CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-818

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 50-818

NDA 50-818

Submission Dates: 6/10/08, 8/14/08, 9/8/08

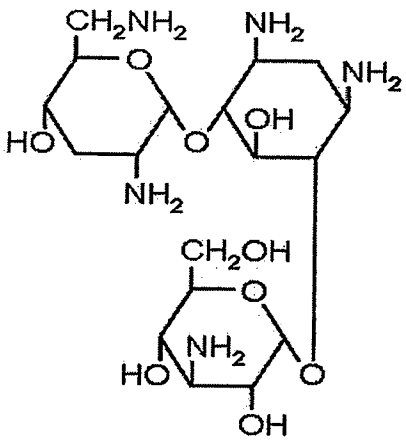
Medical Officer's Review #2

Review Completed: 2/6/09

Proposed Trademark: Tobradex ST

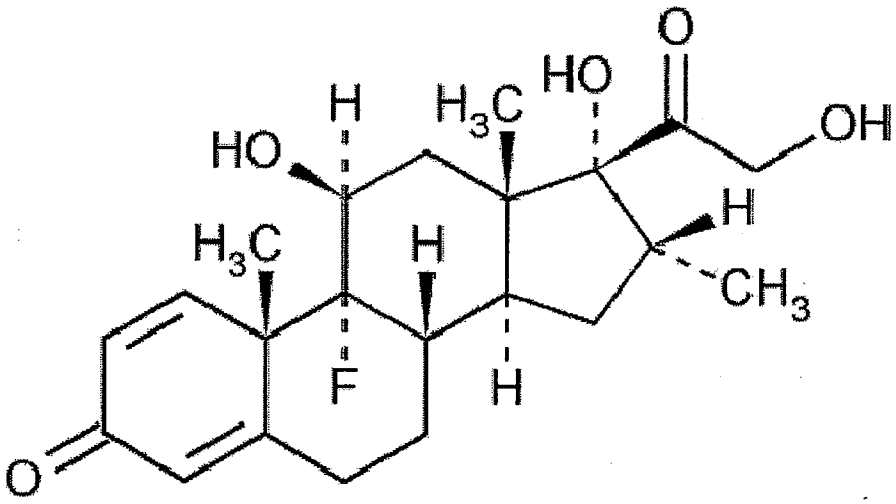
Generic Name tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05%

Chemical Name:



Tobramycin (Mol. Wt. 467.52)

Empirical Formula: $C_{18}H_{37}N_5O_9$



Dexamethasone (Mol. Wt. 392.47)

Empirical Formula: $C_{22}H_{29}N_5FO_9$

Sponsor:

Alcon Universal, Ltd
P.O. Box 62
Bosch 69
CH-6331 Hunenberg, Switzerland

Authorized U.S. Agent
Alcon Research, Ltd
6201 South Freeway
Fort Worth, Texas 76134-2099
(817) 568-6116

Pharmacologic Category: Anti-infective/corticosteroid

Proposed Indication: 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.

Submitted: Submitted is applicant's response to an approvable letter dated April15, 2008 and proposed package insert.

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 decreased ⌐ ¬ b(4)

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)

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The product quality microbiology review assessed xanthan gum [

b(4)

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

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) [a]	Positive
Dexamethasone Identity (UPLC) [a]	Positive
Dexamethasone Assay (UPLC)	Label
Dexamethasone Related Impurities (UPLC) [b]	NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone NMT of dexamethasone
Tobramycin Identity (TLC) [a]	Positive
Tobramycin Identity (HPLC) [a]	Positive
Tobramycin Assay (HPLC)	Label
Tobramycin Related Impurities (HPLC) [b]	NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin NMT of tobramycin
Benzalkonium Chloride Identity (HPLC) [a]	Positive
Benzalkonium Chloride Assay (HPLC)	Label
Edetate Disodium Identity (HPLC) [a]	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 [a]	
Sterility	Meets USP Requirements

[a] Release test only
[b] Includes all impurities other than drug substance process impurities.

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.

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 LT —— 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 —— b(4)
——— That solution was subsequently ————————

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

b(4)

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.

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.

The proposed package insert is as follows:

Reviewer's Comments:

Acceptable.

Recommended Regulatory Action:

NDA 50-818 with the proposed package insert is recommended for approval.

Lucious Lim, M.D., M.P.H.
Medical Officer

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

/s/

Lucious Lim
2/9/2009 04:15:34 PM
MEDICAL OFFICER

William Boyd
2/9/2009 04:25:21 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA 50-818
Submission Number	000
Submission Code	Original
Letter Date	June 14, 2007
Stamp Date	June 15, 2007
PDUFA Goal Date	April 15, 2008
Reviewer Name	Lucious Lim, M.D., M.P.H.
Review Completion Date	February 1, 2008
Established Name	tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension
(Proposed) Trade Name	TobraDex ST
Therapeutic Class	anti-infective/corticosteroid
Applicant	Alcon, Inc.
Priority Designation	S
Formulation	active ingredient: tobramycin 0.3%/dexamethasone 0.05%
Dosing Regimen	one drop into the conjunctival sac(s) every four (4) to six (6) hours. During the initial 24 to 48 hours, the dosage may be increased to one drop every two (2) hours.
Indication	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.
Intended Population	adults and children 2 years and older with steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or risk of bacterial ocular infection exists

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Executive Summary

1.1 Recommendation on 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 Tob 0.3%/Dex 0.05% 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 comparing Tob 0.3%/Dex 0.05% with sterile saline, tobramycin, and Tobradex be performed.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No additional studies are recommended.

1.2.2 Required Phase 4 Commitments

No additional studies are recommended.

1.2.3 Other Phase 4 Requests

No additional studies are recommended.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

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 application proposes to market tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension (Tob 0.3%/Dex 0.05%) using the same active ingredients and preservative as Tobradex and for the same indication. Tob 0.3%/Dex 0.05% 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 to 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 Tob 0.3%/Dex 0.05% to the reference product, Tobradex. The goal of this program is 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.

Reviewer's Comments:

For bioequivalence to be demonstrated for dexamethasone at 0 – 5 hours, the 90% confidence limits for dexamethasone's AUC_{0-5} should lie within the pre-specified interval of 80 to 125% for the primary analysis population.

The two in vitro microbial kill rate studies (N-06-015, N-07-040) used Tobradex as the active control agent. Tobramycin should be included as a control agent in the studies. It is recommended that an in vitro microbial kill rate study comparing Tob 0.3%/Dex 0.05% with sterile saline, tobramycin, and Tobradex be performed.

1.3.2 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* microbial kill rate studies to demonstrate equivalence between Tob 0.3%/Dex 0.05% and Tobradex

The bioequivalence database consists of one pharmacokinetics study (C-99-33) conducted in healthy volunteers, one aqueous humor bioavailability study (C-05-43), two aqueous humor bioequivalence studies (C-05-23 and C-06-37) conducted in patients undergoing cataract surgery. The microbial kill rate database consists of two *in vitro* microbial kill rate studies (N-06-015 and N-07-040). Bioequivalence study C-06-37 and the two *in vitro* microbial kill rate studies (N-06-015 and N-07-040) are the primary support of efficacy (bioequivalence) for this NDA.

NDA 50-818 supports the bioequivalence of Tob 0.3%/Dex 0.05% to Tobradex in its ability to deliver dexamethasone to the expected site of action (aqueous humor). The application does not support that Tob 0.3%/Dex 0.05% has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

1.3.3 Safety

The safety database consists of Studies C-05-43, C-05-23, C-06-37, and postmarketing safety experience for the reference product tobramycin 0.3%/dexamethasone 0.1% (Tobradex) eye drops/ointment/ear drops for the period October 1, 2002 to January 31, 2007.

The application supports the safety of Tob 0.3%/Dex 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.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is one drop into the conjunctival sac(s) every four (4) to six (6) hours. During the initial 24 to 48 hours, the dosage may be increased to one drop every two (2) hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

1.3.5 Drug-Drug Interactions

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.

1.3.6 Special Populations

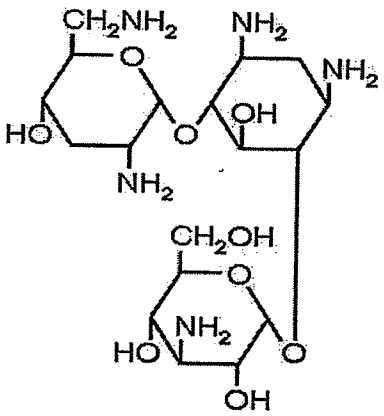
There were no known differences with respect to age, gender, race, or iris color noted in the original approval of Tobradex. No information has been submitted to alter those conclusions.

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

2 INTRODUCTION AND BACKGROUND

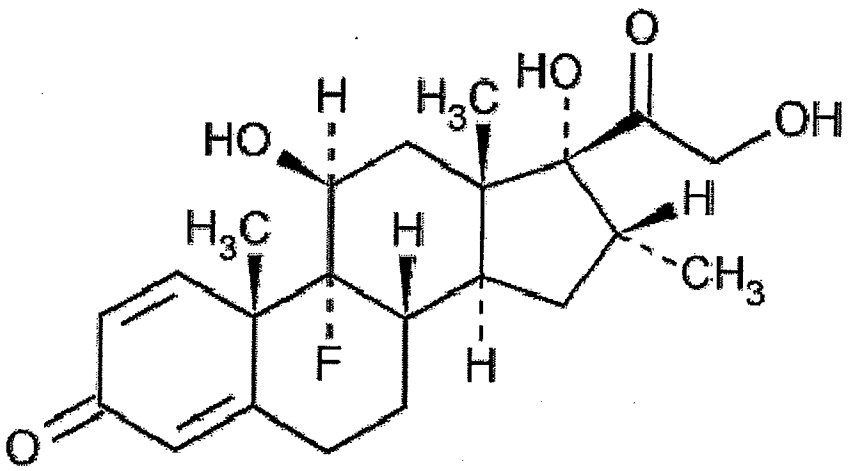
2.1 Product Information

Tobramycin 0.3%/dexamethasone 0.05% ophthalmic suspension (Tob 0.3%/Dex 0.05%) is combination anti-infective (tobramycin 0.3%)/corticosteroid (dexamethasone 0.05%) agent. It is a sterile, isotonic, multi-dose ophthalmic suspension formulation preserved with benzalkonium chloride. The anti-infective component's chemical name is D-Streptamine, *O*-3-amino-3-deoxy-α-D-glucopyranosyl-(1□ 6)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl-(1□ 4)]-2-deoxy-. The corticosteroid component's chemical name is –Pregna-1,4-diene-3,20-dione, 9-fluoro-11,17,21-trihydroxy-16-methyl-,(11β, 16α)-. The active ingredients are represented by the following chemical structures:



Tobramycin (Mol. Wt. 467.52)

Empirical Formula: $C_{18}H_{37}N_5O_9$



Dexamethasone (Mol. Wt. 392.47)

Empirical Formula: $C_{22}H_{29}N_5FO_9$

The proposed indication is for treatment of steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists in adults and children 2 years and older. The proposed dosing regimen is one drop in the conjunctival sac(s) every four (4) to six (6) hours. During the initial 24 to 48 hours, the dosage may be increased to one drop every two (2) hours.

2.2 Currently Available Treatment for Indications

Corticosteroids, such as dexamethasone, are a class of products approved for steroid-responsive inflammatory ocular conditions.

There are currently multiple topical anti-infective/corticosteroid combinations available by prescription to treat steroid-responsive inflammatory ocular conditions where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Products available containing dexamethasone, the steroid, and/or tobramycin, the anti-infective, component of Tob 0.3%/Dex 0.05% include:

- Maxidex, (dexamethasone)
- Tobrex (tobramycin)
- Tobradex (tobramycin and dexamethasone)
- Zylet (loteprednol and tobramycin)
- Maxitrol (dexamethasone, neomycin,and polymyxin B)

2.3 Availability of Proposed Active Ingredient in the United States

Fixed ophthalmic combinations of anti-infective and anti-inflammatory active pharmaceutical ingredients have a long history of approval for use in ophthalmic clinical conditions. Blephamide (sulfacetamide sodium and prednisolone acetate) was first permitted by FDA in 1961. The combination tobramycin and dexamethasone, TobraDex was approved in the U.S. in 1988. Other fixed combinations of anti-infective and anti-inflammatory drugs approved and marketed for ophthalmic use include Pred-G, Poly-Pred, Neodecadron, and Zylet.

Products approved and marketed containing the active pharmaceutical ingredient (dexamethasone, the steroid anti-inflammatory component) of Tob 0.3%/Dex 0.05% include: Maxidex (dexamethasone), Tobradex (tobramycin and dexamethasone), and Maxitrol (dexamethasone, neomycin, and polymyxin B).

Products approved and marketed containing the active pharmaceutical ingredient (tobramycin, the anti-fective component) of Tob 0.3%/Dex 0.05% include: Tobrex (tobramycin), Tobradex (tobramycin and dexamethasone), and Zylet (loteprednol and tobramycin).

2.4 Important Issues With Pharmacologically Related Products

The safety and efficacy effects seen with this product are class effects related to the steroid component.

Ocular steroids are contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Prolonged use may also suppress the host immune response and thus increase the hazard of secondary ocular infections. Various ocular diseases and long-term use of topical corticosteroids have been known to cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. Acute purulent infections of the eye may be masked or activity enhanced by the presence of corticosteroid medication.

2.5 Presubmission Regulatory Activity

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. Alcon 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.

2.6 Other Relevant Background Information

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.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Drug Product Composition

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			NF
Propylene Glycol			USP
Sodium Sulfate			USP
Sodium Chloride			USP
Tyloxapol			USP

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Sodium Hydroxide and/or Hydrochloric Acid	[redacted]	pH adjuster	NF
Purified Water	q.s 100	Vehicle	USP

[b] 0.21-0.29% sodium chloride is used to achieve target viscosity.

b(4)

No major CMC issues have been identified to date by the Chemistry Reviewer. The CMC Review has not been finalized.

3.2 Animal Pharmacology/Toxicology

No nonclinical pharmacology studies were conducted with Tob 0.3%/Dex 0.05%. A nonclinical *in-vitro* microbial kill study that compared Tob 0.3%/Dex 0.05% to Tobradex was performed. Sponsor performed a three week toxicology study in rabbits at exposure levels of dexamethasone two times greater than the dexamethasone concentration used in the clinical trials (Tob 0.3%/Dex 0.05%).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

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 (Tob 0.3%/Dex 0.05%) is equivalent to Tobradex (Tob 0.3%/Dex 0.1%). 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. See Clinical Pharmacology and Biopharmaceutics Review for detailed results of studies C-05-43, C-05-23, and C-06-37. 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.

4.2 Tables of Clinical Studies

Clinical Studies

Study Number and Study Period	Country (No of Study	Population Studied	Design	Treatment Groups and Dosing Regimen	Study Duration	# Pts Enrolled and

	Sites)					Treated
Phase 1 Studies						
Pharmacokinetics Study C-99-33 July 11, 2000 to July 14, 2000	Wales, UK	Healthy volunteers	Single-center, open-label, multi-dose study	Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop 1 drop in both eyes, four-times-a day, for two consecutive days	2 Days	12
Bioavailability Study C-05-43 November 11, 2005 to January 6, 2006	USA (10)	Patients requiring cataract surgery	Multi-center, randomized, single-masked, parallel-group, single-dose study	Tob 0.3%/Dex 0.025% topical ocular drop Tob 0.3%/Dex 0.05% topical ocular drop Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop 1 drop in the study eye at 1, 2, or 4 hours prior to aqueous humor sampling	1 Day	130
Phase 3 Studies						
Bioequivalence Study C-05-23 April 4, 2006 to August 31, 2006	USA (40)	Patients requiring cataract surgery	Multi-center, randomized, double-masked, parallel-group, single-dose study	Tob 0.3%/Dex 0.033% topical ocular drop Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop 1 drop in the study eye at 0.5, 1, 2, 3, or 5 hours prior to aqueous humor sampling	1 Day	995
Bioequivalence Study C-06-37 November 27, 2006 to February 22, 2007	USA (24)	Patients requiring cataract surgery	Multi-center, randomized, double-masked, parallel-group, single-dose study	Tob 0.3%/Dex 0.05% topical ocular drop Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop	1 Day	987

				1 drop in the study eye at 0.5, 1, 2, 3, or 5 hours prior to aqueous humor sampling		
Clinical Microbiology						
Microbial Kill Rate Study N-06-015 September, 2006	N/A	N/A	N/A	Tob 0.3%/Dex 0.05% topical ocular drop Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop	N/A	N/A
Microbial Kill Rate Study N-07-040 May, 2007	N/A	N/A	N/A	Tob 0.3%/Dex 0.05% topical ocular drop Tobradex (Tob 0.3%/Dex 0.1%) topical ocular drop	N/A	N/A

4.3 Review Strategy

The major sources of clinical data utilized in this review include:

- Pharmacokinetics study C-99-33
- Bioavailability study C-05-43
- Bioequivalence studies C-05-23 and C-06-37
- Microbial kill rate study N-06-015
- Microbial kill rate study N-07-040
- Post-marketing safety data for Tobradex

4.4 Data Quality and Integrity

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.

4.5 Compliance with Good Clinical Practices

The clinical trials submitted in NDA 50-818 were performed in accordance with the principles of good clinical practice.

4.6 Financial Disclosures

The applicant 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.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Based on Applicant and FDA analysis of dexamethasone aqueous humor concentrations obtained up to 5 hours post dose (AUC_{0-5}) in Study C-06-37, the proposed drug product TobraDex®-ST (tobramycin 0.3%/ dexamethasone 0.05%) ophthalmic suspension met the criteria for equivalence for the primary pharmacokinetic parameter AUC_{0-5} compared to the reference product TobraDex®. The 90% confidence interval (0.983, 1.16) around the ratio (1.07) of the aqueous humor dexamethasone AUC_{0-5} values for TobraDex®-ST and TobraDex® were within 0.80 to 1.25, demonstrating that the two formulations are equivalent. Agency analyses of partial areas support equivalence of the two products for the exposure parameters AUC_{0-2}, AUC_{0-3}, and the primary parameter AUC_{0-5}. The upper bound of the calculated 90% confidence interval for the comparison of AUC_{0-1} fell outside the pre-specified 80 to 125% interval; the 90% confidence limits were 90.6% to 126.8% for AUC_{0-1}. 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. Safety information from patients administered TobraDex®-ST prior to cataract surgery, data following long-term, multiple dose administration of TobraDex®, and the safety profile following systemic administration of much higher doses of dexamethasone support the conclusion that the upper bound for the AUC_{0-1} comparison of 126.8% is not expected to be clinically relevant from a safety standpoint.

5.2 Pharmacodynamics

No pharmacodynamics data were collected.

5.3 Exposure-Response Relationships

Adequate assessments of exposure-response relationships were performed.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication is:

> 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.

6.1.1 Methods

The major sources of clinical data utilized in this review include:

- Bioequivalence study C-06-37
- Microbial kill rate studies N-06-015 and C-07-040

6.1.2 General Discussion of Endpoints

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 Tob 0.3%/Dex 0.05% and Tobradex

6.1.3 Study Design

Study C-06-37: "A Double-Masked, Parallel-Group, Randomized, Single-Dose Bioequivalence Study of Tobradex AF Suspension and Tobradex Ophthalmic Suspension."

Principle Investigators and Subjects Enrolled

Principle Investigator	Principle Investigator Number	City and State	Number of Subjects Enrolled
Lisa Cibik, MD	3900	West Mifflin, PA 15122	0*
Andrew Cottingham, MD	3349	San Antonio, TX 78229	46
Thomas Croley, MD	2557	Ocala, FL 34474	50
Peter Dawson, MD	2678	Houston, TX 77008	60
Harvey DuBiner, MD	1927	Morrow, GA 30260	57
Gary Foster, MD	3903	Fort Collins, CO 80525	22
Paul Jorizzo, MD	4547	Medford, OR 97504	47
Michael Kottler, MD	355	Salt Lake City, UT 84117	47
Bradley Kwapiszeski, MD	3112	Shawnee Mission, KS 66204	34
Robert Lehmann, MD	970	Nacogdoches, TX 75965	42
Douglas Lorenz, DO	2302	Henderson, NV 89074	30

Ranjan Malhotra, MD	4824	Creve Coeur, MO 63141	60
Satish Modi, MD	3828	Poughkeepsie, NY 12603	55
Patrick O'Connor, MD	4983	San Antonio, TX 78222	4
Matthew Paul, MD	3025	Danbury, CT 06810	30
Harvey Reiser, MD	3747	Kingston, PA 18704	59
Kenneth Sall, MD	1806	Artesia, CA 90701	25
Philip Lee Shettle, DO	3346	Largo, FL 33770	41
Steven Silverstein, MD	3807	Kansa City, MO 64133	58
Stephen Smith, MD	3988	Ft. Myers, FL 33901	60
Emil Stein, MD	3851	Las Vegas, NV 89119	35
Robert Stewart, MD	271	Houston, TX 77025	58
George C. Thorne, MD	2353	Austin, TX 78756	7
Thomas Walters, MD	1007	Austin, TX 78705	60

*Dr. Cibik resceived test article but did not enroll any patients in the study.

Inclusion Criteria:

Patients must meet the following inclusion criteria for enrollment:

1. Male and female patients 18 years of age and older, of any race;
2. Have a need for cataract surgery in the study eye;
3. Patients whose health (based on medical history, physical examination, clinical labs, serology, and ophthalmic examinations as deemed appropriate by the study investigator) would not interfere with optimal participation in the study, and would not present a health risk to the patient. Appropriate documentation should be provided as part of the source documents.
4. Patients must be able to follow instructions and be willing and able to attend required study visits.

Exclusion Criteria:

Patients meeting any of the following exclusion criteria may not be enrolled:

1. Have previously participated in a study involving Tobradex AF suspension (Alcon Protocol C-05-23 or C-05-43);
2. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for 1 year) if they meet any of the following conditions:
   - They are currently pregnant,
   - They have a positive result on the pregnancy test at the Screening Visit,
   - They intend to become pregnant during the study period,
   - They are breast-feeding or,
   - They are not using any of the following birth control measures:
     1) Abstinence;
     2) Hormonal – oral, implanted, topical, or injected contraceptives (should be used for at least 3 months prior to the Screening Visit);

3) Mechanical – spermicide in conjunction with a barrier such as a condom or diaphragm or IUD (should be used consistently for at least 1 month prior to the Screening Visit);
4) Surgically sterilized partner.

3. Cannot be dosed in the study eye;
4. A visually nonfunctioning fellow eye with best-corrected logMAR visual acuity of 1.0 or greater. NOTE: a logMAR visual acuity of 1.0 or greater that is reduced by cataract is allowed if a Potential Acuity Meter (or similar instrument)or the Investigator's medical judgement demonstrates a potential for visual acuity of 20/60 or better;
5. History of or current ocular herpes simplex in the study eye;
6. History (within the previous 12 months) of or current evidence of uveitis in the study eye;
7. History (within the previous 3 months) of LASIK (Laser-assisted *in situ* keratomileusis), PRK (photorefractive keratectomy), RK (radial keratotomy), or similar surgery in the study eye;
8. History (within the previous 3 months) of or current evidence of ocular trauma in the study eye;
9. Presence of active external ocular disease, infection, or inflammation of the eye or eyelids (mild blepharitis is permitted if the ocular surface is clear) of the study eye;
10. Concurrent corneal disease or a disruption of the ocular epithelial surface in the study eye;
11. Any corneal abnormality that would prevent a reliable assessment of the visual acuity;
12. Known or suspected allergy or hypersensitivity to corticosteroids, tobramycin or other aminoglycosides (e.g., neomycin, gentamicin, streptomycin, kanamycin, amikacin, netilmicin), benzalkonium chloride, or other inactive ingredients present in the study eye;
13. Patients who have used any medication, by any route, containing dexamethasone or beclomethasone within 7 days prior to the Day 1 Visit;
14. History of HIV, hepatitis B; hepatitis C, or active hepatitis A; or a positive test for HIV and/or hepatitis B surface antigen, or hepatitis C antibody, or active hepatitis A antibody as determined by screening serology values;
15. History of drug and/or alcohol abuse within the past 5 years;
16. Participation in any investigational clinical study within 30 days prior to the Screening Visit, or during the study;
17. Study site staff or relatives of study site staff or other individuals who would have access to the clinical study protocol;
18. Patients whose condition, in the opinion of the Investigator, would interfere with optimal participation in the study or which would present a special risk to the patient.

In addition, the Alcon Medical Monitor and/or the Principal Investigator may declare any patient ineligible based upon sound medical reasons.

Study Plan: The primary objective of the study was to determine the bioequivalence of dexamethasone in Tob 0.3%/Dex 0.05% as compared to Tobradex by measuring concentrations of dexamethasone in the aqueous humor of cataract surgery subjects following a single topical ocular administration. Nine hundred eighty-seven (987) subjects were enrolled and randomized to receive Tob 0.3%/Dex 0.05% or Tobradex and to one of five post-dose aqueous humor

sampling time points (75 subjects per treatment group were randomized to each of the sampling time points [0.5, 1.0, 2.0, 3.0, and 5.0 hours]). The concentration of dexamethasone in aqueous humor samples from both treatment groups were compared at each of the five time points.

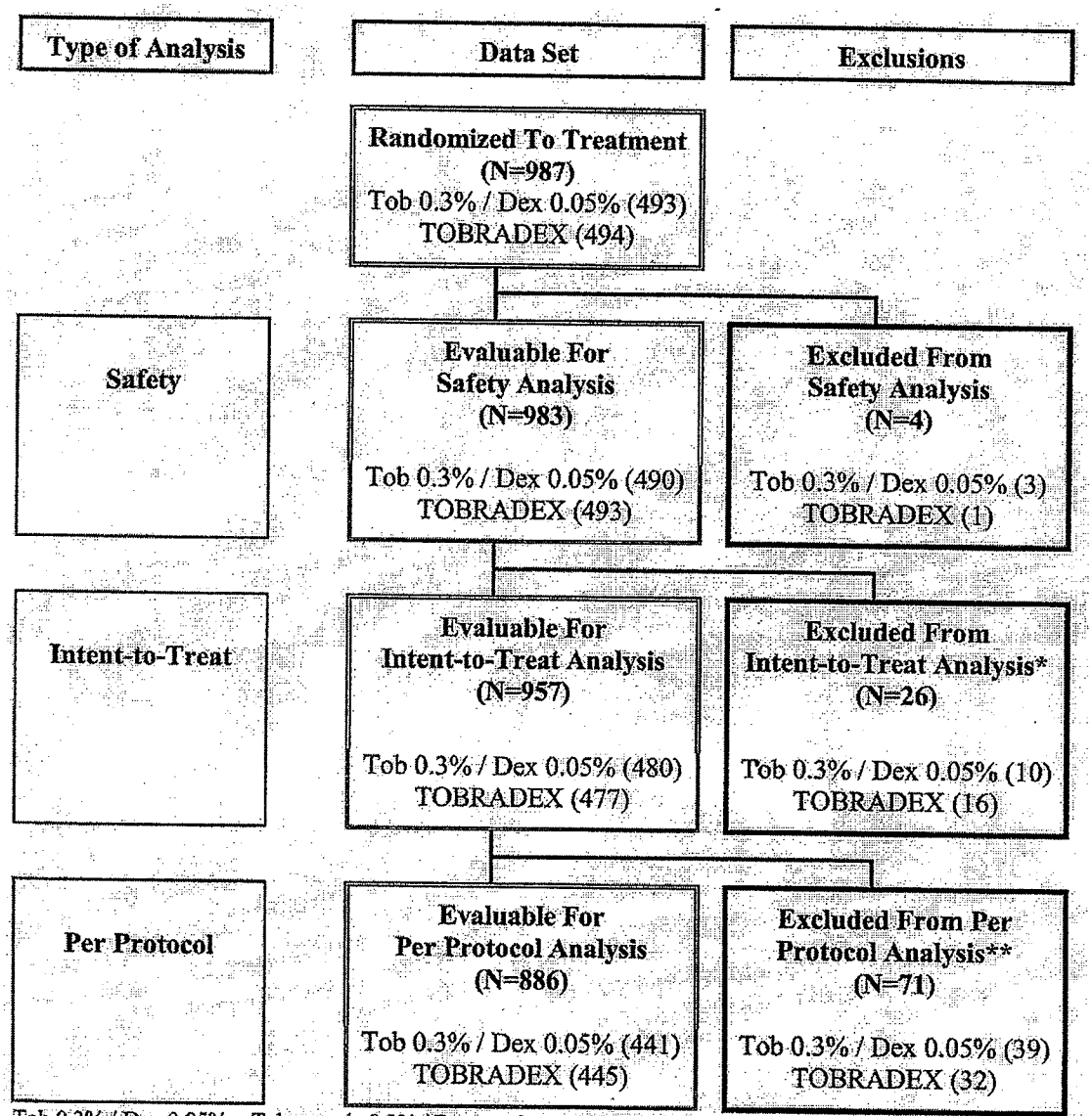
The primary pharmacokinetic variable was area under the concentration-time curve up to the last measured concentration (AUC_{0-5}). The pharmacokinetic variable was estimated from the mean aqueous humor drug concentrations of dexamethasone at each of the five sparse sampling time points. Bioequivalence was to be declared if the lower and upper limits of a two-sided 90% confidence interval about the ratio of the area under the concentration-time curve values (AUC_{0-5}) fell between 0.80 and 1.25, respectively.

Study Plan

Activity	Screening Visit Day -42 to Day -1[a]	Surgery / Exit Visit Day 1
Informed Consent	X	
Inclusion/Exclusion Criteria	X	X
Demographics	X	
Medical History	X	X
Concomitant Medications	X	X
Pregnancy Test[b]	X	
LogMAR Visual Acuity	X[c]	
Slit Lamp Exam	X[c]	
Intraocular Pressure	X[c]	
Call IVRS[d] for Patient Time Point Assignment	X	
Call IVRS[d] for Patient Number Assignment		X
Administer Study Medication		X[e]
Aqueous Humor Sample Collection		X[e,f]
Perform Cataract Surgery		X[e]
Monitor for Adverse Events		X[g]
Complete Exit Form		X[h]

[a] Screening procedures were to have been completed prior to patient number assignment (randomization) and test article dosing
[b] For females of child-bearing potential only
[c] Both eyes
[d] IVRS: Interactive Voice Response System
[e] Study eye only
[f] Sample was to be collected at the assigned time point for each patient (0.5, 1, 2, 3 or 5 hours after dosing test article)
[g] After instillation of test article
[h] Upon study exit for early discontinued patients, and after post-operative recovery for completed patients

Distribution of Patient for Analysis



Tob 0.3% / Dex 0.05% = Tobramycin 0.3% / Dexamethasone 0.05% Ophthalmic Suspension
TOBRADEX = Tobramycin 0.3% / Dexamethasone 0.1% Ophthalmic Suspension
* This is in addition to the number of patients excluded from the safety analysis
** This is in addition to the number of patients excluded from the safety analysis and the intent-to-treat analysis

Study N-07-040: "An In Vitro Study to Compare Microbial Kill Rates: Tobramycin 0.3%/Dexamethasone 0.05% Ophthalmic Suspension Compared to Tobradex Ophthalmic Suspension (Tobramycin 0.3%/Dexamethasone 0.1%)"

Study Plan: A total of 23 bacterial isolates from the 18 different species as listed in the package insert for Tobradex ophthalmic suspension were tested. A sterile control, Tob 0.3%/Dex 0.05%, and Tobtradex were challenged in two test runs for each organism, at room temperature conditions. Additionally, for methicillin-resistent S. aureus MCC 30281, two tests were conducted at 33°C. Colony counts were determined at time 0, 30 and 60 minutes for bacteria, and at time 0, 30 and 180 minutes for fungi.

Study N-06-015: "Microbiology Results of an In Vitro Study to Compare Microbial Kill Rates: Tobradex AF ophthalmic Suspension Compared to Tobradex Ophthalmic Suspension"

Study Plan: A total of 24 bacterial isolates from 18 different species as listed in the package insert for Tobradex ophthalmic suspension were tested. A sterile control, Tob 0.3%/Dex 0.05%, and Tobtradex were challenged in two test runs for each organism. Colony counts were determined at time 0, 30 and 60 minutes for bacteria, and at time 0, 30 and 180 minutes for fungi.

6.1.4 Efficacy Findings

This application relies on the submitted bioequivalence studies and *in vitro* kill studies to demonstrate equivalence between Tob 0.3%/Dex 0.05% and Tobradex. Bioequivalence study C-06-37 demonstrates bioequivalence between Tob 0.3%/Dex 0.05% and Tobradex in its ability to deliver dexamethasone to the expected site of action (aqueous humor). The submitted *In vitro* microbial kill rate studies do not demonstrate that Tob 0.3%/Dex 0.05% has the ability to effectively kill superficial bacteria thought to be susceptible to tobtramycin.

6.1.5 Clinical Microbiology

Study C-07-040

Results: The negative control group (sterile saline) showed recovery values nearly equivalent for a majority of the organisms to the initial inoculum at all time periods. For Tob 0.3%/Dex 0.05%, seven (7) organisms showed activity at 30 minutes with three (3) of the organisms remaining viable at 60 minutes. For Tobradex, eight (8) organisms showed activity at 30 minutes with seven (7) of the organisms remaining viable at 60 minutes.

Summary of Mean Per Cent (%) Survivors

Study N-07-040	% Survivors								
Microorganism (MCC#)	Saline			Tob 0.3%/Dex 0.05%			Tobradex		
Time (minutes)	0	30	60	0	30	60	0	30	60
S. aureus-ATCC (2348)	100	109	82	106	0	0	115	0	0
S. aureus-MSSA (41028)	100	83	92	65	0.4	0	68	0.2	0
S. aureus-MRSA (30281)	100	81	95	100	38	22	104	51	29
S. aureus-MRSA (30281) at 33°C	100	80	89	95	0	0	87	0	0
S. epidermidis-ATCC (3245)	100	93	91	0	0	0	2	0	0
S. epidermidis-MSSE (41001)	100	102	68	0.8	0	0	10	0	0
S. epidermidis-MRSE (50093)	100	111	78	0.3	0	0	4	0	0
S. pneumoniae-PSSP (52385)	100	72	52	0	0	0	0	0	0
S. pneumoniae-PRSP (41314)	100	102	110	0	0	0	0	0	0
S. pyogenes (80632)	100	107	101	0	0	0	0.2	0	0
S. mutans (52161)	100	87	110	8	0	0	5	0	0
A. calcoaceticus (15300)	100	100	72	0	0	0	0	0	0
E. aerogenes (41217)	100	99	104	54	0	0	84	0	0
E. coli-ATCC (2361)	100	92	108	81	9	0.9	82	22	5
H. aegyptius (2389)	100	109	95	4	0	0	0	0	0
H. influenzae (41098)	100	103	83	42	0	0	2	0	0
K. pneumoniae (41153)	100	101	110	70	0	0	107	25	8
M. lacunata (4414)	100	99	89	0	0	0	0	0	0
M. morganii (91038)	100	98	106	67	0.5	0	82	48	24
N. perflava (65248)	100	110	111	20	0	0	48	0	0
N. sicca (61708)	100	79	71	10	0	0	9	0	0
P. mirabilis (91511)	100	85	48	46	0.2	0	77	8	2
P. vulgaris (62029)	100*	109	107	82	17.5	4	86	8	0.7
P. aeruginosa-ATCC (2365)	100	94	83	18	0.2	0	26	7	4

Study C-06-015

Results: The negative control group (sterile saline) showed recovery values nearly equivalent for a majority of the organisms to the initial inoculum at all time periods. For Tob 0.3%/Dex 0.05%, seven (7) organisms showed activity at 30 minutes with five (5) of the organisms remaining viable at 60 minutes. For Tobradex, ten (10) organisms showed activity at 30 minutes with seven (7) of the organisms remaining viable at 60 minutes.

Summary of Mean Per Cent (%) Survivors

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

Reviewer's Comments:

In studies N-07-040 and N-06-015, both Tob 0.3%/Dex 0.05% and Tobradex demonstrate ineffective microbial kill rates for multiple organisms at both 30 and 60 minutes following inoculation. The results raise the question as to whether multiple organisms have developed resistance to Tobradex since its approval in 1988. It is recommended that an in vitro microbial kill rate study comparing Tob 0.3%/Dex 0.05% with sterile saline, tobramycin, and Tobradex be performed.

6.1.6 Efficacy Conclusions

This application relies on the submitted bioequivalence studies and *in vitro* microbial kill rate studies to demonstrate equivalence between Tob 0.3%/Dex 0.05% and Tobradex. There is sufficient evidence to establish the bioequivalence of Tob 0.3%/Dex 0.05% to Tobradex in its ability to deliver dexamethasone to the expected site of action (aqueous humor). There is insufficient evidence to conclude that Tob 0.3%/Dex 0.05% effectively kills superficial bacteria thought to be susceptible to tobramycin.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety database consists of Studies C-05-43, C-05-23, C-06-37, and postmarketing experience with the reference product, Tobradex. The study reports for these studies and post-marketing experience with Tobradex were reviewed and form the basis of the safety review for this application.

The entire application was submitted in electronic and paper format.

7.1.1 Deaths

No deaths occurred during the study.

7.1.2 Other Serious Adverse Events

Serious Adverse Events for Studies C-05-43, C-05-23, C-06-37

Study No.	Investigator No./ Patient No.	Treatment	Coded Adverse Event	Discontinued from Study
C-05-23	1908/6003	Tobradex	Cardiac failure	No
C-05-23	2678/2125	Tobradex	Cholelithiasis	No
C-05-23	1007/7954	Tobradex	Gastroenteritis	No
C-05-23	3747/5559	Tob 0.3%/Dex 0.033%	Congestive heart failure	No
C-05-23	3828/4803	Tob 0.3%/Dex 0.033%	Endophthalmitis	No
C-06-37	3747/2515	Tob 0.3%/Dex 0.05%	Sinus tachycardia	No

7.1.3 Dropouts and Other Significant Adverse Events

Dropouts and Significant Adverse Events

Study No.	Investigator No./ Patient No.	Treatment	Coded Adverse Event	Discontinued from Study
C-05-23	2302/4225	Tobradex	Blood pressure increased	Yes
C-05-23	2302/4226	Tobradex	Blood pressure increased	Yes

7.1.3.1 Overall profile of dropouts

Frequency and Incidence of Patient Discontinuation Due to Adverse Events
(Studies C-05-43, C-05-23, C-06-37)

Treatment	Total Subjects Enrolled N	Discontinued Subjects N (%)
Tobradex	1032	2 (0.2)
Tob 0.3%/Dex 0.05%	533	0 (0)
Tob 0.3%/Dex 0.033%	491	0 (0)
Tob 0.3%/Dex 0.025%	44	0 (0)

7.1.3.2 Adverse events associated with dropouts

A total of two subjects from Study C-05-23 discontinued from the study. Both discontinued due to an adverse event. See section 7.1.1 for details.

7.1.3.3 Other significant adverse events

See section 7.1.1 for details.

7.1.4 Other Search Strategies

Alcon submitted postmarketing safety data for the reference product, tobramycin 0.3%/dexamethasone 0.1% (Tobradex) eye drops/ointment/ear drops compiled for the period October 1, 2002 to January 31, 2007. The safety information included spontaneous adverse reactions that were reported in the Periodic Safety Update Report for tobramycin 0.3%/ dexamethasone 0.1% eye drops/ointment/ear drops.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

All adverse events were observed by the study investigator, or reported by the subject spontaneously or in response to direct questioning.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were appropriately summarized by MedDRA body system and preferred term.

7.1.5.3 Incidence of common adverse events

See section 7.1.3.4 below.

7.1.5.4 Common adverse event tables

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 (%)
All Events	10 (1.9)	46 (9.4)	4 (9.1)	71(6.9)
OCULAR				
Eye Disorder				
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)		

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)		
NON-OCULAR				
Infections and Infestations				
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)	
Blood and Lymphatic System Disorders				
Anaemia		1 (0.2)		
Metabolism and Nutrition Disorders				
Diabetes mellitus inadequate control		2 (0.4)		
Dehydration		1 (0.2)		
Hypercholestrolaemia		1 (0.2)		
Nervous System Disorders				
Headache	1 (0.2)	2 (0.4)		5 (0.5)
Migraine				1 (0.1)
Paraesthesia				1 (0.1)
Syncope vasovagal				1 (0.1)
Cardiac Disorders				
Cardiac failure				1 (0.1)
Sinus Tachycardia	1 (0.2)			
Angina unstable		1 (0.2)		
Congestive		1 (0.2)		
Respiratory, Thoracic and Mediastinal Disorders				
Pneumonitis		1 (0.2)		
Gastrointestinal Disorders				
Nausea				1 (0.1)
Vomiting			1 (2.3)	
Hepatobiliary Disorders				
Cholelithiasis				1 (0.1)
Skin and Subcutaneous Tissue Disorders				
Hyperhidrosis				1 (0.1)
Musculoskeletal and Connective Tissue Disorders				
Back pain				1 (0.1)
Arthritis		1 (0.2)		
Investigations				

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
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)
Injury, Poisoning and Procedural Complications				
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)		

7.1.5.5 Identifying common and drug-related adverse events

See Table under Section 7.1.5.4.

7.1.5.6 Additional analyses and explorations

No additional analyses and explorations were indicated and none were performed.

7.1.6 Less Common Adverse Events

No less common adverse events occurred during the study.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

No laboratory assessments were performed.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

See section 7.1.7.1 above.

7.1.7.3 Standard analyses and explorations of laboratory data

See section 7.1.7.1 above.

7.1.7.4 Additional analyses and explorations

See section 7.1.7.1 above.

7.1.7.5 Special assessments

There are no special laboratory assessments indicated for this drug product.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs assessment was not performed.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.8.1 above.

7.1.8.3 Standard analyses and explorations of vital signs data

See section 7.1.8.1 above.

7.1.8.4 Additional analyses and explorations

See section 7.1.8.1 above.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

ECG testing was not performed.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.9.1 above.

7.1.9.3 Standard analyses and explorations of ECG data

See section 7.1.9.1 above.

7.1.9.4 Additional analyses and explorations

See section 7.1.9.1 above.

7.1.10 Immunogenicity

Reference is made to the Agency's non-clinical findings in NDA 50-592 (Tobradex).

7.1.11 Human Carcinogenicity

Reference is made to the Agency's non-clinical findings in NDA 50-592 (Tobradex).

7.1.12 Special Safety Studies

Visual acuity (logMAR), ocular signs, and intraocular pressure (IOP) were evaluated in study C-05-23. In study C-05-43, dilated fundus parameters in addition to the above mentioned safety variables were evaluated. Analyses of these safety variables did not reveal any safety issues.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No evidence of drug abuse or withdrawal phenomena has been reported for this drug product.

7.1.14 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies in pregnant women.

7.1.15 Assessment of Effect on Growth

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

7.1.16 Overdose Experience

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation.

7.1.17 Postmarketing Experience

This is no postmarketing experience for this drug product. This is a new formulation and it has not been marketed in any country.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Exposure to Study Drug by Protocol (Studies C-05-43, C-05-23, C-06-37)

Treatment	Total N	C-06-37 N	C-05-23 N	C-05-43 N
Total subjects	2100	983	987	130
Tobradex	1032	493	496	43
Tob 0.3%/Dex 0.05%	533	490	0	43
Tob 0.3%/Dex 0.033%	491	0	491	0
Tob 0.3%/Dex 0.025%	44	0	0	44

7.2.1.2 Demographics

Demographic Summary by Treatment Group for Study C-06-37

Study C-06-37		Total (Studies C-06-37, C-05-23, C-05-43) N (%)	Tobradex N (%)	Tob 0.3%/Dex 0.05% N (%)
Total		2100 (100.0)	493 (100.0)	490 (100.0)
Age (years)	Adults (18-64 years)	479 (22.8)	122 (24.7)	122 (24.9)
	Elderly (≥65 years)	1621 (77.2)	371 (75.3)	368 (75.1)
Sex	Male	941 (44.8)	235 (47.7)	225 (45.9)
	Female	1159 (55.2)	258 (52.3)	265 (54.1)
Race	White	1925 (91.7)	466 (64.5)	455 (92.9)
	Black or African American	112 (5.3)	17 (3.4)	24 (4.9)
	Asian	37 (1.8)	7 (1.4)	8 (1.6)
	Native Hawaiian or Other Pacific Islander	2 (0.1)	0 (0.0)	0 (0.0)
	American Indian or Alaska Native	10 (0.5)	1 (0.2)	0 (0.0)
	Multi-racial	3 (0.1)	0 (0.0)	0 (0.0)
	Other	11 (0.5)	2 (0.4)	3 (0.6)
Ethnicity	Hispanic, Latino, or Spanish	213 (10.1)	36 (7.3)	46 (9.4)
	Not Hispanic, Latino, or Spanish	1887 (89.9)	457 (92.7)	444 (90.6)
Iris Color	Brown	888 (42.3)	192 (38.9)	188 (38.4)
	Hazel	339 (16.1)	90 (18.3)	86 (17.6)

Study C-06-37		Total (Studies C-06-37, C-05-23, C-05-43) N (%)	Tobradex N (%)	Tob 0.3%/Dex 0.05% N (%)
	Green	126 (6.0)	27 (5.5)	33 (6.7)
	Blue	703 (33.5)	174 (35.3)	171 (34.9)
	Grey	44 (2.1)	10 (2.0)	12 (2.4)

Demographic Summary by Treatment Group for Study C-05-23

Study C-05-23		Total (Studies C-06-37, C-05-23, C-05-43) N (%))	Tobradex N (%)	Tob 0.3%/Dex 0.033% N (%)
Total		2100 (100.0)	496 (100.0)	491 (100.0)
Age (years)	Adults (18-64 years)	479 (22.8)	107 (21.6)	98 (20.0)
	Elderly (≥65 years)	1621 (77.2)	389 (78.4)	393 (80.0)
Sex	Male	941 (44.8)	225 (45.4)	199 (40.5)
	Female	1159 (55.2)	271 (54.6)	292 (59.5)
Race	White	1925 (91.7)	440 (88.7)	443 (90.2)
	Black or African American	112 (5.3)	39 (7.9)	27 (5.5)
	Asian	37 (1.8)	9 (1.8)	13 (2.6)
	Native Hawaiian or Other Pacific Islander	2 (0.1)	0 (0.0)	1 (0.2)
	American Indian or Alaska Native	10 (0.5)	3 (0.6)	3 (0.6)
	Multi-racial	3 (0.1)	2 (0.4)	(0.2)
	Other	11 (0.5)	3 (0.6)	3 (0.6)
Ethnicity	Hispanic, Latino, or Spanish	213 (10.1)	62 (12.5)	53 (10.8)
	Not Hispanic, Latino, or Spanish	1887 (89.9)	434 (87.5)	438 (89.2)
Iris Color	Brown	888 (42.3)	224 (45.2)	234 (47.7)
	Hazel	339 (16.1)	75 (15.1)	67 (13.6)
	Green	126 (6.0)	32 (6.5)	25 (5.1)
	Blue	703 (33.5)	156 (31.5)	155 (31.6)
	Grey	44 (2.1)	9 (1.8)	10 (2.0)

Demographic Summary by Treatment Group for Study C-05-43

Study C-05-43		Total (Studies C-06-37, C-05-23, C-05-43) N (%)	Tobradex N (%)	Tob 0.3%/Dex 0.05% N (%)	Tob 0.3%/Dex 0.025% N (%)
Total		2100 (100.0)	43 (100.0)	43 (100.0)	44 (100.0)
Age (years)	Adults (18-64 years)	479 (22.8)	12 (27.9)	12 (27.9)	6 (13.6)
	Elderly (≥65 years)	1621 (77.2)	31 (72.1)	31 (72.1)	38 (86.4)

Study C-05-43		Total (Studies C-06-37, C-05-23, C-05-43) N (%)	Tobradex N (%)	Tob 0.3%/Dex 0.05% N (%)	Tob 0.3%/Dex 0.025% N (%)
Sex	Male	941 (44.8)	17 (39.5)	22 (51.2)	18 (40.9)
	Female	1159 (55.2)	26 (60.5)	21 (48.8)	26 (59.1)
Race	White	1925 (91.7)	40 (93.0)	40 (93.0)	41 (93.2)
	Black or African American	112 (5.3)	3 (7.0)	1 (2.3)	1 (2.3)
	Asian	37 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
	Native Hawaiian or Other Pacific Islander	2 (0.1)	0 (0.0)	1 (2.3)	0 (0.0)
	American Indian or Alaska Native	10 (0.5)	0 (0.0)	1 (2.3)	2 (4.5)
	Multi-racial	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
	Other	11 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity	Hispanic, Latino, or Spanish	213 (10.1)	2 (4.7)	6 (14.0)	8 (18.2)
	Not Hispanic, Latino, or Spanish	1887 (89.9)	41 (95.3)	37 (86.0)	36 (81.8)
Iris Color	Brown	888 (42.3)	13 (30.2)	15 (34.9)	22 (50.0)
	Hazel	339 (16.1)	9 (20.9)	5 (11.6)	7 (15.9)
	Green	126 (6.0)	4 (9.3)	3 (7.0)	2 (4.5)
	Blue	703 (33.5)	16 (37.2)	20 (46.5)	11 (25.0)
	Grey	44 (2.1)	1 (2.3)	0 (0.0)	2 (4.5)

7.2.1.3 Extent of exposure (dose/duration)

All subjects were exposed to a single dose of study drug prior to cataract surgery in Studies C-05-43, C-05-23, C-06-037.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Alcon prepared a listing of postmarketing experiences for the reference product, tobramycin 0.3%/dexamethasone 0.1% (Tobradex) eye drops/ointment/ear drops compiled for the period October 1, 2002 to January 31, 2007. The safety information includes spontaneous adverse reactions that were reported in the Periodic Safety Update report for tobramycin 0.3%/ dexamethasone 0.1% eye drops/ointment/ear drops.

7.2.2.1 Other studies

No other studies were conducted.

7.2.2.2 Postmarketing experience

This is no postmarketing experience for this drug product. This is a new formulation and it has not been marketed in any country.

7.2.2.3 Literature

A review of the literature did not reveal any new information for this drug class.

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience is adequate.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Reference is made to the Agency's non-clinical findings in NDA 50-592.

7.2.5 Adequacy of Routine Clinical Testing

Reference is made to the Agency's clinical findings in NDA 50-592.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Reference is made to the Agency's non-clinical, clinical pharmacology, and clinical findings in NDA 50-592.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There has been adequate evaluation for potential adverse events for this drug and for drugs in this class, and there are no recommendations for further study.

7.2.8 Assessment of Quality and Completeness of Data

The data submitted for the assessment of safety for Tob 0.3%/Dex 0.05% is adequate and of good quality.

7.2.9 Additional Submissions, Including Safety Update

There were no additional submissions.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

There is no information, from Alcon's submitted trials or from the Agency's conclusions regarding the class common to ocular topical steroid products, which alters the current adverse event profile for this drug product.

7.4 General Methodology

The safety database consists of Studies C-05-43, C-05-23, C-06-37, and postmarketing experience with the reference product, Tobradex. The study reports for these studies and post-marketing experience with Tobradex were reviewed and form the basis of the safety review for this application.

8 ADDITIONAL CLINICAL ISSUES

There are no additional clinical issues.

8.1 Dosing Regimen and Administration

No change in dosing is proposed or recommended.

8.2 Drug-Drug Interactions

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.

8.3 Special Populations

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.

8.4 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.

8.5 Advisory Committee Meeting

No Advisory Committee Meeting was convened for this application.

8.6 Literature Review

No literature references have been identified which are contrary to the information provided in this application for the proposed indication.

8.7 Postmarketing Risk Management Plan

No additional studies are considered necessary.

8.8 Other Relevant Materials

Submitted were postmarketing safety data for the reference product, tobramycin 0.3%/dexamethasone 0.1% (Tobradex) eye drops/ointment/ear drops compiled for the period October 1, 2002 to January 31, 2007. The safety information included spontaneous adverse reactions that were reported in the Periodic Safety Update Report for tobramycin 0.3%/ dexamethasone 0.1% eye drops/ointment/ear drops. The postmarketing experiences data supports the long term safety of products containing the combination tobramycin/ dexamethasone.

9 OVERALL ASSESSMENT

9.1 Conclusions

The bioequivalence of Tob 0.3%/Dex 0.05% to Tobradex in its ability to deliver dexamethasone to the expected site of action (aqueous humor) has been adequately demonstrated. The ability of Tob 0.3%/Dex 0.05% to effectively kill superficial bacteria thought to be susceptible to tobramycin has not been adequately demonstrated.

9.2 Recommendation on 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 Tob 0.3%/Dex 0.05% has the ability to effectively kill superficial bacteria thought to be susceptible to tobramycin.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No additional studies are recommended.

9.3.2 Required Phase 4 Commitments

No additional studies are recommended.

9.3.3 Other Phase 4 Requests

No additional studies are recommended.

9.4 Labeling Review

Labeling is deferred.

9.5 Comments to Applicant

It is recommended that an in vitro microbial kill rate study comparing Tob 0.3%/Dex 0.05% with sterile saline, tobramycin, and Tobradex be performed.

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/s/

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