other components present in the formulation are benzalkonium chloride as preservative, editate disodium dihydrate as \_\_\_\_\_ xanthan gum as viscosity agent, propylene glycol, sodium sulfate and sodium chloride for \_\_\_\_\_ and sodium hydroxide and hydrochloric acid for pH adjustment. Dexamethasone is: \_\_\_\_\_. The applicant's similar product approved previously contains tobramycin 0.3% and 0.1% dexamethasone. However, the approved drug product contains hydroxyethylcellulose instead of xanthan gum. Also, the approved product does not contain propylene glycol but contains a \_\_\_\_\_ of sodium sulfate than in the proposed formulation for \_\_\_\_\_.

b(4)

The manufacturing process for the proposed product uses \_\_\_\_\_ techniques for product sterilization.

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The suspension was filled in 4 mL 8 mL and 10 mL bottles using: \_\_\_\_\_ techniques. The fill volume for  the trade presentation 2.5 mL, 5 mL and 10 mL. All packaging components were \_\_\_\_\_ The bottles and plugs were  and closures were:  The product is unstable when exposed to direct light; however, it is stable when placed in a carton.

**June 6 and September 8, 2008, Amendments Regarding Endotoxin Limits:**

Per the CMC review dated February 4, 2009, page 5:

The approvable letter dated April 15, 2008 in which FDA requested to provide commitment to lower the currently proposed endotoxin limit for the finished drug product. The amendments include in addition to lowering the endotoxin limit minor process and in process controls; it will allow the firm to consistently achieve the reduction in endotoxin limits.

The original NDA included preparation of xanthan gum solution  
┌ preparation of dexamethasone suspension  
┌ and tobramycin solution containing the remaining components prior to  
combining these components in a finished drug product. One of the components in  
tobramycin solution is

b(4)

Xanthan gum is the primary source of bacterial endotoxin since it is produced by bacterial fermentation process. The proposed manufacturing changes were made in processing xanthan gum to achieve reduction in endotoxin level and maintaining high viscosity of the solution. The original NDA proposal was

b(4)

The product quality microbiology review assessed xanthan gum

┌ The proposed process changes were recommended for approval from microbiology consideration.

b(4)

**REVISED REGULATORY SPECIFICATIONS:**  
From the CMC review dated February 4, 2009, page 8:

**Regulatory specifications for Tobramycin 0.3% and dexamethasone 0.05% Ophthalmic Suspension**

Test	Specifications
Dexamethasone Identity (TLC) <sup>a</sup>	Positive
Dexamethasone Identity (UPLC) <sup>a</sup>	Positive
Dexamethasone Assay (UPLC)	Label
Dexamethasone Related Impurities (UPLC) <sup>b</sup>	NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone
Tobramycin Identity (TLC) <sup>a</sup>	Positive
Tobramycin Identity (HPLC) <sup>a</sup>	Positive
Tobramycin Assay (HPLC)	Label
Tobramycin Related Impurities (HPLC) <sup>b</sup>	NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin
Benzalkonium Chloride Identity (HPLC) <sup>a</sup>	Positive
Benzalkonium Chloride Assay (HPLC)	Label
Edetate Disodium Identity (HPLC) <sup>a</sup>	Positive
Edetate Disodium Assay (HPLC)	Label
pH	
Osmolality	
Viscosity	
Simulated Post-Dose Viscosity	
Redispersibility	NMT
Appearance of Suspension: Color Uniformity	White to Off-white Uniform Suspension
Particle Size	
Bacterial Endotoxin <sup>3</sup>	
Sterility	Meets USP Requirements

<sup>a</sup> Release test only

<sup>b</sup> Includes all impurities other than drug substance process impurities.

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b(4)

Inspections were completed and all facilities found acceptable on 2/11/08; the Office of Compliance confirmed that facilities are still adequate. See the CMC review dated February 4, 2009, page 9.

## 4. Nonclinical Pharmacology/Toxicology

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.

Alcon has not conducted any nonclinical pharmacology studies with Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%. Both active ingredients have a history of clinical use individually (TOBEX and MAXIDEX, respectively) and as a combination product (TOBRADEX) and are well characterized following topical and systemic application.

### **CARCINOGENICITY:**

Alcon has not provided carcinogenicity data relevant to the proposed drug product. The reviewer of the IND for TOBI (tobramycin inhalation solution) 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.

Alcon 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.

## 5. Clinical Pharmacology/Biopharmaceutics

To support product approval, Alcon's objective was to demonstrate bioequivalence of dexamethasone in aqueous humor following administration of Tobradex ST versus the marketed product TOBRADEX. The test product contains the same concentration of tobramycin (0.3%) and a two-fold lower dexamethasone concentration than that of TOBRADEX (0.05% vs. 0.1%). The Tobradex ST formulation includes a retention-enhancing agent, xanthan gum, which allows the use of a lower dexamethasone concentration to achieve equivalent dexamethasone aqueous humor exposure to that of TOBRADEX.

### BIOEQUIVALANCE:

Three clinical trials were conducted in the U.S. to support the bioequivalence of Tobradex ST to TOBRADEX: a pilot aqueous humor bioavailability study (C-05-43) and two aqueous humor bioequivalence studies (C-05-23 and C-06-37) involving 2100 cataract surgery patients. Based on both Alcon's analysis and the FDA analysis of dexamethasone aqueous humor concentration data obtained from Study C-06-37, the comparison of the test product Tobradex-ST versus the reference product TOBRADEX met the equivalence limits of 80 to 125% for the primary pharmacokinetic parameter  $AUC_{0-5}$  for both the per protocol and ITT populations. Results from additional analyses performed by the FDA support equivalence of the two products for the parameters  $AUC_{0-2}$ ,  $AUC_{0-3}$ , and the primary parameter  $AUC_{0-5}$ . Although the upper bound for the  $AUC_{0-1}$  comparison was outside the limits, the actual ratios for all AUC comparisons were similar, suggesting this finding was due to the variability in calculated  $AUC_{0-1}$  values from bootstrapping. Because the upper bound of the 90% confidence interval for  $AUC_{0-1}$  exceeded 125% (i.e. dexamethasone concentrations were higher with the test product), it is unlikely this finding would have a negative impact on efficacy compared to the reference product.

Tobradex-ST and TOBRADEX exhibited similar safety profiles in Study C-06-37. The long-term safety profile following multiple dosing of TOBRADEX has been well-established, as has the safety profile following systemic administration of much higher doses of dexamethasone. Thus, an upper bound for the  $AUC_{0-1}$  comparison of 126.8% is not expected to be clinically relevant from a safety standpoint, and Alcon adequately established equivalence of the two products based on the primary comparison of  $AUC_{0-5}$ .

### GENERAL CONSIDERATIONS:

No data are available on the extent of systemic absorption of dexamethasone or tobramycin from Tobradex ST ophthalmic suspension. Following multiple-dose (QID for 2 days) bilateral ocular administration of TOBRADEX in healthy male and female volunteers, peak plasma

concentrations of dexamethasone were less than 1 ng/mL and occurred within 2 hours post-dose across all subjects.

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

No special dosing instructions in the elderly are required.

There were no known differences with respect to age, gender, race, or iris color noted in the original approval of TOBRADEX. No information has been submitted to alter those conclusions.

No specific drug interaction studies were performed. There were no drug-drug interactions noted in the original approval for TOBRADEX. No information has been submitted to alter those conclusions.

## 6. Sterility Assurance

No endotoxin specification for the final product was provided with the original submission. An information request (see below) was transmitted to Alcon on 12 DEC 2007 requesting that a bacterial endotoxin specification of NLT \_\_\_\_\_ be submitted: **b(4)**

Please provide release and on-going stability specifications for bacterial endotoxin for the final drug product. The specifications should be consistent with the dosing described in the drug product labeling. Such specifications should not exceed \_\_\_\_\_ of drug product. **b(4)**

Alcon provided (as Tab 1, 29 FEB 2008 (BZ) Amendment) a revised NDA Section 3.2.P.5.1 "Specifications," to include the bacterial endotoxin specification of \_\_\_\_\_ EU/dose (i.e., NMT \_\_\_\_\_ EU/mL for an average dose of a 34 µL drop). **b(4)**

- The endotoxin limit proposed is not scientifically supported. It is recommended that endotoxin be monitored and a timeframe for setting a lower specification be established.

### June 6 and September 8, 2008, Amendments Regarding Endotoxin Limits:

Per the Product Quality Microbiology Review dated 12/10/2008:

The current amendments lower the final drug product endotoxin limit to \_\_\_\_\_. In order to achieve this endotoxin reduction a process modification was needed. The Applicant is, therefore, also requesting approval of manufacturing process changes and in-process control changes in order to achieve this reduction in endotoxins. **b(4)**

The manufacturing process flow chart described in the initial review (26 March 2008, Microbiology Review #1) described a xanthan gum dissolution step employing \_\_\_\_\_ That solution was subsequently \_\_\_\_\_

b(4)

The applicant has subsequently determined that the xanthan gum raw material, produced via fermentation processes, was the major source of endotoxin in the drug product. They further determined that \_\_\_\_\_

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Xanthan gum \_\_\_\_\_

b(4)

b(4)

The only change in the regulatory acceptance specifications is the tightening of the bacterial endotoxins specification from NMT \_\_\_\_\_ to LT \_\_\_\_\_

b(4)

The applicant has adequately addressed all outstanding product quality microbiology deficiencies and issues. The application is now recommended for approval from a microbiology product quality standpoint.

## 7. Clinical/Statistical - Efficacy

The efficacy of the drug product components, dexamethasone and tobramycin, have been established during the original approval of the reference product, TOBRADEX. This application relies on the submitted bioequivalence studies and *in vitro* kill studies to

demonstrate equivalence between Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% and TOBRADEX.

Four clinical studies and two microbial kill rate studies are submitted in NDA 50-818. The clinical studies include one pharmacokinetics study (C-99-33) conducted in healthy volunteers, and one aqueous humor bioavailability study (C-05-43) and two aqueous humor bioequivalence studies (C-05-23 and C-06-37) conducted in patients undergoing cataract surgery.

The selection of 0.05% dexamethasone was based on the results from bioavailability study C-05-43 (Tob 0.3%/Dex 0.025% and Tob 0.3%/Dex 0.05%) and bioequivalence study C-05-23 (Tob 0.3%/Dex 0.033%). This submission relies on the findings from bioequivalence study C-06-37 to demonstrate that the dexamethasone concentration in the aqueous humor as assayed for the corticosteroid component of the corticosteroid/anti-infective combination drug product Tobradex ST is equivalent to TOBRADEX.

The two microbial kill rate studies (N-06-015 and N-07-040) were conducted to demonstrate the equivalence of the anti-infective component, tobramycin, of Tob 0.3%/Dex 0.05% to Tobradex.

Bioequivalence study C-06-37 and the two microbial kill rate studies (N-06-015 and N-07-040) are the primary support of efficacy (bioequivalence). Studies C-05-43, C-05-23, and C-06-37 contribute to the safety database.

Bioequivalence study C-06-37 demonstrates bioequivalence between Tobradex ST and TOBRADEX in their ability to deliver dexamethasone to the expected site of action (aqueous humor). The submitted *In vitro* microbial kill rate studies **do not** demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

See the following tables from the original Medical Officer's Review, Section 6.1.5.

Study N-07-040 Microorganism (MCC#)	% Survivors								
	Saline			Tob 0.3%/Dex 0.05%			Tobradex		
Time (minutes)	0	30	60	0	30	60	0	30	60
<i>S. aureus</i> -ATCC (2348)	100	109	82	106	0	0	115	0	0
<i>S. aureus</i> -MSSA (41028)	100	83	92	65	0.4	0	68	0.2	0
<i>S. aureus</i> -MRSA (30281)	100	81	95	100	38	22	104	51	29
<i>S. aureus</i> -MRSA (30281) at 33°C	100	80	89	95	0	0	87	0	0
<i>S. epidermidis</i> -ATCC (3245)	100	93	91	0	0	0	2	0	0
<i>S. epidermidis</i> -MSSE (41001)	100	102	68	0.8	0	0	10	0	0
<i>S. epidermidis</i> -MRSE (50093)	100	111	78	0.3	0	0	4	0	0

Cross-Discipline Team Leader Review #2

William M. Boyd, M.D.

NDA 50-818

Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

<i>S. pneumoniae</i> -PSSP (52385)	100	72	52	0	0	0	0	0	0
<i>S. pneumoniae</i> -PRSP (41314)	100	102	110	0	0	0	0	0	0
<i>S. pyogenes</i> (80632)	100	107	101	0	0	0	0.2	0	0
<i>S. mutans</i> (52161)	100	87	110	8	0	0	5	0	0
<i>A. calcoaceticus</i> (15300)	100	100	72	0	0	0	0	0	0
<i>E. aerogenes</i> (41217)	100	99	104	54	0	0	84	0	0
<i>E. coli</i> -ATCC (2361)	100	92	108	81	9	0.9	82	22	5
<i>H. aegyptius</i> (2389)	100	109	95	4	0	0	0	0	0
<i>H. influenzae</i> (41098)	100	103	83	42	0	0	2	0	0
<i>K. pneumoniae</i> (41153)	100	101	110	70	0	0	107	25	8
<i>M. lacunata</i> (4414)	100	99	89	0	0	0	0	0	0
<i>M. morgani</i> (91038)	100	98	106	67	0.5	0	82	48	24
<i>N. perflava</i> (65248)	100	110	111	20	0	0	48	0	0
<i>N. sicca</i> (61708)	100	79	71	10	0	0	9	0	0
<i>P. mirabilis</i> (91511)	100	85	48	46	0.2	0	77	8	2
<i>P. vulgaris</i> (62029)	100	109	107	82	17.5	4	86	8	0.7
<i>P. aeruginosa</i> -ATCC (2365)	100	94	83	18	0.2	0	26	7	4

Study N-06-015 Microorganism (MCC#)	% Survivors								
	Time (minutes)	Saline		Tob 0.3%/Dex 0.05%			Tobradex		
		0	30	60	0	30	60	0	30
<i>S. aureus</i> -ATCC (2348)	100	95	99	95	0	0	58	0	0
<i>S. aureus</i> -MSSA (41028)	100	99	75	51	0.9	0.1	50	0	0
<i>S. aureus</i> -MSSA (41053)	100	58	63	45	0	0	38	0	0
<i>S. aureus</i> -MRSA (30281)	100	99	84	121	36	7	124	2	0
<i>S. epidermidis</i> -ATCC (3245)	100	116	113	4	0	0	18	0.1	0
<i>S. epidermidis</i> -MSSE (41001)	100	70	62	4	0	0	9	0	0
<i>S. epidermidis</i> -MRSE (50093)	100	86	76	8	0	0	22	0.1	0
<i>S. pneumoniae</i> -PSSP (52385)	100	46	42	0	0	0	0	0	0
<i>S. pneumoniae</i> -PRSP (41314)	100	93	95	0	0	0	0	0	0
<i>S. pyogenes</i> (80632)	100	128	133	0	0	0	0	0	0
<i>S. mutans</i> (52161)	100	99	94	21	0	0	11	0	0
<i>A. calcoaceticus</i> (15300)	100	91	81	63	0	0	10	0	0
<i>E. aerogenes</i> (41217)	100	93	89	59	0	0	77	2	0.1
<i>E. coli</i> -ATCC (2361)	100	100	103	92	26	8	102	35	20
<i>H. aegyptius</i> (2389)	100	71	50	3	0	0	0	0	0
<i>H. influenzae</i> (41098)	100	95	116	30	0	0	6	0	0
<i>K. pneumoniae</i> (41153)	100	91	123	61	0	0	87	7	1
<i>M. lacunata</i> (4414)	100	126	112	0	0	0	0	0	0
<i>M. morgani</i> (91038)	100	103	99	78	4	0	79	44	27
<i>N. perflava</i> (65248)	100	98	95	12	0	0	2	0	0
<i>N. sicca</i> (61708)	100	105	114	15	0	0	7	0	0
<i>P. mirabilis</i> (91511)	100	91	102	54	3	0	71	7	0.6

<i>P. vulgaris</i> (62029)	100	112	111	68	31	21	87	13	2
<i>P. aeruginosa</i> -ATCC (2365)	100	103	82	16	0.5	0.1	22	2	1

In studies N-07-040 and N-06-015, both Tobradex ST and Tobradex demonstrate ineffective microbial kill rates for multiple organisms at both 30 and 60 minutes following inoculation.

On April 11, 2008, Alcon submitted a response to concerns raised by the FDA that dexamethasone in Tobradex ST was possibly interfering with the antibacterial activity of tobramycin as demonstrated by the percent survivors reported at 15 or 30 minutes for three of the test bacteria, i.e., *Staphylococcus aureus* (MCC 41028), *S. aureus* (MCC 30281) and *Morganella morganii* (MCC 91038). Alcon proposed that the minor differences in antimicrobial activity of TOBREX, TOBRADEX and TobraDex ST in the in vitro model are due to their formulated pH rather than the presence or absence of dexamethasone. The Agency requested additional clarification regarding these results.

On April 14, 2008, Alcon provided additional clarification:

Tobradex ST was formulated at pH 5.7 in order to enhance the stability of dexamethasone. In addition, since this formulation contains xanthan gum as a viscosity modifier, the pH at 5.7 is necessary to maintain a droppable "solution-like" viscosity in the bottle. Upon instillation, the product viscosity increases due to the pH and ionic strength of the tears. The higher viscosity in the eye was designed to maintain the availability of the actives on the ocular surface for a longer period of time.

Since the average pH at the ocular surface is 7.5, the pH of Tobradex ST, which contains no buffer, rapidly equilibrates to that of the tears upon instillation. Therefore, additional microbial kill testing was performed on *S. aureus* and *M. morganii* with formulations of TOBRADEX and Tobradex ST adjusted up from pH 5.7 to 7.5.

In this testing paradigm, the rate of kill of *S. aureus* and *M. morganii* for each of the three formulations at pH 7.5 is complete within 15 minutes. These findings add further support to the conclusions presented in the previous response that:

- 1) There is no evidence that dexamethasone interferes with the antimicrobial activity of tobramycin,
- and
- 2) The differences in the rate of kill observed in vitro between TOBREX and Tobradex ST are due to the differences in the pH of the two formulations.

The Agency does not agree that this testing paradigm as applied is appropriate. The additional microbial kill testing was only performed on *S. aureus* and *M. morganii* with formulations of TOBRADEX and Tobradex ST adjusted up from pH 5.7 to 7.5 (i.e. the survivors reported at 15 or 30 minutes for three of the test bacteria, i.e., *Staphylococcus aureus* (MCC 41028), *S. aureus* (MCC 30281) and *Morganella morganii* (MCC 91038) in the original submission).

## **August 14, 2008, Amendment Regarding Tobradex ST Kinetics of Kill Study:**

Per the Clinical Microbiology Review dated 11/3/08:

### ANALYSIS OF "KINETICS OF KILL TEST" (TDOC 0008396) RESULTS

The Applicant provided the raw data for each of the summary tables in the submission and this data confirms the data in the summary tables.

The results of the data indicate that for the following organisms there was 99.9% kill by the end of the 7.5, 15, 30 and 60 minute exposure times for all three test solutions (Tobrex, TOBRADEX, and Tobradex ST) for all three tests.

Criteria for accepting kill results: 1) Two out of three test results had control results showing that there was at least 70% or better of the control organisms surviving at each sample time; 2) there was 99.9% percent kill for all time periods for at least two out of the three tests; 3) the percent survivor rate was at least 70% at the final test sample time of 60 minutes in two of the three tests.

*Staphylococcus aureus* MCC 2348  
*S. aureus* MCC 41028  
*S. aureus* MCC 30281  
*Staphylococcus epidermidis* MCC 41001  
*S. epidermidis* MCC 50093  
*S. epidermidis* MCC 52385  
*Streptococcus pneumoniae* MCC 41314  
*Streptococcus pyogenes* MCC 80632  
*Streptococcus mutans* MCC 52161  
*Acinetobacter calcoaceticus* MCC 15300  
*Enterobacter aerogenes* MCC 41217  
*Escherichia coli* MCC 2361  
*Haemophilus influenzae* MCC 52044  
*H. bio-type aegypticus* MCC 2389  
*Klebsiella pneumoniae* MCC 41153  
*Moraxella lacunata* MCC 4414  
*Morganella morganii* MCC 91038  
*Neisseria perflava* MCC 65248  
*N. sicca* MCC 61708  
*Proteus mirabilis* MCC 91511  
*Proteus vulgaris* MCC 62029  
*Pseudomonas aeruginosa* MCC 2365

The data from the validation studies showed that the survival rate of certain bacteria was

decreased in the cold compared to recovery of organisms kept at room temperature. These results, however, did not seem to effect the results of the “Kinetics of Kill” study.

In the “Kinetics of Kill” study it was shown that all three solutions (Tobrex, TOBRADEX, and Tobradex ST) were able to achieve 99.9% kill for all bacteria tested in at least two of the three tests. From an in vitro time kill perspective the Tobradex ST was shown to be equivalent to both the TOBRADEX and Tobrex solutions in respect to its performance in the “Kinetics of Kill” study.

## 8. Safety

The safety database consists of Studies C-05-43, C-05-23, C-06-37, and postmarketing safety experience for the reference product TOBRADEX including ophthalmic suspension, ophthalmic ointment, and otic preparation for the period October 1, 2002 to January 31, 2007.

The application supports the safety of Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. TOBRADEX has been marketed in the United States since it was approved in August, 1988. The postmarketing experiences data for Tobradex supports the long term safety of products containing the combination tobramycin/dexamethasone.

See the following table from the Medical Officer’s original review, Section 7.1.5.4.

**Frequency and Incidence of Ocular and Non-ocular Adverse Events  
 (Studies C-05-43, C-05-23, C-06-37)**

Coded Adverse Event	Tob 0.3%/Dex 0.05% N=533	Tob 0.3%/Dex 0.033% N=491	Tob 0.3%/Dex 0.025% N=44	Tobradex N=1032
	N (%)	N (%)	N (%)	N (%)
<b>All Events</b>	10 (1.9)	46 (9.4)	4 (9.1)	71(6.9)
<b>OCULAR</b>				
<b>Eye Disorder</b>				
Eye pain	2 (0.4)	3 (0.6)		4 (0.4)
Conjunctival hemorrhage		2 (0.4)		2 (0.2)
Corneal oedema		3 (0.6)		1 (0.1)
Foreign body sensation		1 (0.2)		3 (0.3)
Iritis		1 (0.2)		3 (0.3)
Anterior chamber inflammation				1 (0.1)
Eye irritation		2 (0.4)		1 (0.1)
Lacrimation increased		1 (0.2)		
Conjunctivitis				1 (0.1)
Conjunctivitis allergic		1 (0.2)		
Eye pruritis	1 (0.2)			1 (0.1)
Corneal epithelium defect		1 (0.2)		

Cross-Discipline Team Leader Review #2

William M. Boyd, M.D.

NDA 50-818

Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

Coded Adverse Event	Tob 0.3%/Dex 0.05% N=533	Tob 0.3%/Dex 0.033% N=491	Tob 0.3%/Dex 0.025% N=44	Tobradex N=1032
Keratitis		1 (0.2)		
Corneal striae				1 (0.1)
Eye disorder				1 (0.1)
Eye swelling				1 (0.1)
Eyelid pain				1 (0.1)
Blepharitis		1 (0.2)		
Visual acuity reduced		1 (0.2)		1 (0.1)
Posterior capsule rupture				2 (0.2)
Endophthalmitis		1 (0.2)		
Macular oedema				1 (0.1)
Retinoschisis				1 (0.1)
Vitreous detachment				1 (0.1)
Vitreous hemorrhage				1 (0.1)
Vitreous floaters		1 (0.2)		
<b>NON-OCULAR</b>				
<b>Infections and Infestations</b>				
Gastroenteritis				1 (0.1)
Gastrointestinal infection				1 (0.1)
Tooth abscess				1 (0.1)
Tooth infection				1 (0.1)
Bronchitis		1 (0.2)		
Upper respiratory tract infection		1 (0.2)		
Nasopharyngitis			1 (2.3)	
<b>Blood and Lymphatic System Disorders</b>				
Anaemia		1 (0.2)		
<b>Metabolism and Nutrition Disorders</b>				
Diabetes mellitus inadequate control		2 (0.4)		
Dehydration		1 (0.2)		
Hypercholesterolaemia		1 (0.2)		
<b>Nervous System Disorders</b>				
Headache	1 (0.2)	2 (0.4)		5 (0.5)
Migraine				1 (0.1)
Paraesthesia				1 (0.1)
Syncope vasovagal				1 (0.1)
<b>Cardiac Disorders</b>				
Cardiac failure				1 (0.1)
Sinus Tachycardia	1 (0.2)			
Angina unstable		1 (0.2)		
Congestive		1 (0.2)		
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Pneumonitis		1 (0.2)		
<b>Gastrointestinal Disorders</b>				
Nausea				1 (0.1)
Vomiting			1 (2.3)	
<b>Hepatobiliary Disorders</b>				

Coded Adverse Event	Tob 0.3%/Dex 0.05% N=533	Tob 0.3%/Dex 0.033% N=491	Tob 0.3%/Dex 0.025% N=44	Tobradex N=1032
Cholelithiasis				1 (0.1)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Hyperhidrosis				1 (0.1)
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Back pain				1 (0.1)
Arthritis		1 (0.2)		
<b>Investigations</b>				
Intraocular pressure increased		8 (1.6)	2 (4.5)	12 (1.2)
Blood pressure increased	3 (0.6)	2 (0.4)		2 (0.2)
Blood glucose decreased				1 (0.1)
Blood glucose increased				1 (0.1)
Intraocular pressure decreased				1 (0.1)
<b>Injury, Poisoning and Procedural Complications</b>				
Corneal abrasion		1 (0.2)		5 (0.5)
Procedural complication	2 (0.4)			2 (0.2)
Post procedural complication		1 (0.2)		2 (0.2)
Injury		1 (0.2)		

## 9. Advisory Committee Meeting

Not applicable; this product is a non-NME.

## 10. Pediatrics

Reference is made the Agency's finding of safety and effectiveness for pediatric patients in NDA 50-592; safety and effectiveness have not been established in pediatric patients below the age of 2 years.

Alcon has requested a waiver to conduct pediatric studies in patients below the age of 2 years.

## 11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. An audit of the analytical and clinical portions of Study C-06-07 revealed no significant deficiencies. There is no evidence to suggest that the trials submitted in NDA 50-818 were not conducted in accordance with accepted ethical standards.

Alcon has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical*

*Investigators.* There is no evidence to suggest that the results of the studies were impacted by any financial payments.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed Alcon's proposed product labeling (PI) for Tobradex ST submitted to the Agency on June 14, 2007.

DDMAC has reviewed the proposed PI for Tobradex ST and has no comments at this time. A majority of the information included in this proposed Tobradex ST PI is identical to the information included in the TOBRADEX PI. Per DDMAC, there were no misleading competitive claims incorporated into the proposed labeling.

A consult was requested from the Office of Surveillance and Epidemiology regarding a trade name review for the proposed name "Tobradex ST." No formal response was placed in DFS, but in an email dated Thursday, January 8, 2008, from Henry Francis to Edward Cox, DMEPA/OSE agrees that "Tobradex ST" would present lesser potential for confusion than naming this new formulation "Tobradex." Per DMEPA/OSE, medication errors are still anticipated with the currently marketed Tobradex and the proposed Tobradex ST product. DMEPA's postmarketing experience has shown that modifiers may be overlooked or omitted from prescriptions thus leading the original Tobradex to be dispensed in error.

## **12. Labeling**

NDA 50-818 is recommended for approval for the indication steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists with the labeling submitted by Alcon on 5 February 2009 and found in this Cross-Discipline Team Leader Review (see Appendix 1).

## **13. Recommendations/Risk Benefit Assessment**

### **RECOMMENDED REGULATORY ACTION:**

NDA 50-818 is recommended for approval for the indication steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

The labeling submitted by Alcon on 5 February 2009 and found in this Cross-Discipline Team Leader Review (see Appendix 1) is acceptable for approval.

### **RISK BENEFIT ASSESSMENT:**

Bioequivalence study C-06-37 demonstrates bioequivalence between Tobradex ST and TOBRADEX in their ability to deliver dexamethasone to the expected site of action (aqueous

humor). The submitted *in vitro* microbial kill rate studies **do not** demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

The application supports the safety of Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. TOBRADEX has been marketed in the United States since it was approved in August, 1988. The postmarketing experiences data for Tobradex supports the long term safety of products containing the combination tobramycin/dexamethasone.

In the report 08-058 (Results of Tobradex ST Kinetics of Kill Study) it was shown that all three solutions (Tobrex, TOBRADEX, and Tobradex ST) were able to achieve 99.9% kill for all bacteria tested in at least two of the three tests. From an *in vitro* time kill perspective the Tobradex ST was shown to be equivalent to both the TOBRADEX and Tobrex solutions in respect to its performance in the "Kinetics of Kill" study.

CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

The Biostatistics review states that the results support equivalence of the 2 products.

Clinical Microbiology and the Medical Officer recommend approval.

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

Cross-Discipline Team Leader Review #2  
William M. Boyd, M.D.  
NDA 50-818  
Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

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## **Appendix 1**

The following package insert and carton and container labeling was submitted by Alcon on 10 February 2009.

9   Page(s) Withheld

       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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

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William Boyd  
2/11/2009 08:25:39 AM  
MEDICAL OFFICER

Wiley Chambers  
2/13/2009 01:58:47 PM  
MEDICAL OFFICER

## Cross-Discipline Team Leader Review

<b>Date</b>	April 1, 2008
<b>From</b>	William M. Boyd, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	50-818
<b>Supplement#</b>	
<b>Applicant</b>	Alcon, Inc.
<b>Date of Submission</b>	6/15/2007
<b>PDUFA Goal Date</b>	4/15/2008
<b>Proprietary Name / Established (USAN) names</b>	Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%
<b>Dosage forms / Strength</b>	ophthalmic suspension
<b>Proposed Indication(s)</b>	Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists
<b>Recommended:</b>	Approvable

### 1. Introduction

The combination corticosteroid/anti-infective agent, tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension (TOBRADEX) was approved in the U.S. in 1988 (NDA 50-592) for the indication: steroid responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

The submitted 505(b)(2) application proposes to market Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% using the same active ingredients and preservative as TOBRADEX and for the same indication. Tobradex ST has a lower concentration of dexamethasone (0.05%) and a retention-enhancing vehicle (xanthan gum), which is theorized by Alcon to allow the new formulation to provide similar efficacy as TOBRADEX. The concentration of tobramycin (0.3%) is unchanged.

The selection of 0.05% dexamethasone was based on the results of a bioavailability study (C-05-43) and a bioequivalence study (C-05-23). Alcon conducted a phase 3 bioequivalence study (C-06-37) and two *in vitro* microbial kill rate studies (N-06-015, N-07-040) to demonstrate the equivalence of Tobradex ST to the reference product, TOBRADEX. The goal of this program was to demonstrate that the new formulation and the reference product,

TOBRADEX, are equivalent in their ability to deliver dexamethasone to the expected site of action (aqueous humor) and kill superficial bacteria thought to be susceptible to tobramycin.

NDA 50-818 is **not** recommended for approval for the indication steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The application failed to demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

- It is recommended that an *in vitro* microbial kill rate study in an environment (i.e. media) that is substantially similar to the human eye be conducted comparing Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% with sterile saline, tobramycin, and TOBRADEX. This environment would include similar pH, pH buffer, temperature, and cations.

## 2. Background

A Pre-Investigational New Drug Application (PIND 72,063) meeting was conducted on August 19, 2005, to discuss Alcon's planned product development of an alternative formulation of its approved and marketed product, TOBRADEX (tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension), with a lower concentration of dexamethasone and proposed to demonstrate its equivalence to Tobradex. Alcon was advised that in order to develop the proposed drug product for the same indication and dosing regimen as TOBRADEX, it was acceptable to conduct a bioequivalence clinical pharmacokinetic study comparing the concentration of dexamethasone between the proposed drug product and TOBRADEX. In addition, Alcon was advised to conduct an *in vitro* "microbial kill rate" study comparing tobramycin to the proposed alternative formulation.

Original IND 72,063 was submitted on October 7, 2007. A protocol for a pilot aqueous humor bioavailability study (C-05-43) was submitted with the IND. The study compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of two alternative formulations of Tobradex (tobramycin 0.3%/dexamethasone 0.025% and tobramycin 0.3%/dexamethasone 0.05%) to TOBRADEX.

A special protocol assessment request was submitted to the IND on December 12, 2005, for a phase 3 aqueous humor bioequivalence study (C-05-23) that compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of alternative formulation, tobramycin 0.3%/dexamethasone 0.033% to TOBRADEX. Results from study C-05-23 showed that AUC and  $C_{max}$  for this alternative formulation were below that of Tobradex and did not meet the bioequivalence limits requirement.

Alcon then conducted a second phase 3 aqueous humor bioequivalence study (C-06-37) that compared the concentration of dexamethasone in aqueous humor of subjects following cataract surgery, of alternative formulation, tobramycin 0.3%/dexamethasone 0.05% to TOBRADEX.

### 3. CMC

#### DRUG SUBSTANCE:

Dexamethasone: Dexamethasone is a corticosteroid drug primarily used for its anti-inflammatory and anti-allergic activities. Clinically, it has been demonstrated that anti-inflammatory activity of corticosteroids correlates well with mineral corticoid activity, i.e., sodium retention activity, e.g., dexamethasone and betamethasone compared to other corticosteroids have highest anti-inflammatory activities and neither compound cause sodium retention in body fluids.

Dexamethasone has been approved for oral, injectable and topical drug products. Dexamethasone and combination with tobramycin were previously approved in ophthalmic drug products (Tobradex). Dexamethasone solubility in water at 25°C is approximately 8-10 mg /100 mL (slightly soluble per USP). The concentration in the proposed drug product is 0.05%, i.e., 0.5 mg/mL as a suspension. Although, dexamethasone is available in several morphic forms, only one form exists in the drug product. The drug substance is \_\_\_\_\_ before combining with other excipients during manufacturing the drug product. b(4)

Tobramycin: Tobramycin is an aminoglycoside antibiotic, exhibits bactericidal activity against a broad spectrum of bacteria. It inhibits bacterial protein synthesis. The drug substance is prepared by \_\_\_\_\_ Tobramycin is freely soluble in water (1 in 1.5 parts) and the pH of the aqueous solution is 9-11. Tobramycin in aqueous solution is stable at a controlled pH and temperature. Several drug products of tobramycin solution have been approved as injectable and inhalation solution. b(4)

#### DRUG PRODUCT:

The drug product contains 0.3% tobramycin and 0.05% dexamethasone in aqueous suspension. Other components present in the formulation are benzalkonium chloride as preservative, editate disodium dihydrate as \_\_\_\_\_ xanthan gum as viscosity agent, propylene glycol, sodium sulfate and sodium chloride for \_\_\_\_\_ and sodium hydroxide and hydrochloric acid for pH adjustment. Dexamethasone is \_\_\_\_\_. The applicant's similar product approved previously contains tobramycin 0.3% and 0.1% dexamethasone. However, the approved drug product contains hydroxyethylcellulose instead of xanthan gum. Also, the approved product does not contain propylene glycol but contains a \_\_\_\_\_ of sodium sulfate than in the proposed formulation for : \_\_\_\_\_. b(4)

The manufacturing process for the proposed product uses \_\_\_\_\_ techniques for product sterilization. b(4)

Cross-Discipline Team Leader Review  
William M. Boyd, M.D.  
NDA 50-818  
Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

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\_\_\_\_\_ The suspension was filled in 4 mL 8 mL and 10 mL bottles using \_\_\_\_\_ techniques. The fill volume for \_\_\_\_\_ the trade presentation 2.5 mL, 5 mL and 10 mL. All packaging components were \_\_\_\_\_. The bottles and plugs were \_\_\_\_\_ and closures were \_\_\_\_\_. The product is unstable when exposed to direct light; however, it is stable when placed in a carton.

b(4)

**REGULATORY SPECIFICATIONS:**  
From the CMC review, page 25:

**Table 8: Regulatory Specifications for the Drug Product**

Test	Specifications
Dexamethasone Identity (TLC) <sup>a</sup>	Positive
Dexamethasone Identity (UPLC) <sup>a</sup>	Positive
Dexamethasone Assay (UPLC)	
Dexamethasone Related Impurities (UPLC) <sup>b</sup>	NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone
Tobramycin Identity (TLC) <sup>a</sup>	Positive
Tobramycin Identity (HPLC) <sup>a</sup>	Positive
Tobramycin Assay (HPLC)	Label
Tobramycin Related Impurities (HPLC) <sup>b</sup>	NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin
Benzalkonium Chloride Identity (HPLC) <sup>a</sup>	Positive
Benzalkonium Chloride Assay (HPLC)	Label
Edetate Disodium Identity (HPLC) <sup>a</sup>	Positive
Edetate Disodium Assay (HPLC)	Label
pH	
Osmolality	
Viscosity ( )	
Simulated Post-Dose Viscosity ( )	
Redispersibility	NMT
Appearance of Suspension:	
Color	White to Off-white
Uniformity	Uniform Suspension
Particle Size ( )	
Bacterial Endotoxins <sup>a</sup>	NMT
Sterility	Meets USP Requirements

b(4)

b(4)

b(4)

b(4)

b(4)

b(4)

<sup>a</sup> Release test only  
<sup>b</sup> Includes all impurities other than drug substance process impurities.

All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable. See the CMC review, pages 48-50.

## 4. Nonclinical Pharmacology/Toxicology

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.

Alcon has not conducted any nonclinical pharmacology studies with Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%. Both active ingredients have a history of clinical use individually (TOBEX and MAXIDEX, respectively) and as a combination product (TOBRADEX) and are well characterized following topical and systemic application.

### **CARCINOGENICITY:**

Alcon has not provided carcinogenicity data relevant to the proposed drug product. The reviewer of the IND for TOBI (tobramycin inhalation solution) 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.

Alcon 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.

## 5. Clinical Pharmacology/Biopharmaceutics

To support product approval, Alcon's objective was to demonstrate bioequivalence of dexamethasone in aqueous humor following administration of Tobradex ST versus the marketed product TOBRADEX. The test product contains the same concentration of tobramycin (0.3%) and a two-fold lower dexamethasone concentration than that of TOBRADEX (0.05% vs. 0.1%). The Tobradex ST formulation includes a retention-enhancing agent, xanthan gum, which allows the use of a lower dexamethasone concentration to achieve equivalent dexamethasone aqueous humor exposure to that of TOBRADEX.

### **BIOEQUIVALANCE:**

Three clinical trials were conducted in the U.S. to support the bioequivalence of Tobradex ST to TOBRADEX: a pilot aqueous humor bioavailability study (C-05-43) and two aqueous humor bioequivalence studies (C-05-23 and C-06-37) involving 2100 cataract surgery patients. Based on both Alcon's analysis and the FDA analysis of dexamethasone aqueous humor concentration data obtained from Study C-06-37, the comparison of the test product Tobradex-ST versus the reference product TOBRADEX met the equivalence limits of 80 to 125% for the primary pharmacokinetic parameter  $AUC_{0-5}$  for both the per protocol and ITT populations. Results from additional analyses performed by the FDA support equivalence of the two products for the parameters  $AUC_{0-2}$ ,  $AUC_{0-3}$ , and the primary parameter  $AUC_{0-5}$ . Although the upper bound for the  $AUC_{0-1}$  comparison was outside the limits, the actual ratios for all AUC comparisons were similar, suggesting this finding was due to the variability in calculated  $AUC_{0-1}$  values from bootstrapping. Because the upper bound of the 90% confidence interval for  $AUC_{0-1}$  exceeded 125% (i.e. dexamethasone concentrations were higher with the test product), it is unlikely this finding would have a negative impact on efficacy compared to the reference product.

Tobradex-ST and TOBRADEX exhibited similar safety profiles in Study C-06-37. The long-term safety profile following multiple dosing of TOBRADEX has been well-established, as has the safety profile following systemic administration of much higher doses of dexamethasone. Thus, an upper bound for the  $AUC_{0-1}$  comparison of 126.8% is not expected to be clinically relevant from a safety standpoint, and Alcon adequately established equivalence of the two products based on the primary comparison of  $AUC_{0-5}$ .

### **GENERAL CONSIDERATIONS:**

No data are available on the extent of systemic absorption of dexamethasone or tobramycin from Tobradex ST ophthalmic suspension. Following multiple-dose (QID for 2 days) bilateral ocular administration of TOBRADEX in healthy male and female volunteers, peak plasma concentrations of dexamethasone were less than 1 ng/mL and occurred within 2 hours post-dose across all subjects.

Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

The selection of 0.05% dexamethasone was based on the results from bioavailability study C-05-43 (Tob 0.3%/Dex 0.025% and Tob 0.3%/Dex 0.05%) and bioequivalence study C-05-23 (Tob 0.3%/Dex 0.033%). This submission relies on the findings from bioequivalence study C-06-37 to demonstrate that the dexamethasone concentration in the aqueous humor as assayed for the corticosteroid component of the corticosteroid/anti-infective combination drug product Tobradex ST is equivalent to TOBRADEX.

The two microbial kill rate studies (N-06-015 and N-07-040) were conducted to demonstrate the equivalence of the anti-infective component, tobramycin, of Tob 0.3%/Dex 0.05% to Tobradex.

Bioequivalence study C-06-37 and the two microbial kill rate studies (N-06-015 and N-07-040) are the primary support of efficacy (bioequivalence). Studies C-05-43, C-05-23, and C-06-37 contribute to the safety database.

Bioequivalence study C-06-37 demonstrates bioequivalence between Tobradex ST and TOBRADEX in their ability to deliver dexamethasone to the expected site of action (aqueous humor). The submitted *In vitro* microbial kill rate studies **do not** demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

See the following tables from the Medical Officer's Review, Section 6.1.5.

Study N-07-040 Microorganism (MCC#)	% Survivors								
	Saline			Tob 0.3%/Dex 0.05%			Tobradex		
	0	30	60	0	30	60	0	30	60
<i>S. aureus</i> -ATCC (2348)	100	109	82	106	0	0	115	0	0
<i>S. aureus</i> -MSSA (41028)	100	83	92	65	0.4	0	68	0.2	0
<i>S. aureus</i> -MRSA (30281)	100	81	95	100	38	22	104	51	29
<i>S. aureus</i> -MRSA (30281) at 33°C	100	80	89	95	0	0	87	0	0
<i>S. epidermidis</i> -ATCC (3245)	100	93	91	0	0	0	2	0	0
<i>S. epidermidis</i> -MSSE (41001)	100	102	68	0.8	0	0	10	0	0
<i>S. epidermidis</i> -MRSE (50093)	100	111	78	0.3	0	0	4	0	0
<i>S. pneumoniae</i> -PSSP (52385)	100	72	52	0	0	0	0	0	0
<i>S. pneumoniae</i> -PRSP (41314)	100	102	110	0	0	0	0	0	0
<i>S. pyogenes</i> (80632)	100	107	101	0	0	0	0.2	0	0
<i>S. mutans</i> (52161)	100	87	110	8	0	0	5	0	0
<i>A. calcoaceticus</i> (15300)	100	100	72	0	0	0	0	0	0
<i>E. aerogenes</i> (41217)	100	99	104	54	0	0	84	0	0
<i>E. coli</i> -ATCC (2361)	100	92	108	81	9	0.9	82	22	5

Cross-Discipline Team Leader Review

William M. Boyd, M.D.

NDA 50-818

Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

<i>H. aegyptius</i> (2389)	100	109	95	4	0	0	0	0	0
<i>H. influenzae</i> (41098)	100	103	83	42	0	0	2	0	0
<i>K. pneumoniae</i> (41153)	100	101	110	70	0	0	107	25	8
<i>M. lacunata</i> (4414)	100	99	89	0	0	0	0	0	0
<i>M. morgani</i> (91038)	100	98	106	67	0.5	0	82	48	24
<i>N. perflava</i> (65248)	100	110	111	20	0	0	48	0	0
<i>N. sicca</i> (61708)	100	79	71	10	0	0	9	0	0
<i>P. mirabilis</i> (91511)	100	85	48	46	0.2	0	77	8	2
<i>P. vulgaris</i> (62029)	100	109	107	82	17.5	4	86	8	0.7
<i>P. aeruginosa</i> -ATCC (2365)	100	94	83	18	0.2	0	26	7	4

Study N-06-015 Microorganism (MCC#)	% Survivors									
	Time (minutes)	Saline			Tob 0.3%/Dex 0.05%			Tobradex		
		0	30	60	0	30	60	0	30	60
<i>S. aureus</i> -ATCC (2348)	100	95	99	95	0	0	58	0	0	
<i>S. aureus</i> -MSSA (41028)	100	99	75	51	0.9	0.1	50	0	0	
<i>S. aureus</i> -MSSA (41053)	100	58	63	45	0	0	38	0	0	
<i>S. aureus</i> -MRSA (30281)	100	99	84	121	36	7	124	2	0	
<i>S. epidermidis</i> -ATCC (3245)	100	116	113	4	0	0	18	0.1	0	
<i>S. epidermidis</i> -MSSE (41001)	100	70	62	4	0	0	9	0	0	
<i>S. epidermidis</i> -MRSE (50093)	100	86	76	8	0	0	22	0.1	0	
<i>S. pneumoniae</i> -PSSP (52385)	100	46	42	0	0	0	0	0	0	
<i>S. pneumoniae</i> -PRSP (41314)	100	93	95	0	0	0	0	0	0	
<i>S. pyogenes</i> (80632)	100	128	133	0	0	0	0	0	0	
<i>S. mutans</i> (52161)	100	99	94	21	0	0	11	0	0	
<i>A. calcoaceticus</i> (15300)	100	91	81	63	0	0	10	0	0	
<i>E. aerogenes</i> (41217)	100	93	89	59	0	0	77	2	0.1	
<i>E. coli</i> -ATCC (2361)	100	100	103	92	26	8	102	35	20	
<i>H. aegyptius</i> (2389)	100	71	50	3	0	0	0	0	0	
<i>H. influenzae</i> (41098)	100	95	116	30	0	0	6	0	0	
<i>K. pneumoniae</i> (41153)	100	91	123	61	0	0	87	7	1	
<i>M. lacunata</i> (4414)	100	126	112	0	0	0	0	0	0	
<i>M. morgani</i> (91038)	100	103	99	78	4	0	79	44	27	
<i>N. perflava</i> (65248)	100	98	95	12	0	0	2	0	0	
<i>N. sicca</i> (61708)	100	105	114	15	0	0	7	0	0	
<i>P. mirabilis</i> (91511)	100	91	102	54	3	0	71	7	0.6	
<i>P. vulgaris</i> (62029)	100	112	111	68	31	21	87	13	2	
<i>P. aeruginosa</i> -ATCC (2365)	100	103	82	16	0.5	0.1	22	2	1	

In studies N-07-040 and N-06-015, both Tobradex ST and Tobradex demonstrate ineffective microbial kill rates for multiple organisms at both 30 and 60 minutes following inoculation.

On April 11, 2008, Alcon submitted a response to concerns raised by the FDA that dexamethasone in Tobradex ST was possibly interfering with the antibacterial activity of tobramycin as demonstrated by the percent survivors reported at 15 or 30 minutes for three of the test bacteria, i.e., *Staphylococcus aureus* (MCC 41028), *S. aureus* (MCC 30281) and *Morganella morganii* (MCC 91038). Alcon proposed that the minor differences in antimicrobial activity of TOBREX, TOBRADEX and TobraDex ST in the in vitro model are due to their formulated pH rather than the presence or absence of dexamethasone. The Agency requested additional clarification regarding these results.

On April 14, 2008, Alcon provided additional clarification:

Tobradex ST was formulated at pH 5.7 in order to enhance the stability of dexamethasone. In addition, since this formulation contains xanthan gum as a viscosity modifier, the pH at 5.7 is necessary to maintain a droppable "solution-like" viscosity in the bottle. Upon instillation, the product viscosity increases due to the pH and ionic strength of the tears. The higher viscosity in the eye was designed to maintain the availability of the actives on the ocular surface for a longer period of time.

Since the average pH at the ocular surface is 7.5, the pH of Tobradex ST, which contains no buffer, rapidly equilibrates to that of the tears upon instillation. Therefore, additional microbial kill testing was performed on *S. aureus* and *M. morganii* with formulations of TOBRADEX and Tobradex ST adjusted up from pH 5.7 to 7.5.

In this testing paradigm, the rate of kill of *S. aureus* and *M. morganii* for each of the three formulations at pH 7.5 is complete within 15 minutes. These findings add further support to the conclusions presented in the previous response that:

- 1) There is no evidence that dexamethasone interferes with the antimicrobial activity of tobramycin,
- and
- 2) The differences in the rate of kill observed in vitro between TOBREX and Tobradex ST are due to the differences in the pH of the two formulations.

The Agency does not agree that this testing paradigm as applied is appropriate. The additional microbial kill testing was only performed on *S. aureus* and *M. morganii* with formulations of TOBRADEX and Tobradex ST adjusted up from pH 5.7 to 7.5 (i.e. the survivors reported at 15 or 30 minutes for three of the test bacteria, i.e., *Staphylococcus aureus* (MCC 41028), *S. aureus* (MCC 30281) and *Morganella morganii* (MCC 91038) in the original submission).

- If this new testing paradigm is to be appropriately applied, all organisms should be retested with formulations of TOBRADEX and Tobradex ST; if the testing is to mimic the conditions as found on the ocular surface, other factors such as temperature and tear composition should be included.

## 8. Safety

The safety database consists of Studies C-05-43, C-05-23, C-06-37, and postmarketing safety experience for the reference product TOBRADEX including ophthalmic suspension, ophthalmic ointment, and otic preparation for the period October 1, 2002 to January 31, 2007.

The application supports the safety of Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. TOBRADEX has been marketed in the United States since it was approved in August, 1988. The postmarketing experiences data for Tobradex supports the long term safety of products containing the combination tobramycin/dexamethasone.

See the following table from the Medical Officer's review, Section 7.1.5.4.

**Frequency and Incidence of Ocular and Non-ocular Adverse Events  
 (Studies C-05-43, C-05-23, C-06-37)**

Coded Adverse Event	Tob 0.3%/Dex 0.05% N=533	Tob 0.3%/Dex 0.033% N=491	Tob 0.3%/Dex 0.025% N=44	Tobradex N=1032
	N (%)	N (%)	N (%)	N (%)
<b>All Events</b>	10 (1.9)	46 (9.4)	4 (9.1)	71(6.9)
<b>OCULAR</b>				
<b>Eye Disorder</b>				
Eye pain	2 (0.4)	3 (0.6)		4 (0.4)
Conjunctival hemorrhage		2 (0.4)		2 (0.2)
Corneal oedema		3 (0.6)		1 (0.1)
Foreign body sensation		1 (0.2)		3 (0.3)
Iritis		1 (0.2)		3 (0.3)
Anterior chamber inflammation				1 (0.1)
Eye irritation		2 (0.4)		1 (0.1)
Lacrimation increased		1 (0.2)		
Conjunctivitis				1 (0.1)
Conjunctivitis allergic		1 (0.2)		
Eye pruritis	1 (0.2)			1 (0.1)
Corneal epithelium defect		1 (0.2)		
Keratitis		1 (0.2)		
Corneal striae				1 (0.1)
Eye disorder				1 (0.1)
Eye swelling				1 (0.1)
Eyelid pain				1 (0.1)
Blepharitis		1 (0.2)		
Visual acuity reduced		1 (0.2)		1 (0.1)
Posterior capsule rupture				2 (0.2)
Endophthalmitis		1 (0.2)		

Cross-Discipline Team Leader Review  
 William M. Boyd, M.D.  
 NDA 50-818  
 Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

Coded Adverse Event	Tob 0.3%/Dex 0.05% N=533	Tob 0.3%/Dex 0.033% N=491	Tob 0.3%/Dex 0.025% N=44	Tobradex N=1032
Macular oedema				1 (0.1)
Retinoschisis				1 (0.1)
Vitreous detachment				1 (0.1)
Vitreous hemorrhage				1 (0.1)
Vitreous floaters		1 (0.2)		
<b>NON-OCULAR</b>				
<b>Infections and Infestations</b>				
Gastroenteritis				1 (0.1)
Gastrointestinal infection				1 (0.1)
Tooth abscess				1 (0.1)
Tooth infection				1 (0.1)
Bronchitis		1 (0.2)		
Upper respiratory tract infection		1 (0.2)		
Nasopharyngitis			1 (2.3)	
<b>Blood and Lymphatic System Disorders</b>				
Anaemia		1 (0.2)		
<b>Metabolism and Nutrition Disorders</b>				
Diabetes mellitus inadequate control		2 (0.4)		
Dehydration		1 (0.2)		
Hypercholesterolaemia		1 (0.2)		
<b>Nervous System Disorders</b>				
Headache	1 (0.2)	2 (0.4)		5 (0.5)
Migraine				1 (0.1)
Paraesthesia				1 (0.1)
Syncope vasovagal				1 (0.1)
<b>Cardiac Disorders</b>				
Cardiac failure				1 (0.1)
Sinus Tachycardia	1 (0.2)			
Angina unstable		1 (0.2)		
Congestive		1 (0.2)		
<b>Respiratory, Thoracic and Mediastinal Disorders</b>				
Pneumonitis		1 (0.2)		
<b>Gastrointestinal Disorders</b>				
Nausea				1 (0.1)
Vomiting			1 (2.3)	
<b>Hepatobiliary Disorders</b>				
Cholelithiasis				1 (0.1)
<b>Skin and Subcutaneous Tissue Disorders</b>				
Hyperhidrosis				1 (0.1)
<b>Musculoskeletal and Connective Tissue Disorders</b>				
Back pain				1 (0.1)
Arthritis		1 (0.2)		
<b>Investigations</b>				

Cross-Discipline Team Leader Review  
 William M. Boyd, M.D.  
 NDA 50-818  
 Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%

<b>Coded Adverse Event</b>	<b>Tob 0.3%/Dex 0.05% N=533</b>	<b>Tob 0.3%/Dex 0.033% N=491</b>	<b>Tob 0.3%/Dex 0.025% N=44</b>	<b>Tobradex N=1032</b>
Intraocular pressure increased		8 (1.6)	2 (4.5)	12 (1.2)
Blood pressure increased	3 (0.6)	2 (0.4)		2 (0.2)
Blood glucose decreased				1 (0.1)
Blood glucose increased				1 (0.1)
Intraocular pressure decreased				1 (0.1)
<b>Injury, Poisoning and Procedural Complications</b>				
Corneal abrasion		1 (0.2)		5 (0.5)
Procedural complication	2 (0.4)			2 (0.2)
Post procedural complication		1 (0.2)		2 (0.2)
Injury		1 (0.2)		

## 9. Advisory Committee Meeting

Not applicable; this product is a non-NME.

## 10. Pediatrics

Reference is made the Agency's finding of safety and effectiveness for pediatric patients in NDA 50-592; safety and effectiveness have not been established in pediatric patients below the age of 2 years.

Alcon has requested a waiver to conduct pediatric studies in patients below the age of 2 years.

## 11. Other Relevant Regulatory Issues

A Division of Scientific Investigations (DSI) audit was requested. An audit of the analytical and clinical portions of Study C-06-07 revealed no significant deficiencies. There is no evidence to suggest that the trials submitted in NDA 50-818 were not conducted in accordance with accepted ethical standards.

Alcon has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators*. There is no evidence to suggest that the results of the studies were impacted by any financial payments.

The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed Alcon's proposed product labeling (PI) for Tobradex ST submitted to the Agency on June 14, 2007.

DDMAC has reviewed the proposed PI for Tobradex ST and has no comments at this time. A majority of the information included in this proposed Tobradex ST PI is identical to the information included in the TOBRADEX PI. Per DDMAC, there were no misleading competitive claims incorporated into the proposed labeling.

## 12. Labeling

A formal, final labeling review is deferred until data is submitted to support that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

## 13. Recommendations/Risk Benefit Assessment

### RECOMMENDED REGULATORY ACTION:

NDA 50-818 is **not** recommended for approval for the indication steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. The application failed to demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

- It is recommended that an *in vitro* microbial kill rate study in an environment (i.e. media) that is substantially similar to the human eye be conducted comparing Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% with sterile saline, tobramycin, and TOBRADEX. This environment would include similar pH, pH buffer, temperature, and cations.

### RISK BENEFIT ASSESSMENT:

Bioequivalence study C-06-37 demonstrates bioequivalence between Tobradex ST and TOBRADEX in their ability to deliver dexamethasone to the expected site of action (aqueous humor). The submitted *in vitro* microbial kill rate studies **do not** demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

The application supports the safety of Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% in the treatment of steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists. TOBRADEX has been marketed in the United States since it was approved in August, 1988. The postmarketing experiences data for Tobradex supports the long term safety of products containing the combination tobramycin/dexamethasone.

CMC, Pharmacology/Toxicology, Clinical Pharmacology, and Product Quality Microbiology have recommended approval for this application.

The Biostatistics review states that the results support equivalence of the 2 products.

Clinical Microbiology and the Medical Officer do not recommend approval; Alcon did not test using the Agency's recommended time-kill rate methodology and compare their proposed new drug product, Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05%, to the Agency's recommended comparator, TOBRADEX (tobramycin and dexamethasone ophthalmic suspension).

**RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:**

There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

**COMMENTS TO THE APPLICANT:**

The endotoxin limit proposed is not scientifically supported. It is recommended that endotoxin be monitored and a timeframe for setting a lower specification be established.

Data should be submitted to support that Tobradex ST has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

Specifically, it is recommended that an in vitro microbial kill rate study in an environment (i.e. media) that is substantially similar to the human eye be conducted comparing Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% with sterile saline, tobramycin, and TOBRADEX. This environment would include similar pH, pH buffer, temperature, and cations.

If a new testing paradigm is to be appropriately applied, all organisms should be retested with formulations of TOBRADEX and Tobradex ST using testing which mimics the conditions found on the ocular surface (i.e. similar pH, pH buffer, temperature, and cations).

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William Boyd  
4/15/2008 03:23:50 PM  
MEDICAL OFFICER

Wiley Chambers  
4/15/2008 09:03:12 PM  
MEDICAL OFFICER