CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

050616sOrig1s010

Trade Name:	**TobraDex, Ophthalmic Ointment**
Generic or Proper Name:	(Tobramycin and Dexamethasone)
Sponsor:	**Novartis**
Approval Date:	November 29, 1996
Indication:	TOBRADEX Ophthalmic Ointment is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacteria ocular infection or a risk of bacterial ocular infection exists.

CENTER FOR DRUG EVALUATION AND RESEARCH

050616sOrig1s010

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	
Product Quality Review(s)	**X**
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	**X**
Clinical Pharmacology Review(s)	
Other Reviews	
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s010

APPROVAL LETTER

NDA 50-555/S-011
NDA 50-616/S-010
NDA 50-065/S-032
NDA 50-344/S-015

NOV 29 1996

Alcon Laboratories, Inc.
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Caballa:

Please refer to your August 22, 1996, supplemental new drug applications submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for the following NDAs:

NDA 50-555/S-011 TOBREX (tobramycin ointment)
NDA 50-616/S-010 TOBRADEX (tobramycin and dexamethasone ointment)
NDA 50-065/S-032 MAXITROL (neomycin sulfate, polymixin B, and dexamethasone ointment)
NDA 50-344/S-015 STATROL (neomycin sulfate and polymixin B ointment)

We also refer to our letter dated August 28, 1996.

We acknowledge receipt of your correspondence dated August 26, 1996.

These supplemental applications provide for the sterilization of the ointment filler parts and accessories with (b) (4) which is currently used.

We have completed the review of this supplemental application and it is approved effective as of the date of this letter. In addition, we acknowledge the commitment made during the November 18, 1996, telephone conversation between Susan Caballa (Alcon Laboratories) and Joanne Holmes (FDA). Alcon Laboratories agreed to provide full information and data for (b) (4)

This approval affects only the change specifically submitted in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected. We remind you that changes of the type listed in these supplements are not permitted to be made prior to approval.

We remind you that you must comply with requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

If you have any questions, please contact:

Joanne Holmes, M.B.A.
Project Manager
(301) 827-2090

Sincerely yours,

WAC 11/29/96

Wiley A. Chambers, M.D.
Acting Division Director
Division of Analgesic, Anti-Inflammatory, and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDAs Original NDAs 50-555, 50-616, 50-065, 50-344
HFD-550/Div. Files
HFD-550/Proj Mgr/Holmes 11/21/96
HFD-550/Chem/Bavnagri
HFD-550/Acting Chem TL/Patel
HFD-160/Micro/Stinavage
HFD-160/Micro Sup/Cooney
HFD-550/ Acting Div Dir/Chambers
HFD-830/E.Sheinin
HFD-80
HFD-100
HFD-232
DISTRICT OFFICE

drafted: jh/November 14, 1996/50555s11.ap

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s010

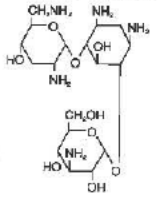
LABELING

TobraDex®

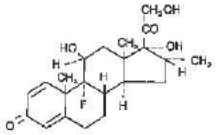
(Tobramycin and Dexamethasone Ophthalmic Ointment) Sterile

DESCRIPTION: TOBRADEX® (Tobramycin and Dexamethasone) Ophthalmic Ointment is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use. The chemical structures for tobramycin and dexamethasone are presented below:

Tobramycin
Empirical Formula: $C_{18}H_{37}N_5O_9$
Chemical Name:
O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosyl-(1→6)]-2-deoxy-L-streptamine



Dexamethasone
Empirical Formula: $C_{22}H_{29}FO_5$
Chemical Name:
9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione



Each gram of TOBRADEX® Ointment contains: Actives: Tobramycin 0.3% (3mg) and Dexamethasone 0.1% (1mg). **Preservative:** Chlorobutanol 0.5%. **Inactives:** Mineral Oil and White Petrolatum. DM-00

CLINICAL PHARMACOLOGY: Corticoids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticoids may inhibit the body's defense mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Dexamethasone is a potent corticoid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin.

No data are available on the extent of systemic absorption from TOBRADEX Ophthalmic Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. The usual physiologic replacement dose is 0.75 mg daily. The administered dose for TOBRADEX Ophthalmic Ointment in both eyes four times daily would be 0.4 mg of dexamethasone daily.

INDICATIONS AND USAGE: TOBRADEX Ophthalmic Ointment is indicated 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.

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

CONTRAINDICATIONS: Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to a component of the medication.

WARNINGS: NOT FOR INJECTION INTO THE EYE. Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use.

Prolonged use of steroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. Intraocular pressure should be routinely monitored even though it may be difficult in children and uncooperative patients. Prolonged use may suppress the host response and thus increase the hazard of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

PRECAUTIONS:

General. The possibility of fungal infections of the cornea should be considered after long-term steroid dosing. As with other antibiotic preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgement dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Cross-sensitivity to other aminoglycoside antibiotics may occur; if hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Information for Patients: Do not touch tube tip to any surface, as this may contaminate the contents.

Carcinogenesis, Mutagenesis, Impairment of Fertility. No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

Pregnancy Category C. Corticosteroids have been found to be teratogenic in animal studies. 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. Reproduction studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. TOBRADEX® Ophthalmic Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Because many drugs are excreted in human milk, caution should be exercised when TOBRADEX® Ophthalmic Ointment is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS: Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX®) are hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary Infection. The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

OVERDOSAGE: Clinically apparent signs and symptoms of an overdose of TOBRADEX Ophthalmic Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

DOSAGE AND ADMINISTRATION: Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) up to three or four times daily.

How to apply TOBRADEX Ophthalmic Ointment:

1. Tilt your head back.
2. Place a finger on your cheek just under your eye and gently pull down until a "V" pocket is formed between your eyeball and your lower lid.
3. Place a small amount (about ½ inch) of TOBRADEX Ophthalmic Ointment in the "V" pocket. Do not let the tip of the tube touch your eye.
4. Look downward before closing your eye.

Not more than 8 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

HOW SUPPLIED: Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

STORAGE: Store at 8° to 27°C (46° to 80°F).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

U.S. Patent No. 5,149,694

Alcon®
OPHTHALMIC
ALCON LABORATORIES, INC.
FORT WORTH, TEXAS 76134 USA

341515 Revised: August 1995

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s010

PRODUCT QUALITY REVIEW(S)

NOV 1 4 1996

Chemistry Review	1. Division HFD-550	2. NDA Number 50-616
3. Name and Address of Applicant Alcon Laboratories Inc., 6201 South Freeway, Forth Worth, TX 76134		4. Supplemet Number Date SCS-010 Aug 22,1996 SNC-010 Aug 26, 1996
5. Name of Drug Tobradex® Ophthalmic Ointment	6. Nonproprietary Name Tobramycin and dexamethazone ointment	
7. Supplement Provides for Change in the method of sterilization (b) (4) [redacted]		8. Amendment(s) From CBE supplement to an expedited review supplement
9. Pharmacological Category As an Antiinflammatory for the eye where a risk of bacterial infection also exists.	10. How Dispensed Rx	11. Related Documents ANDA 80-021 (Cetamide) and NDA 50-555 (Tobrex)
12. Dosage Form Ophthalmic Ointment	13. Potency(ies) 0.3% tobramycin and 0.1% dexamethasone	

(b) (4) [redacted]

16. Conclusions and Recommendations From the CMC stand point the supplement is approvable, subject to the microbiology team finding the sterilization method acceptable.

17.Reviewing Chemist Vispi P. Bhavnagri Ph.D.	Signature Vispi P. Bhavnagri	Date Sept 18, 1996
18. Team Leader Hasmukh B. Patel Ph.D.	Signature Hasmukh B. Patel	Date 11-14-96

cc:

NDA 50-616
HFD-550/Division File
HFD-550/V.Bhavnagri
HFD-550/J. Bull
HFD-550/J. Holmes
R/D Init. by H. Patel
F/T by V.Bhavnagri

The reviewing microbiologist has recommended approval of this ~~appl~~ suppl. See attached micro review.

RECOMMENDATION: APPROVAL

HBP

APPROVABLE

Doc ID - A:\review\suppl\50616_010.rev (disk #3)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s010

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

OCT 21 1996

REVIEW FOR HFD-550
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
Microbiologist's Review No. 1 of NDA 50-555
October 21, 1996

A. 1. NDAs: 50-555/S-011
50-616/S-010
50-065/S-032
18-796/S-009
50-344/~~S-019~~ 015

APPLICANT: Alcon Laboratories Inc.
6201 south Freeway
Fort Worth, Texas 76134-2099

2. PRODUCT NAMES:

NDA 50-555, TOBREX Ophthalmic Ointment
NDA 50-616, TOBRADEX Ophthalmic Ointment
NDA 50-065, MAXITROL Ophthalmic Ointment
NDA 18-796, PILOPINE HS Gel 4% Ophthalmic Ointment
NDA 50-344 STATROL Ophthalmic Ointment

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Topical Ophthalmic Ointments
Ointment

4. METHOD(S) OF STERILIZATION: Aseptic processing

5. PHARMACOLOGICAL CATEGORY: Anti-inflammatory/antibiotic

B. 1. DATE OF INITIAL SUBMISSION: August 22, 1996

2. DATE OF AMENDMENT: N/A

3. SUPPORTING DOCUMENTS: N/A

C. REMARKS:

The supplements provide for a change in the sterilization process for the ointment filler parts and accessories used in the manufacture of the subject drugs. The basis for the change is concern over environmental quality associated with the use of (b) (4)

The supplement was submitted as a Special Supplement - Changes Being Effected. In support of this classification, the applicant referenced two supplemental NDAs submitted on July 12, 1996. These submissions, providing for the same change in the sterilization process for closure seals, were

considered acceptable as Special Supplements-CBE because the sterilized components were applied to the stoppered product container. The justification is not applicable to the proposed change; the components are used within the sterile core and some have product contact. The applicant was notified that the supplements required prior approval.

It has been noted that the same change was the subject of ANDAs: 80-021/S-015 (Cetamide Ophthalmic Ointment) and 87-771/S-004 (Cetapred Ophthalmic Ointment). These were recommended for approval by the OGD Review Microbiologist on September 17, 1996.

D. CONCLUSIONS: The submissions are recommended for approval on the basis of sterility assurance. See "E. Review Notes".

Vivian Greenman 10/21/96
Vivian Greenman
PHC 10/21/96

cc:
NDA
HFD-160/Consult File
Drafted by: V. Greenman
HFD 550/Joanne Holmes
R/D init. by P.H. Cooney
PC File #ND50555.S11

4 Pages have been Withheld in full as B4 (TS/CCI) Immediately Following this Page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s010

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-344/S-015
NDA 50-555/S-011
NDA 50-616/S-010

Alcon Research, Ltd.
Attention: Scott Krueger
Senior Director, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Mr. Krueger:

We refer to your new drug applications (NDA) submitted under the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Drug Name
50-344/S-015	Statrol (neomycin sulfate and polymyxin B ointment) Sterile Ophthalmic Ointment
50-555/S-011	Tobrex (tobramycin ophthalmic ointment) Sterile Ophthalmic Ointment
50-616/S-010	TobraDex (tobramycin and dexamethasone ophthalmic ointment) Sterile Ophthalmic Ointment

We have received your submissions dated August 4, 1997, reporting on the following postmarketing study commitment:

Full information and data for thermal qualifications of the production cycles.

We have reviewed your submissions and conclude that the above commitment was fulfilled.

This completes all of your postmarketing study commitments acknowledged in our November 29, 1996, letter.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Linda L. Ng, Ph.D.
Chemistry Team Leader, for the
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, (HFD-550)
DNDC III, Office of New Drug Chemistry

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

/s/

Linda Ng

6/1/01 01:06:13 PM

NDA 50-555/S-011
NDA 50-616/S-010
NDA 50-065/S-032
NDA 18-796/S-009
NDA 50-344/S-~~019~~ 015

AUG 28 1996

Alcon Laboratories, Inc.
Attention: Susan H. Caballa
Associate Director, Regulatory Affairs
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Ms. Caballa:

We acknowledge receipt of your supplemental applications for the following:

NDA Number	Supplement Number	Drug Name
50-555	S-011	TOBREX Ophthalmic Ointment
50-616	S-010	TOBRADEX Ophthalmic Ointment
50-065	S-032	MAXITROL Ophthalmic Ointment
18-796	S-009	PILOPINE HS Gel 4% Ophthalmic Ointment
50-344	S-019	STATROL Ophthalmic Ointment

Therapeutic Classifications: Standard

Date of Supplements: August 22, 1996

Date of Receipt: August 23, 1996

These supplements, submitted as "Special Supplement - Changes Being Effected" under 21 CFR 314.70(c), provide for changing from [redacted] (b) (4)

Changes of the kind that you have proposed, in our opinion, are not the kind of changes permitted by regulation to be put into effect prior to approval of a supplement. An approved supplement is required for the proposed changes, therefore, these supplements are being reviewed under 21 CFR 314.70(b).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 22, 1996, in accordance with 21 CFR 314.101(a).

All communications concerning these supplemental applications should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFD-550
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions, please contact:

Joanne Holmes, M.B.A.
Project Manager
Telephone: (301) 827-2090

Sincerely yours,

MAC 8/28/96

Wiley A. Chambers, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDAs 50-555, 50-616, 50-065, 18-796, 50-344
HFD-550/Div. Files
HFD-550/Chem TL/Patel
HFD-550/Acting Div Dir/Chambers
HFD-550/Acting SCSO/Holmes
DISTRICT OFFICE
HFD-830/E.Sheinin

drafted: jh/August 28, 1996/50555not.cbe
SUPPLEMENT ACKNOWLEDGEMENT