CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

050616sOrig1s008

Trade Name:	**TobraDex, Ophthalmic Ointment**
Generic or Proper Name:	(Tobramycin and Dexamethasone)
Sponsor:	**Novartis**
Approval Date:	March 18, 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

050616sOrig1s008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s008

APPROVAL LETTER

7.1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 13-422/S-023
NDA 17-468/S-015
NDA 17-469/S-021
NDA 19-079/S-007
NDA 50-023/S-014
NDA 50-592/S-011
NDA 50-065/S-031
NDA 50-344/S-014
NDA 50-616/S-008

MAR 18 1996

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Attention: Susan H. Caballa
Associate Director, Regulatory Affairs

Dear Madam:

Please refer to your November 3, 1995 supplemental new drug applications submitted under Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following NDA's:

13-422/S-023, Maxidex® (dexamethasone suspension) Sterile Ophthalmic Suspension, 0.1%

17-468/S-015, Econopred® (prednisolone acetate suspension) Ophthalmic Suspension, 1/8%

17-469/S-021, Econopred® Plus (prednisolone acetate suspension) Ophthalmic Suspension, 1%

19-079/S-007, Flarex® (fluorometholone suspension) Ophthalmic Suspension, 0.1%

50-023/S-014, Maxitrol® (neomycin and polymyxin B sulfates and dexamethasone suspension) Sterile Ophthalmic Suspension

50-065/S-031, Maxitrol® (neomycin and polymyxin B sulfates and dexamethasone ointment) Sterile Ophthalmic Ointment

50-344/S-014, Statrol® (neomycin and polymyxin B sulfates ointment) Ophthalmic Ointment

50-592/S-011, Tobradex® (tobramycin and dexamethasone suspension) Sterile Ophthalmic Suspension

50-616/S-008, Tobradex® (tobramycin and dexamethasone ointment) Sterile Ophthalmic Ointment

Re: Supplements Dated 11/03/95

We acknowledge receipt of your amendments dated November 17, 1995, providing a correction to Table 6 as found in the listed applications.

The supplemental applications provide for a change in the sterilization [redacted] (b) (4)

We have completed our review of these supplemental applications and they are approved effective as of the date of this letter.

This approval affects only those changes specifically submitted in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected.

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

Sincerely yours,

Charlotte A. Yaciw 3/14/96

Charlotte A. Yaciw,
Chemistry Team Leader (Acting)
Division of Anti-Inflammatory, Analgesic,
and Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc: NDA 13-422
NDA 17-468
NDA 17-469
NDA 19-079
NDA 50-023
NDA 50-065
NDA 50-344
NDA 50-592
NDA 50-616
HFD-540/Division File
HFD-550/Division File
HFD-550/DivDir/WAChambers WAC 3/14/96
HFD-550/ProjMgr/JMHolmes
HFD-540/Pharm I M M
HFD-540/Chem/JSHathaway 3/14/96
HFD-629/PSchwartz
HFD-540/WHDeCamp

R/D Init. By:WChambers-3/14/96
F/T by:MMatheny-3/14/96

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s008

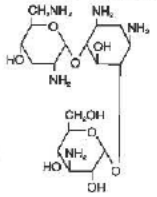
LABELING

TobraDex®

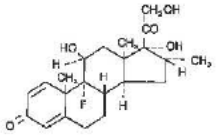
(Tobramycin and Dexamethasone Ophthalmic Ointment) Sterile

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:

050616sOrig1s008

PRODUCT QUALITY REVIEW(S)

DW.

FEB 28 1996

DIVISION OF TOPICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 50-616	CHEM.REVIEW #: 1	REVIEW DATE:	22-FEB-1996

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
SUPPLEMENT/SCS-008	03-NOV-1995	06-NOV-1995	13-NOV-1995
AMENDMENT/BC	17-NOV-1995	27-NOV-1995	13-NOV-1995

NAME & ADDRESS OF APPLICANT:

Alcon Laboratories, Inc.
6201 South Freeway
Ft. Worth, TX 76134-2099

Susan H. Caballa
Assoc. Director, Regulatory Affairs

DRUG PRODUCT NAME

Proprietary: Tobradex® Ophthalmic
Nonproprietary/USAN: tobramycin and dexamethasone

Code Names/#'s:
Chemical Type/ Therapeutic Class: Antibiotic/corticosteroid
3S

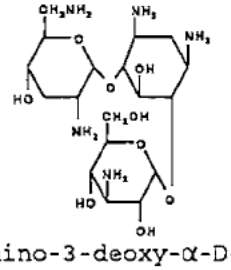
ANDA Suitability Petition/DESI/Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: For steroid-responsive inflammatory ocular conditions

DOSAGE FORM: Ointment, sterile
STRENGTHS: 0.3%/ 0.1%
ROUTE OF ADMINISTRATION: Topical (ophthalmic)
DISPENSED: __X__ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

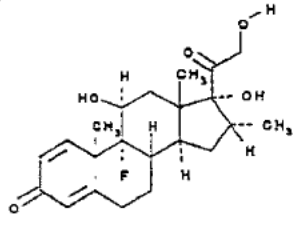
Tobramycin



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

Molecular Formula: $C_{18}H_{37}N_5O_9$
Molecular Weight: 467.5[(D)(4)]
CAS No. [32986-56-4]

Dexamethasone



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

Molecular Formula: $C_{22}H_{29}FO_5$
Molecular Weight: 392.47[(D)(4)]
CAS No. [50-02-2]

SUPPORTING DOCUMENTS:

Letter of Authorization to Alcon Laboratories from [redacted] (b) (4) for submissions referring to [redacted] (b) (4) of products or raw materials. Letter states that the firm is in compliance with GMPs, state, federal and local environmental laws and regulations, and the [redacted] (b) (4) Letter is dated 29-SEP-1995 and signed by [redacted] (b) (4) General Manager.

REMARKS/COMMENTS:

This supplement seeks approval of [redacted] (b) (4) for the sterilization of [redacted] (b) (4) to be used in Alcon products as listed above, using a [redacted] (b) (4). This sterilization [redacted] (b) (4) The following are supplements covered under this consolidated review:

NDA 13-422 Maxidex Ophthalmic Suspension, Supplement SCS-023
NDA 17-468 Econopred Ophthalmic Suspension, Supplement SCS-015
NDA 17-469 Econopred Plus 1% Ophthalmic Suspension, Supplement SCS-021
NDA 19-079 Flarex Ophthalmic Suspension, Supplement SCS-007
NDA 50-023 Maxitrol Ophthalmic Suspension, Supplement SCS-014
NDA 50-065 Maxitrol Ophthalmic Ointment, Supplement SCS-031
NDA 50-344 Statrol Ophthalmic Ointment, Supplement SCS-014
NDA 50-592 Tobradex Ophthalmic Suspension, Supplement SCS-(b) (4)
NDA 50-616 Tobradex Ophthalmic Ointment, Supplement SCS-008

The following supplements were submitted concurrently to the Office of Generic Drugs for review:

ANDA 80-021 Cetamide Ophthalmic Ointment, Supplement (b) (4)
ANDA 87-771 Cetapred Ophthalmic Ointment, Supplement S-002
ANDA 87-547 Isopto Cetapred Ophthalmic Suspension, Supplement S-017
AADA 62-341 Maxidex Ophthalmic Suspension, Supplement S-011

CONCLUSIONS & RECOMMENDATIONS: **Approval**

The Microbiology staff's review recommends approval of this supplement in a consolidated review. The data submitted support the contention that the change in sterilization does not adversely affect the purity or stability of the drug product. Approval is recommended.

2/22/96

J. S. Hathaway, Ph. D.
Review Chemist

cc: Orig. NDA 50-616
HFD-540/Division File
HFD-550/Division File
HFD-550/DivDir/WAChambers
HFD-550/ProjMgr/JMHolmes
HFD-540/Pharm/
HFD-540/Chem/JSHathaway
HFD-540/TeamLdr/WHDeCamp
R/D Init by: WHDeCamp 2/28/96

filename: C:\WPFILES\NDAS\NDA50616\N50616R.S08

Chemist's Notes

The following are supplements covered under this consolidated review:

NDA 13-422 Maxidex Ophthalmic Suspension, Supplement SCS-023
NDA 17-468 Econopred Ophthalmic Suspension, Supplement SCS-015
NDA 17-469 Econopred Plus 1% Ophthalmic Suspension, Supplement SCS-021
NDA 19-079 Flarex Ophthalmic Suspension, Supplement SCS-007
NDA 50-023 Maxitrol Ophthalmic Suspension, Supplement SCS-014
NDA 50-065 Maxitrol Ophthalmic Ointment, Supplement SCS-031
NDA 50-344 Statrol Ophthalmic Ointment, Supplement SCS-014
NDA 50-592 Tobradex Ophthalmic Suspension, Supplement SCS-011
NDA 50-616 Tobradex Ophthalmic Ointment, Supplement SCS-008

The following supplements were submitted concurrently to the Office of Generic Drugs for review:

ANDA 80-021 Cetamide Ophthalmic Ointment, Supplement S-021
ANDA 87-771 Cetapred Ophthalmic Ointment, Supplement (b) (4)
ANDA 87-547 Isopto Cetapred Ophthalmic Suspension, Supplement S-017
AADA 62-341 Maxidex Ophthalmic Suspension, Supplement S-011

This supplement seeks approval of (b) (4) for the sterilization of (b) (4) to be used in Alcon products as listed above, using a (b) (4) This sterilization (b) (4) In addition, supplements were administratively filed to cover the new sterilization facility provided by (b) (4)

Alcon Laboratories, Inc. previously had agreed to provide data on the presence of (b) (4) from the sterilization process (b) (4) Data were to be submitted comparing the analytical purity of material sterilized by (b) (4) and to show that packaging integrity has not been affected. In addition, a proposal for the stability protocol was offered. This information was set forth in a letter to FDA dated 18-NOV-1994. A letter from FDA dated 09-FEB-1995 to Alcon accepted the proposals, and stated that the preferred stability program should place on room-temperature and accelerated stability testing three representative products which utilize the drug substances sterilized by the new process. Three-month data from the accelerated stability testing program was to be provided at the time of submission.

The applicant has committed to place the first three production batches of each product onto the routine stability program, and to report the results in the Annual Reports. Any results outside the approved specifications will be cause for withdrawal of the product from the market, and any deviation which does not affect the safety or efficacy of the product(s) will be reported to the FDA for discussion and evaluation.

Microbiology Review

Review of the sterilization protocols and procedures was performed by the Microbiology staff of the Office of New Drug Chemistry, who referred to the reviews of the ANDA/AADA applications listed above, which were performed by the Office of Generic Drugs. A copy of the Microbiology review is attached following this review. The conclusion of the OGD and ONDC Microbiology staffs is a recommendation for approval.

ACCEPTABLE

Analytical Comparision of (b) (4)

Assay specifications and results were provided for each (b) (4) Assays were performed prior to and after sterilization, using both the old (b) (4) method and the proposed (b) (4) method. In each case, the assay results after sterilization are at or above the minimum assay value. In a few cases, the assay after sterilization is above the specification range; this does not appear to be a significant deviation. Results are given in the attachment (Table 8).

ACCEPTABLE

Product Stability Matrix and Results

Three products were chosen for accelerated stability study for the purposes of this submission. These three products collectively represent all of the powderd raw materials. The attached Table 6 shows the matrix of drug product vs. raw material; (b) (4) The specific products and lots are listed below:

Product Name	Lot Number(s)	Time (mos.)	Conditions
Cetapred Ointment;	VCXL-35	3	35°C (accel.)
	VCXL-RT	3	22°C (room T)
Flarex Oph. Suspension	VCWZ-40	3	40°C (accel.)
	VCWZ-RT	3	22°C (room T)
Maxitrol Ointment	VCWY-35	3	35°C (accel.)
	VCWY-RT	3	22°C (room T)

Stability data are within specifications at all time points for lots tested under both accelerated and room temperature conditions.

ACCEPTABLE

Facilities Inspection

Facility inspection of [redacted] (b) (4) was requested 22-JAN-1996, [redacted] (b) (4) The facility was deemed acceptable by the Office of Compliance on 05-FEB-1996. A photocopy of the memo is attached; the original was filed with the review for NDA 13-422/SCM-023.

ACCEPTABLE

DRAFT OF CHEMIST'S LETTER TO FIRM

NDA 13-422/SCS-023	Maxidex® (dexamethasone 0.1%) Sterile Ophthalmic Suspension
NDA 17-468/SCS-015	Econopred® (prednisolone acetate ⅛%) Ophthalmic Suspension
NDA 17-469/SCS-021	Econopred® Plus (prednisolone acetate 1%) Ophthalmic Suspension
NDA 19-079/SCS-007	Flarex® (fluorometholone 0.1%) Sterile Ophthalmic Suspension
NDA 50-023/SCS-014	Maxitrol® (neomycin and polymyxin B sulfates and dexamethasone) Sterile Ophthalmic Suspension
NDA 50-065/SCS-031	Maxitrol® (neomycin and polymyxin B sulfates and dexamethasone) Sterile Ophthalmic Ointment
NDA 50-344/SCS-014	Statrol® (neomycin and polymyxin B sulfates) Ophthalmic Ointment
NDA 50-592/SCS-011	Tobradex® (tobramycin and dexamethasone) Sterile Ophthalmic Suspension
NDA 50-616/SCS-008	Tobradex® (tobramycin and dexamethasone) Sterile Ophthalmic Ointment

Reference is made to your supplemental New Drug Applications (NDA) dated November 3, 1995, submitted pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act for the drug products listed above.

These supplemental applications provide for [redacted (b)(4)] to perform sterilizations of [redacted (b)(4)] to be used in Alcon products. These sterilizations are performed using [redacted (b)(4)]

We also acknowledge the receipt of amendments dated November 27, 1995, providing a correction to Table 6 as found in the listed applications.

We have completed our review and the supplemental applications are approved effective as of the date of this letter.

This approval affects only those changes specifically submited in these supplemental applications. Other changes that may have been approved or are pending evaluation are not affected.

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

2/22/96

J. S. Hathaway, Ph. D.
Review Chemist

ATTACHMENTS

I. Table 8: Assay Comaprison Chart

II. Table 6: Matrix for Drug Products

III. Establishment Inspection Report

IV. Microbiology Review

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s008

CLINICAL MICROBIOLOGY/VIROLOGY REVIEW(S)

FEB 2 1996

REVIEW FOR HFD-540
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
2 February 1996

A. 1. Application Numbers:

NDA 19-079/SCS-007	NDA 50-616/SCS-008
NDA 13-422/SCS-023	NDA 50-065/SCS-031
NDA 17-468/SCS-015	NDA 50-344/SCS-014
NDA 17-469/SCS-021	NDA 50-592/SCS-011
NDA 50-023/SCS-023	

APPLICANT: Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76134-2099

2. PRODUCT NAMES: Various Ophthalmic Ointments or Suspensions

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The products are applied to the eye.

4. METHODS OF STERILIZATION:
The raw materials are sterilized by [redacted] (b) (4)

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The products are used for a variety of indications.

B. 1. DATE OF INITIAL SUBMISSION: 3 November 1995

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: ANDA 80-021/S-013
ANDA 87-771/S-002
ANDA 87-547/S-017
AADA 62-341/S-011

4. ASSIGNED FOR REVIEW: 29 January 1996

C. REMARKS: The Supplements provide a change from sterilization using a [redacted] (b) (4) This change has previously been reviewed and recommended for approval for the above mentioned ANDA and AADA products by Dr. Kenneth Muhvich of the Office of Generic Drugs. Therefore, further review of this change is

unnecessary. A copy of Dr. Muhvich's 11 January 1996 review is attached.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance.

2 February 1996

Paul Stinavage, Ph.D.

PHC 2/2/96

cc: Original Applications

NDA 19-079	NDA 50-616
NDA 13-422	NDA 50-065
NDA 17-468	NDA 50-344
NDA 17-469	NDA 50-592
NDA 50-023	

HFD-805/Stinavage/Consult File
HFD-540/S. Hathaway

Drafted by: P. Stinavage, 2 February 1996
R/D initialed by P. Cooney, 2 February 1996

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s008

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date NOV 8 1995

NDA No. 50-616

Susan H. Caballa
•Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134

Attention: Susan H. Caballa

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Tobradex Ophthalmic Ointment

NDA Number: 50-616

Supplement Number: S-008

Date of Supplement: November 3, 1995

Date of Receipt: November 6, 1995

Unless we find the application not acceptable for filing, the filing date will be 60 days from the receipt date above.

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Attention: Document Control, Room 12B-30
5600 Fishers Lane
Rockville, MD 20857

Sincerely yours,

for Laurel Claga

Supervisory Consumer Safety Officer
Division of Anti-Infective Drug Products
Center for Drug Evaluation and Research

FORM FDA 3217d (12/91)

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