CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

050616sOrig1s001

Trade Name:	**TobraDex, Ophthalmic Ointment**
Generic or Proper Name:	(Tobramycin and Dexamethasone)
Sponsor:	**Novartis**
Approval Date:	June 27, 1989
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

050616sOrig1s001

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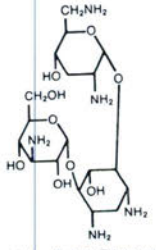
LABELING

TobraDex®

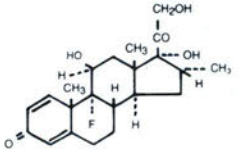
(Tobramycin and Dexamethasone)
Sterile Ophthalmic Suspension and Ointment

DESCRIPTION: TOBRADEX® (Tobramycin* and Dexamethasone) Ophthalmic Suspension and 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:
0-3-Amino-3-deoxy-α-D-glucopyranosyl-(1➡4)-0-[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% (3mg) and Dexamethasone 0.1% (1mg). 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 (Herellea vaginacola)* 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 (Herellea vaginacola)* 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.

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 are excreted in human milk, a decision should be considered to discontinue nursing temporarily while using 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 localized ocular toxicity and hypersensitivity, 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.

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.

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 46° to 80°F (8° to 27°C).

Store suspension upright and shake well before using.

Patent Pending.

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

340633 Revised: January 1990

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s001

CLINICAL REVIEW(S)

HFD-5_0

50616

Medical Officer's Review of NDA 50-616/S001
Supplement/FPL

NDA 50-616
Supplement 1/ FPL

Submitted date: 10/18/88
Received date: 10/21/88
Review date: 11/16/88

Sponsor:

Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76101
(817) 293-0450

Drug:

Tobradex Ointment

Pharmacologic Category:

Ophthalmic combination steroid and antibiotic

Related reviews/memos:

Agency Approval letter 9/28/88.

Submitted:

Final Printed Labeling.

Reviewer's Comments:

The final printed label conforms to the approved draft labeling.

During review with Dr. Albuerne, it was noted that *Acinetobacter calcoaceticus (Herellea vaginicola)* is misspelled in the CLINICAL PHARMACOLOGY section and the INDICATIONS AND USAGE section.

Summary Recommendations:

(Herellea vaginacola) should be changed to *(Herellea vaginicola)* in the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections.

Wiley A. Chambers MD
Wiley A. Chambers, M.D.

cc: NDA 50-616
HFD-520
HFD-340
HFD-520/CSO/RCook
HFD-520/MO/WChambers
HFD-520/MICRO/Silver
HFD-520/PHARM/JDavitt

mda 11/17/88
16 12/88

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616s018

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Microbiology Review # 9

NDA 50-616

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

APR 1 1989

Drug: TOBRADEX ® (tobramycin/dexamethasone)
Ophthalmic Ointment

Submission Reviewed: Final Printed Labeling (10/18/88)

Conclusions: The Final Printed Labeling (package insert, primary container [tube], and individual carton) are satisfactory and the Microbiologist's reviewed sections/parts are approved.

Harold V. Silver (2/28/89)
Harold V.Silver
Microbiologist, HFD-520
February 15,1989

cc: Orig NDA 50-616
HFD-235
HFD-473
HFD-502/JWeissenger
HFD-520
HFD-520/MO/WChambers
HFD-520/Pharm/SJoshi
HFD-520/CSO/RCook
HFD-520/Micro/HVSilver
R/D init by ATSheldon 2/17/89
0968r

AS 3/6/89
RC 3/8/89

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s001

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

HFD-520

NDA 50-616

Christine E. Shank
Manager, Regulatory Affairs
Alcon Laboratories, Inc
6201 South Freeway
Fort Worth, TX 76134-2099

JAN 23 1990

Dear Ms. Shank:

Reference is made to your New Drug Application (NDA) for TobraDex® (tobramycin and dexamethasone) Ophthalmic Ointment.

We acknowledge your submission of Final Printed Labeling (FPL) dated October 18, 1988.

We have reviewed the FPL that you have submitted in accordance with our approval letter dated September 28, 1988, and have the following recommendation:

In the CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE sections, (*Herellea vaginacola*) should be changed to (*Herellea vaginicola*).

Please submit 12 copies of the corrected FPL at the next printing.

Sincerely yours,

Murray M. Lumpkin, M.D.
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Orig NDA
cc:
HFD-82
HFD-710
HFD-520
HFD-520/Pharm/JDavitt HVS (1/8/90)
HFD-520/Micro/HVSilver
HFD-520/MO/WChambers WMC 1/9/90
HFD-520/PMS/JNazario/11-30-89 mml 1/19/90

Acknowledge and Retain MML 1/19/90

NDA 50-616

SEP 29 1988

Robert E. Roehrs, Ph.D.
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, TX 76134-2099

Dear Dr. Roehrs:

Reference is made to the amendment to your New Drug Application (NDA) dated August 25, 1988, received by the Food and Drug Administration on September 6, 1988, for Tobradex (tobramycin, 0.3% and dexamethasone, 0.1%) Ophthalmic Ointment.

We consider your amendment to be a major amendment under 21 CFR section 314.60, and we have determined that 45 additional days will be required for its review.

The new due date is February 24, 1989.

If questions arise concerning this NDA, please contact Maria Rossana Cook, Project Manager at (301) 443-0257.

Sincerely yours,

Lillian Gavrilovich, M.D.
Acting Director
Division of Anti-Infective
Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: DAL-DO
ORIG. NDA 50-616
HFD-82
HFD-520 mailed 9-26-88
HFD-520/CSO/RCook/sdj/9/14/88
HFD-520/MO
HFD-520/CHEM
HFD-520/PHARM
F/D: 9/14/88
F/T: 9/26/88
154lu mld 9/27/88