CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

050616sOrig1s005

Trade Name:	**TobraDex, Ophthalmic Ointment**
Generic or Proper Name:	(Tobramycin and Dexamethasone)
Sponsor:	**Novartis**
Approval Date:	May 21, 1992
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

050616sOrig1s005

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Reviews / Information Included in this NDA Review.

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APPLICATION NUMBER:

050616sOrig1s005

APPROVAL LETTER

HFD 160
DIV-File

NDA 50-616/S-005

Kay Harris
Manager
Regulatory Affairs
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099

MAY 21 1992

Dear Ms. Harris:

Reference is made to your supplemental New Drug Application (NDA) dated April 22, 1991, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for TobraDex (tobramycin/dexamethasone) Ophthalmic Ointment, providing for a labeling revision in the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections of the labeling.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling dated April 22, 1991. Accordingly, the supplemental application is approved effective on the date of this letter.

Should additional information relating to the safety and effectiveness of this drug product become available, further revision of the labeling may be required.

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,
WAC 5/16/92
Wiley A. Chambers, M.D.
Acting Director
Division of Medical Imaging
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: Original NDA
HFC-130*
HFD-82*
HFD-100*
HFD-735*
HFD-160*
HFD-160/DivDir/Chambers*
HFD-160/MO/Knight* CAK 5/12/92
HFD-160/Chem/Sheinin*
HFD-160/Pharm/DeWitt*
HFD/160/CSO/Joyce*
HFD-160/SCSO/Cheever*
Huntley 5/12/92
Approval

* with labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

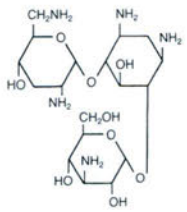
050616sOrig1s005

LABELING

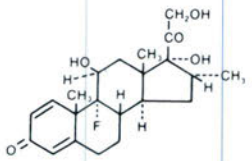
TobraDex®

(Tobramycin and Dexamethasone)
Sterile Ophthalmic Suspension and Ointment

DESCRIPTION: TOBRADEX® (Tobramycin and Dexamethasone) Ophthalmic Suspension and Ointment are sterile, multiple dose antibiotic and steroid combinations 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 mL of TOBRADEX® Suspension contains: Active: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). Preservative: Benzalkonium Chloride 0.01%. Inactive: Tyloxapol, Edetate Disodium, Sodium Chloride, Hydroxyethyl Cellulose, Sodium Sulfate, Sulfuric Acid and/or Sodium Hydroxide (to adjust pH) and Purified Water. DM-00

Each gram of TOBRADEX® Ointment contains: Active: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). Preservative: Chlorobutanol 0.5%. Inactive: 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,* and *Acinetobacter calcoaceticus* and some *Neisseria* species.

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

No data are available on the extent of systemic absorption from TOBRADEX Ophthalmic Suspension or Ointment; however, it is known that some systemic absorption can occur with ocularly applied drugs. If the maximum dose of TOBRADEX Ophthalmic Suspension is given for the first 48 hours (two drops in each eye every 2 hours) and complete systemic absorption occurs, which is highly unlikely, the daily dose of dexamethasone would be 2.4 mg. The usual physiologic replacement dose is 0.75 mg daily. If TOBRADEX Ophthalmic Suspension is given after the first 48 hours as two drops in each eye every 4 hours, the administered dose of dexamethasone would be 1.2 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 Suspension and Ointment are 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,* and *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.

The use of this combination is always contraindicated after uncomplicated removal of a corneal foreign body.

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.

Information for Patients: Do not touch dropper or 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 Suspension and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs excreted in human milk, a decision should be considered to discontinue nursing temporarily while TOBRADEX Ophthalmic Suspension or Ointment.

Pediatric Use. Safety and effectiveness in children 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.

DOSAGE AND ADMINISTRATION: Suspension: One or two drops instilled into the conjunctival sac(s) every four to six hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops 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. **Ointment:** Apply a small amount (approximately ½ inch ribbon) into the conjunctival sac(s) up to three or four times daily.

TOBRADEX Ophthalmic Ointment may be used at bedtime in conjunction with TOBRADEX Ophthalmic Suspension used during the day. Not more than 20 mL or 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 suspension in 2.5 mL (NDC 0065-0647-25) and 5 mL (NDC 0065-0647-05) DROP-TAINER® dispensers. Sterile ophthalmic ointment in 3.5 g ophthalmic tube (NDC 0065-0648-35).

STORAGE: Store at 8° to 27°C (46° to 80°F).
Store suspension upright and shake well before using.

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

342505 Revised: October 1992

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616s005

PRODUCT QUALITY REVIEW(S)

DEC 14 19

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

NDA #: 50-616 **CHEM.REVIEW #:** 01 **REVIEW DATE:** 01-AUG-94

SUBMISSION/TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ANNUAL REPORT/Y	22-NOV-93	24-NOV-93	01-AUG-94

NAME & ADDRESS OF APPLICANT: ALCON LABORATORIES, INC.
6201 South Freeway
Ft. Worth, Texas 76134

DRUG PRODUCT NAME

Proprietary:	Tobradex Ophthalmic Ointment
Nonproprietary/USAN:	tobramycin & dexamethasone
Code Names/#'s:	
Chemical Type/ Therapeutic Class:	

PHARMACOLOGICAL CATEGORY/INDICATION: for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection exists or a risk of bacterial ocular infection exists.

DOSAGE FORM:	Ophthalmic Ointment
STRENGTHS:	
ROUTE OF ADMINISTRATION:	ophthalmic
DISPENSED:	xxx Rx _____ OTC

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

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

and

9-Fluoro-11β,17,21-trihydroxy-6α-methylpregna-1,4-diene-3,20-dione

REMARKS/COMMENTS:

1. LABELING:

Insert:
Two changes were instituted on the insert number 340633-0991.
1) The INFORMATION FOR PATIENTS section added the following statement: "Do not touch dropper or tube tip to any surface, as this may contaminate the contents."
2) In the ADVERSE REACTIONS section the following phrase was altered: "The most frequent adverse

reaction to topical ocular tobramycin (Tobrex) are localized ocular toxicity and hypersensitivity..." was revised to "The most frequent adverse reaction to topical ocular tobramycin (Tobrex) are hypersensitivity and localized ocular toxicity, including ..."

There were also two revision implemented for insert number 341465-1092.
1) the patent number was added
2) "USA" added

Label:
On the label number 260772-0390 there were no changes since the last annual report.
On the label number 260772-1092 the patent number was added.

(b) (4)

2. CONTROL CHANGES:

The applicant reported several revisions which were made to the Manufacturing Batch Record. The revisions are noted on the first two pages of SECTION III of this annual report.

All of the changes are permitted to be made in an annual report and do not require a supplement.

3. STABILITY:

Seven lots of TOBRADEX OINTMENT were monitored and reported in this annual report. All the data that was submitted met the approved NDA specifications for this drug product. Refer to section III of the submission.

CONCLUSIONS & RECOMMENDATIONS:

The original NDA submission was approved on 9/28/88. This annual report is satisfactory and meets all the criteria under 21CFR314.70(d).

Janet G. Higgins 8/1/94

JANET G. HIGGINS
Review Chemist

cc: Orig. NDA 50-616
HFD-540/Division File
HFD-540/HIGGINS
HFD-540/MO/Chambers
HFD-540/Pharm/
HFD-540/CSO/Joyce
HFD-540/DE CAMP
R/D Init by: SUPERVISOR WD 12/14/94
filename:**N50616.Y05**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s005

OTHER REVIEW(S)

DIV-File

Review of NDA 50-616/S-005
Supplement

MAY 16 1992

NDA 50-616/S-005

Submission date: April 22, 1991

Review date: May 12, 1992

Sponsor:

Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134-2099

Sponsor's Representative:

Kay Harris
Manager
Regulatory Affairs
(817) 293-0450

Drug: TOBRADEX Ophthalmic Ointment

Generic: Tobramycin/Dexamethasone

Pharmacologic Category: Antibiotic/Corticosteroid ,

Submitted:

This supplement was submitted in response to the acknowledge and retain letter dated January 23, 1990 requesting a change in the spelling of *Herellea vaginicola* in the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections of the label. The sponsor after an internal review of the insert has proposed [redacted] (b) (4) because it has been reclassified as *Acinetobacter calcoaceticus* which already appears in the label.

NDA 50-616/5

Recommendation:

The labeling with the exception of the above mentioned change is identical to the labeling upon which this NDA was approved. In regards to the proposed change in the labeling, Mr. Harold Silver, Microbiologist, from the Division of Anti-Infective Drug Products, was consulted and he affirmed that the proposed change was correct. Therefore, NDA 50-616/S-005 TobraDex (tobramycin/dexamethasone) Ophthalmic Ointment with the above mentioned change in the labeling is recommended for approval.

Kathryn Huntley, R.Ph.

cc: NDA 19-387
HFD-160
HFD-160/CSO/Joyce
HFD-160/MO/Knight
HFD-160/DivDir/Chambers
HFD-160/Pharm/DeWitt
HFD-160/Chem/Sheinin

5/16/97