# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

## *APPLICATION NUMBER:*

## 050616sOrig1s007

| | |
|---|---|
| ***Trade Name:*** | **TobraDex, Ophthalmic Ointment** |
| ***Generic or Proper Name:*** | (Tobramycin and Dexamethasone) |
| ***Sponsor:*** | **Novartis** |
| ***Approval Date:*** | October 27, 1994 |
| ***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

## 050616sOrig1s007

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# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050616sOrig1s007**

# APPROVAL LETTER

NDA 50-616/S-007

OCT 27 1994

Cheryl B. Anderson, Pharm.D.
Alcon Laboratories
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Anderson:

Reference is made to your supplemental new drug application (NDA) dated June 8, 1994, submitted pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act for Tobradex (tobramycin 0.3% and dexamethasone 0.1%) Sterile Ophthalmic Ointment.

The supplement provides for labeling revisions to the CLINICAL PHARMACOLOGY and OVERDOSAGE 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 draft labeling. Accordingly, the supplement is approved effective as of the date of this letter.

Please submit twelve (12) copies of the final printed labeling (FPL) when available with the following revisions:

> Under the INDICATIONS AND USAGE section and the CLINICAL PHARMACOLOGY section, between the words *Moraxella lacunata,* and *Acinetobacter calcoaceticus,* the word "and" should be deleted.
>
> Under the CONTRAINDICATIONS section, the sentence "The use of..." should be deleted.

The submission should be designated for administrative purposes as "FPL for NDA 50-616/S-007." Approval of this submission by the Food and Drug Administration (FDA) is not required before the labeling is used.

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 yours,

10/27/94

Jonathan K. Wilkin, M.D.
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 50-616
HFD-540 DivFile
HFD-82
HFD-500
HFD-735/Baresh
HF-2
HFD-735
HFD-240
HFD-638
HFD-540/DivDir/JWilkin 10/27/94
HFD-540/SMO/Chambers - include labeling 10/23/94
HFD-540/SPharm/Alam
HFD-540/Chem/Tso
HFD-540/CSO/Chapman - include labeling
HFD-540/Joyce 10/3/94

**APPROVAL** (Supplement 007)

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050616sOrig1s007**

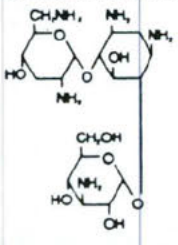
# LABELING

# TobraDex®

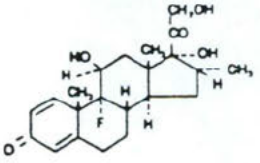
## (Tobramycin and Dexamethasone)
## Sterile Ophthalmic Suspension and Ointment

**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: **Actives:** Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). **Preservative:** Benzalkonium Chloride 0.01%. **Inactives:** 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: **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,* and *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 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 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 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 Suspension or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

**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 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

341465 Revised: February 1994

Printed in USA

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050616sOrig1s007**

# OTHER REVIEW(S)

SEP 1 1995

Clinical Review of NDA 50-616
Labeling Supplement

**NDA 50-616/S-007**

**Submission Date:** 6/15/95
**Review Date:** 7/14/95

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

**Applicant's Representative:**
Cheryl B. Anderson, Pharm. D.

**Drug:**
Tobradex (tobramycin 0.3% and dexamethasone 0.1%) Sterile Ophthalmic Ointment

**Pharmacologic Category:**
Antibiotic and steroid combination

**Submitted:**
Final Printed Labeling is response to the Division's approval letter dated October 27, 1994.

**Reviewers Comment and Recommendation:**
This insert has been split from the suspension as we requested. The labeling is identical to the draft except in the Pediatric Use subsection where the word children has been changed to pediatric patients. The labeling is acceptable. An acknowledge and retain letter should be sent to the company.

Regina D. Joyce

Wiley A. Chambers, M.D.

cc:
NDA 50-616
HFD-540
HFD-540/SMO/Chambers
HFD-540/MO/Bull
HFD-540/Chem/Tso
HFD-540/CSO/Chapman
HFD-540/Clin/Joyce

9/11/95

OCT 27 1994

# Labeling Review of NDA 50-616

NDA 50-616/S-007

**Submission Date:** 6/8/94
**Review Date:** 9/7/94

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

**Applicant's Representative:**
Cheryl B. Anderson, Pharm. D.

**Drug:**
Tobradex (tobramycin 0.3% and dexamethasone 0.1%) Sterile Ophthalmic Ointment

**Pharmacologic Category:**
Antibiotic and steroid combination

**Submitted:**
Draft labeling with changes in the Clinical Pharmacology and Overdosage sections of the package insert.

**Reviewers Comment:**
Recommended additions are shown in shading and deletions by ~~strikeout~~ lines.

The labeling submitted by the company reads as follows:

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 chemical structure goes here)

Tobramycin
Empirical Formula: $C_{18}$ $H_{37}$ $N_5$ $O_9$
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 chemical structure goes here)

Dexamethasone
Empirical Formula: $C_{22}$ $H_{29}$ F $O_5$
Chemical Name:
9-Fluoro-11B,17,21-trihydroxy-16*α*-methylpregna-1,4-diene-3,20-dione

Each mL of TOBRADEX® Suspension contains: **Actives:** Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg). **Preservative:** Benzalkonium Chloride 0.01%. **Inactives:** 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: **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*, ~~and~~ *Acinetobacter calcoaceticus* and some *Neisseria* species.

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

**Reviewer's Comments:** *The sentence "A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use." has been deleted from this section. This follows the Tobrex insert that was approved May 18, 1994. Acceptable*

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.~~

**Reviewer's Comments:** [redacted] (b) (4)

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 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 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.

**Reviewer's Comments:** *The third sentence starting with "The most frequent adverse reaction" the wording "are hypersensitivity and localized ocular toxicity," has been reversed to what had been approved but is consistent in the Tobrex package insert which was approved May 18, 1994. Acceptable*

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 Solution or Ointment (punctate keratitis, erythema, increased lacrimation, edema and lid itching) may be similar to adverse reaction effects seen in some patients.

**Reviewer's Comments:** *This section has been added and is consistent with that in the Tobrex package insert that was recently approved. Acceptable*

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 1/2 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 1/2 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 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 (logo)
**ALCON LABORATORIES, INC.**
FORT WORTH, TEXAS 76134 USA
Printed in USA
**341465**
Revised: February 1994

**Reviewer's Comment/Recommendation:**

*In discussing this insert with Dr. Roehrs it was agreed on September 30, 1994,* (b) (4) [redacted]

*This draft insert has minor editorial changes that should be corrected; otherwise it is approvable. It is recommended that a approval letter be issued asking for the FPL.*

Regina D. Joyce

cc:
NDA 50-616
HFD-540
HFD-540/SMO/Chambers WHC 10/20/94
HFD-540/MO/Bull
HFD-540/Chem/Tso
HFD-540/Joyce

RDJ 10/27/94

# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

**050616sOrig1s007**

# ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

**NDA 50-616/S-007**

SEP 7 1995

Alcon Laboratories
Attention: Cheryl B. Anderson, Pharm.D.
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Ms. Anderson:

Please refer to your supplemental new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Tobradex (tobramycin 0.3% and dexamethasone 0.1%) Sterile Ophthalmic Ointment.

We acknowledge your submission dated June 15, 1995, providing final printed labeling (FPL).

We have reviewed the final printed labeling that you have submitted in accordance with our approval letter dated October 27, 1994, and we find it acceptable.

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,

Jonathan K. Wilkin, M.D. 9/1/95
Director
Division of Topical Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
NDA 50-616
HFD-540 DivFile
HFD-2/Lumpkin
HFD-82
HFD-500
HFD-735
HFD-240
hfd-638
HF-2
HFD-540/DivDir/Wilkin
HFD-540/SMO/Chambers - include labeling MAC 7/22/95
HFD-540/Pharm/Alam
HFD-540/Chem/Tso
HFD-540/CSO/Chapman - include labeling
HFD-540/Clin/Joyce - include labeling RDF 7/14/95

**ACKNOWLEDGE AND RETAIN** (Supplement 007)