NDA 50-616

S-009

NDA 50-616/S-009

SEP 26 1996

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

Dear Ms. Anderson:

Please refer to your July 17, 1996, supplemental new drug application (NDA) submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for Tobradex (tobramycin and dexamethasone ophthalmic ointment).

The supplement provides for updating the PRECAUTIONS, subsection Nursing Mothers of the insert.

We have completed our 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 July 17, 1996 labeling. 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.

Please be advised that this approval affects only those changes specifically submitted in this supplemental new drug application. 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.

If you have any questions, please contact Regina D. Joyce at 301-827-2015.

Sincerely yours,

WAC 9/25/96

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

cc:
NDA 50-616
HFD-550
District Office
HFD-82 - include labeling
HFD-40 - include labeling
HFD-613 - include labeling
HF-2/MedWatch - include labeling
HFD-735 -include labeling
HFD-550/MTL/Chambers - include labeling
HFD-550/MO/Bull
HFD-550/Chem/Tso
HFD-550/CSO/Holmes - include labeling
HFD-550/Clin/Joyce - include labeling 4/4/96

APPROVAL

Labeling Review of NDA 50-616

SEP 26 1996

NDA 50-616/S-009

Submission Date: 7/17/96
Review Date: 8/27/96

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 with changes in the Precautions, Nursing Mothers subsection 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 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 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-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*, 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 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*, 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.

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 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 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.

Reviewer's Comment: *This section has been revised as requested in a telephone conversation July 6, 1995 between the Agency and the company.*

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: Suspension: 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.

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 (logo)
ALCON LABORATORIES, INC.
FORT WORTH, TEXAS 76134 USA
Printed in USA
341515
Revised: August 1995

Reviewer's Comment: *The only change in the insert was in the Nursing Mothers subsection. The insert is acceptable with the revisions made by the company.*

Recommendation: *An approval letter should be issued for this supplement .*

Regina D. Joyce

Wiley A. Chambers, M.D.

cc:
NDA 50-616
HFD-550
HFD-550/MTL/Chambers
HFD-550/MO/Bull
HFD-550/Chem/Tso
HFD-550/CSO/Holmes
HFD-550/Clin/Joyce

ORIGINAL

Certified Mail Z 047 933 789
RETURN RECEIPT REQUESTED

NDA NO. [redacted] REF. NO. [redacted]
NDA SUPPL FOR [redacted]

July 17, 1996

ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TEXAS 76134-2099
(817) 293-0450

Cheryl Beal Anderson, Pharm. D.
Regulatory Affairs Manager

Division of Analgesic, Anti-Inflammatory and
Ophthalmic Drug Products
CDER, HFD-550
Food and Drug Administration
9201 Corporate Boulevard
Building 2, Floor 2, Room 109 South
Rockville, Maryland 20850

RE: NDA 50-592
TOBRADEX SUSPENSION
(Tobramycin and Dexamethasone Ophthalmic Suspension)
NDA 50-616
TOBRADEX OINTMENT
(Tobramycin and Dexamethasone Ophthalmic Ointment)
Special Supplement - Changes Being Effected

Dear Madam or Sir:

Reference is made to a telephone conversation with Ms. Regina Joyce, FDA Clinical Reviewer, on July 6, 1995. At that time, a request was made to revise the Nursing Mothers section for our corticosteroid containing products. The section was requested to be revised as follows:

> "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 (DRUG PRODUCT NAME including dosage form) is administered to a nursing woman."

Following you will find 12 copies of final printed labeling that incorporate the requested change. The revision strengthens the precautions section of the labeling. These changes will be implemented at the time of next printing.

If there are any questions or comments regarding the content or format of this submission, please do not hesitate to contact the undersigned directly at (817) 551-4325.

Sincerely,

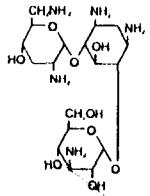
Cheryl Beal Anderson, Pharm.D.

TobraDex®

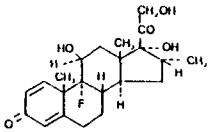
(Tobramycin and Dexamethasone Ophthalmic Ointment) Sterile

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:

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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.

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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.

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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