CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-818

SUMMARY REVIEW

Division Director Review for NDA 50-818

Date	February 13, 2009
Reviewer	Wiley A. Chambers, M.D.
NDA#	50-818
Applicant	Alcon, Inc.
Date of Original Submission	6/15/2007
Established name	tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05%
Dosage forms / Strength	ophthalmic suspension
Proposed Indication(s)	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
Action	Approval

1. Introduction

Tobradex (tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension) is a combination anti-infective/corticosteroid agent which was approved in the U.S. in 1988 (NDA 50-592) for 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.

NDA 50-818 is a 505(b)(2) application submitted for Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% using the same active ingredients and preservative as TOBRADEX and for the same indication. NDA 50-818 references NDA 50-592. It is an old antibiotic, the holder of the application is also Alcon and therefore there are no listed patents. NDA 50-592 references an Alcon application for tobramycin ophthalmic solution and Maxidex (dexamethasone ophthalmic suspension), NDA 13-422. NDA 13-422 was approved in 1962 and references the DESI review for dexamethasone ophthalmic suspension. 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.

2. CMC

The source of the active ingredients for NDA 50-818 is the same as Tobradex. The only change is the formulation, listed below:

	Tobradex ST	Tobradex
Tobramycin	3 mg/mL	Same
Dexamethasone	0.5 mg/mL	1 mg/mL
Benzalkonium chloride	0.1 mg/mL	Same
Edetate disodium dehydrate (EDTA)		Same
Xanthan Gum		None
Propylene glycol		None
Sodium Sulfate		
Sodium Chloride		
Tyloxapol		Same
Hydroxyethyl cellulose	None	
NaOH/HCl	Adjust pH	
NaOH/Sulfuric Acid		Adjust pH
Purified water	q.s. to 100%	Same

b(4)

All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable. The CMC review recommends approval of the application.

3. Nonclinical Pharmacology/Toxicology

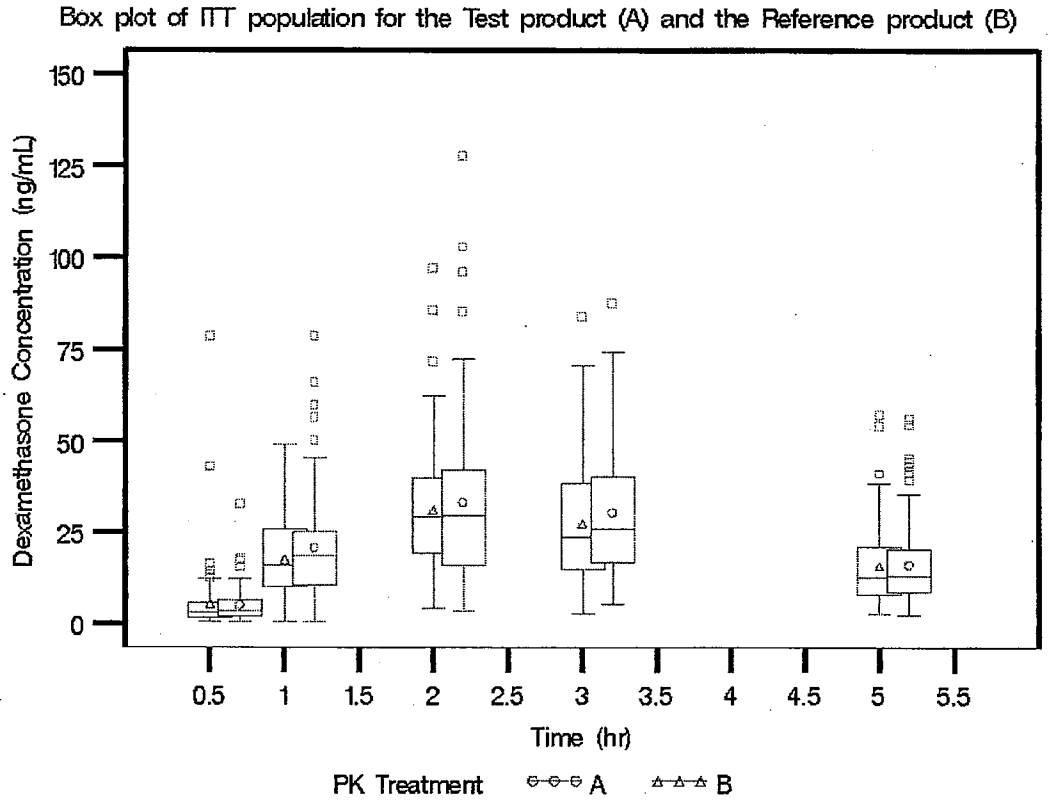
Since the proposed drug product is a new formulation of an existing marketed drug product with the combination of the same two active ingredients and well known inactive ingredients, the clinical risks are well known and are described in the label for the approved product TOBRADEX. There is no new nonclinical information and the Pharmacology/Toxicology review recommends approval of the application.

4. Clinical Pharmacology/Biopharmaceutics

The Biopharmacology Review recommends approval based on the following summary:

> 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 at 126.8%), it is unlikely this finding would have a negative impact on efficacy compared to the reference product.



5. 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. Alcon provided a revised NDA Section 3.2.P.5.1 "Specifications," to include the bacterial endotoxin specification of — EU/dose (i.e., NMT ——— for an average dose of a 34 µL drop). This proposed endotoxin limit is not scientifically supported. It is recommended that endotoxin be monitored and a timeframe for setting a lower ——— specification be established.

b(4)

6. Clinical/Statistical - Efficacy

The efficacy of the drug product components, dexamethasone and tobramycin, have been established during the original approval of the individual components, tobramycin ophthalmic solution and dexamethasone ophthalmic. This application relies on the submitted bioequivalence studies and *in vitro* kill studies to demonstrate equivalence between the test product, Tobradex ST (tobramycin/dexamethasone ophthalmic suspension) 0.3%/0.05% and TOBRADEX for the corticosteroid component and between Tobradex ST and tobramycin ophthalmic solution for the tobramycin component. While it would have been preferred to complete a comparison between Tobradex ST and the original dexamethasone product, this product is no longer marketed and the generically available products have not been demonstrated to be bioequivalent to the original product.

Four clinical studies and three 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.

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). Multiple *in vitro* microbial kill rate studies have been submitted. In studies N-07-040 and N-06-015, compared Tobradex ST and Tobradex. This was not the appropriate comparison. A comparison between Tobradex ST and Tobrex should have been performed. Study C-07-215 was performed with this comparison and did not demonstrate equivalence, but the study had experimental conditions which were not similar to the conditions of the eye.

A new testing paradigm was investigated and all organisms were retested with formulations of Tobrex and Tobradex ST under conditions which mimic the conditions found on the ocular surface including but not limited to factors such as temperature, pH, pH buffers, and cations. This study supported the equivalence of Tobrex and Tobradex ST under the potential conditions of use. Dr. Marsik's Microbiology review has the details of the study and analysis.

Criteria used in this review for accepting kill results were: 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

7. 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.

8. Advisory Committee Meeting

Not applicable; there were no significant new issues.

9. 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 since the product does not represent a therapeutic advantage and it is not likely to be used in a significant number of pediatric patients below the age of 2 years.

10. 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.

DMEPA/OSE is very concerned over OND's acceptance and approval of ambiguous, unstandardized modifiers which have no meaning to the prescriber or dispensing pharmicist. This practice is not consistent with the IOM recommendations for FDA to standardize modifiers used with proprietary names. However, they agree that "Tobradex ST" would present lesser potential for confusion then naming this new formulation "Tobradex". Nevertheless, 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.

11. Labeling

Final labeling review has been reviewed and found acceptable by the review team. Details are included in Dr. Boyd's Team Leader Cross Discipline Review.

12. 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.

Wiley A. Chambers, MD
Acting Director, Division of Anti-Infective and Ophthalmology Products

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Division Director Review for NDA 50-818

Date	April 15, 2008
Reviewer	Wiley A. Chambers, M.D.
NDA#	50-818
Applicant	Alcon, Inc.
Date of Submission	6/15/2007
Established name	tobramycin/dexamethasone ophthalmic suspension 0.3%/0.05%
Dosage forms / Strength	ophthalmic suspension
Proposed Indication(s)	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
Action	Approvable

1. Introduction

Tobradex (tobramycin 0.3%/dexamethasone 0.1% ophthalmic suspension) is a combination anti-infective/corticosteroid agent which was approved in the U.S. in 1988 (NDA 50-592) for 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.

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2. CMC

The source of the active ingredients for NDA 50-818 is the same as Tobradex. The only change is the formulation, listed below:

	Tobradex ST	Tobradex
Tobramycin	3 mg/mL	Same
Dexamethasone	0.5 mg/mL	1 mg/mL
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Edetate disodium dehydrate (EDTA)		Same
Xanthan Gum		None
Propylene glycol		None
Sodium Sulfate		
Sodium Chloride		
Tyloxapol		Same
Hydroxyethyl cellulose	None	
NaOH/HCl	Adjust pH	
NaOH/Sulfuric Acid		Adjust pH
Purified water	q.s. to 100%	Same

b(4)

All facilities inspections have been completed and the Office of Compliance and New Drug Quality have determined these facilities are acceptable. The CMC review recommends approval of the application.

3. Nonclinical Pharmacology/Toxicology

Since the proposed drug product is a new formulation of an existing marketed drug product with the combination of the same two active ingredients and well known inactive ingredients, the clinical risks are well known and are described in the label for the approved product TOBRADEX. There is no new nonclinical information and the Pharmacology/Toxicology review recommends approval of the application.

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The Biopharmacology Review recommends approval based on the following summary:

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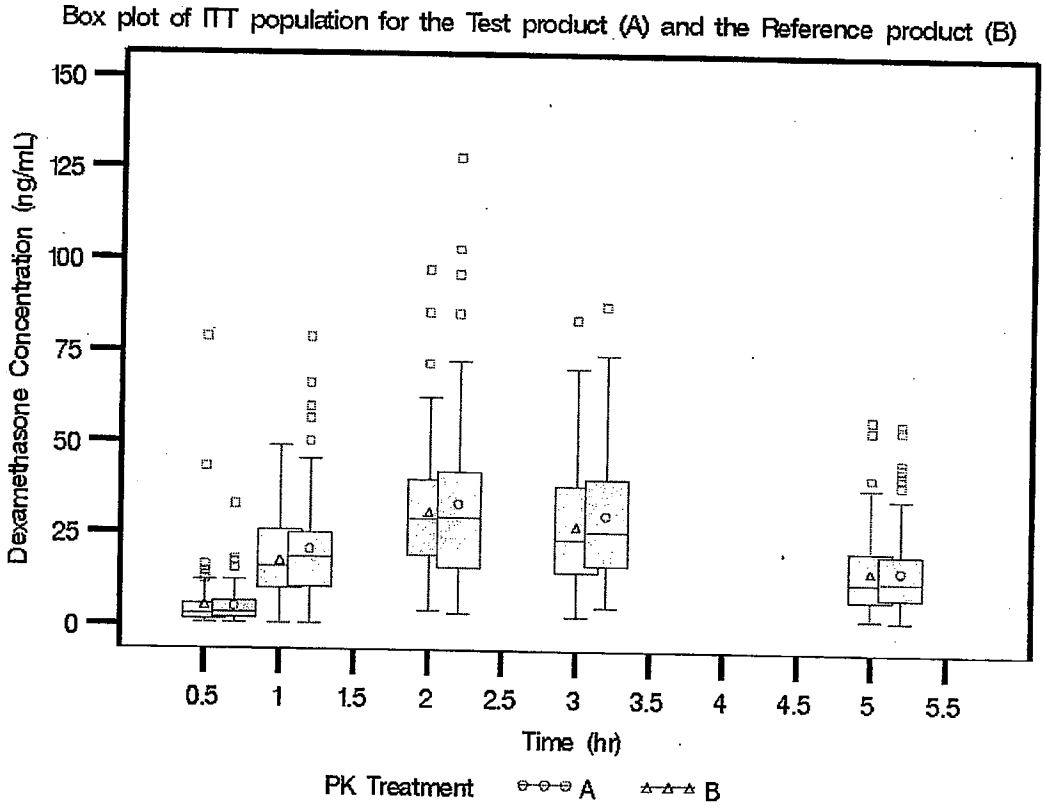
limits of 80 to 125% for the primary pharmacokinetic parameter AUC_{0-5} for both the per protocol and ITT populations. Results from additional analyses performed by the FDA support equivalence of the two products for the parameters AUC_{0-2}, AUC_{0-3}, and the primary parameter AUC_{0-5}. Although 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 at 126.8%), it is unlikely this finding would have a negative impact on efficacy compared to the reference product.



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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 **did not** demonstrate that Tobradex ST has the ability to effectively kill superficial bacteria in a manner equivalent to tobramycin ophthalmic solution. In studies N-07-040 and N-06-015, compared Tobradex ST and Tobradex. This was not the appropriate comparison. A comparison between Tobradex ST and Tobrex should have been performed. Study C-07-215 was performed with this comparison. Partial results are shown below:

Table 1. Summary Table of the Mean Per Cent Survivors (Gram-Positive Isolates) in Study N-07-215[1]

Gram-Positive Bacteria	Strain Number	Test article	#Tests (N)	Sampling Time in Minutes (23°C)				# Tests (N)	Sampling Time in Minutes (33°C)			
				0	15	30	60		0	15	30	60
S. aureus	ATCC 6538	Saline	2	100	95	93	87					
		Tobradex ST	2	32	0	0	0					
		TOBREX	2	18	0	0	0					
S. aureus	MCC 41028	Saline	2	100	156	107	91					
		Tobradex ST	2	53	1.3	0.1	0					
		TOBREX	2	23	0	0	0					
S. aureus	MCC 30281	Saline						2	100	82	65	55
		Tobradex ST						2	77	3	0.1	0
		TOBREX						2	26	0	0	0
S. epidermidis	ATCC 12228	Saline	2	100	72	77	57					
		Tobradex ST	2	0.04	0	0	0					
		TOBREX	2	0	0	0	0					
S. epidermidis	MCC 41001	Saline	2	100	110	63	41					
		Tobradex ST	2	0.1	0	0	0					
		TOBREX	2	0	0	0	0					
S. epidermidis	MCC 50093	Saline	2	100	82	98	83					
		Tobradex ST	2	1.9	0	0	0					
		TOBREX	2	0	0	0	0					

Gram-Negative Bacteria	Strain Number	Test article	#Tests (N)	Sampling Time in Minutes (23°C)				# Tests (N)	Sampling Time in Minutes (33°C)			
				0	15	30	60		0	15	30	60
K. pneumoniae	MCC 41153	Saline						2	100	81	91	90
		Tobradex ST						2	31	0	0	0
		TOBREX						2	5.5	0	0	0
M. lacunata	MCC 4414	Saline	2	100	96	91	84					
		Tobradex ST	2	0	0	0	0					
		TOBREX	2	0	0	0	0					
M. morganii	MCC 91038	Saline						2	100	93	92	108
		Tobradex ST						2	2.5	1.0	0	0
		TOBREX						2	0.8	0	0	0
N. perflava	MCC 65248	Saline	2	100	85	58	52					
		Tobradex ST	2	3.1	0	0	0					
		TOBREX	2	2.0	0	0	0					
N. sicca	MCC 61708	Saline	2	100	87	80	95					
		Tobradex ST	2	0	0	0						
		TOBREX	2	0.2	0	0	0					

The results indicate that under the test conditions studied, *S. aureus* and *M. morgani* was not as quickly killed by Tobradex ST as by Tobrex.

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 Tobrex and Tobradex ST under conditions which mimic the conditions found on the ocular surface including but not limited to factors such as temperature, pH, pH buffers, and cations.

7. 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.

8. Advisory Committee Meeting

Not applicable; there were no significant new issues.

9. 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 since the product does not represent a therapeutic advantage and it is not likely to be used in a significant number of pediatric patients below the age of 2 years.

10. 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.

11. 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.

12. 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. This failure may be due to the environment in which the drug product was tested. 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.

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/s/

Wiley Chambers
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Wiley Chambers
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MEDICAL OFFICER
Acting Division Director