CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

050616sOrig1s011

Trade Name:	**TobraDex, Ophthalmic Ointment**
Generic or Proper Name:	(Tobramycin and Dexamethasone)
Sponsor:	**Novartis**
Approval Date:	April 28, 1999
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

050616sOrig1s011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s011

APPROVAL LETTER

NDA 50-616/S-011

Alcon Laboratories, Inc.
Attention: Sarah J. Cantrell
Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

APR 28 1999

Dear Ms. Cantrell:

Please refer to your supplemental new drug application dated April 4, 1997, received April 10, 1997, submitted under the Federal Food, Drug, and Cosmetic Act for TobraDex® (tobramycin and dexamethasone ophthalmic ointment) Sterile Ophthalmic Ointment.

We acknowledge receipt of your submission dated February 18, 1999. Your submission of February 18, 1999, constituted a complete response to our July 29, 1997, action letter.

This supplemental application provides for a revision to the Pediatric Use subsection of the package insert.

We have completed the review of this supplemental application, as amended, 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 final printed labeling of the package insert submitted February 18, 1999. Accordingly, the supplemental application is approved effective on the date of this letter.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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

If you have any questions, contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

WAC 4/28/99

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
NDA 50-616
HFD-550/Div. Files
HFD-550/Clin Rev/Holmes jh 3/15/99
HFD-550/Dep Dir/Chambers (with labeling)
HFD-550/MO/Boyd (with labeling) 3/16/99
HFD-550/Proj Mgr/Gorski (with labeling) 3/17/99
HFD-550/Pharm TL/Weir 4-5-99
HFD-550/Chem TL/Ng 3/17/99
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-95/DDMS (with labeling)
DISTRICT OFFICE
HFZ-460/DOD (with labeling)
Drafted by: jh/March 9, 1999
final:
filename: 50616s11ap.doc

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s011

LABELING

Labeling: _____

NDA No: _____ Rc'd. _____

Reviewed by: _____

APPROVED

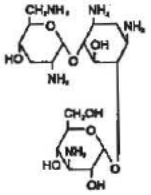
APR 2 8 1999

TobraDex®

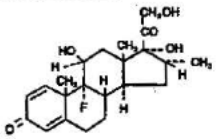
(tobramycin and dexamethasone ophthalmic ointment) Sterile

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 pediatric patients 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.

Ophthalmic ointment may retard corneal wound healing.

Information for Patients: Do not touch tube tip to any surface, as this may contaminate the contents. Contact lenses should not be worn during the use of this product.

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 15.8% 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 below the age of 2 years 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).

Rx Only

U.S. Patent No. 5,149,694

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

100FDA-0199 Revised: January 1999

Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s011

OTHER REVIEW(S)

MAR 8 1999

Clinical Review of NDA 50-616
Labeling Supplement

NDA 50-616/S-011

Submission Date: 2/18/99
Receipt Date: 2/22/99
Review Date: 3/8/99

Applicant:

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

Applicant's Representative:

Sarah J. Cantrell
Manager, Regulatory Affairs
(817) 551-4517

Drug:

TOBRADEX® (tobramycin and dexamethasone ophthalmic ointment) Sterile Ophthalmic Ointment

Pharmacologic Category:

Antibiotic and steroid combination

Submitted:

Final printed labeling in response to the 7/29/97 not approvable letter. This supplement is to revise the Pediatric Use subsection of the Precautions section of the package insert.

Following is the labeling submitted by the company. Recommended additions are shown in shading and deletions by ~~strikeout~~ lines.

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 Structure]

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 Structure]

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% (1 mg). **Preservative:** Chlorobutanol 0.5%. **Inactives:** Mineral Oil and White Petrolatum.

Reviewer's comments: *The generic name has been revised as requested to appear in lower case letters and to include the dosage form.*

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.

Reviewer's comments: *The final printed labeling is printed correctly.*

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.

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Reviewer's comments: (b) (4)

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.

Reviewer's comments: *The errors in the draft labeling were corrected in the FPL.*

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 pediatric patients 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.

Reviewer's comments: *The word "children" was revised to "pediatric patients" in the second sentence of the second paragraph.*

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.

Ophthalmic ointments may retard corneal wound healing.

Reviewer's comments: *The sentence above was added as requested.*

Information for Patients: Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

Contact lenses should not be worn during the use of this product.

Reviewer's comments: *The sentence above was added as requested.*

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.

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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.

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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:

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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).
Rx only.

Reviewer's comments: *The "CAUTION: Federal (U.S.A.) law..." statement was revised.*

U.S. Patent No. 5,149,694

Alcon® Ophthalmic (logo)
ALCON LABORATORIES, INC.
FORT WORTH, TEXAS 76134 USA
Printed in USA

Revised January 1999

Recommendations: Changes were made as requested. An approval letter may be issued.

Joanne M. Holmes

William Boyd, M.D.

cc:
NDA 50-616
HFD-550 Div files
HFD-550/MO/Chambers
HFD-550/MO/Boyd
HFD-550/Clin Rev/Holmes
HFD-550/Proj Mgr/Gorski
HFD-550/Chem TL/Ng
HFD-550/Pharm TL/Weir
HF-2/MedWatch

50616s11rev2.doc

Div.

Labeling Review of NDA 50-616

NDA 50-616/S-011

Submission Date: 4/4/97
Review Date: 7/15/97

Applicant:

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

Applicant's Representative:

Cheryl B. Anderson, Pharm. D.
Manager, Regulatory Affairs
(817) 551-4325

Drug:

TobraDex® (tobramycin and dexamethasone ophthalmic ointment)
Sterile Ophthalmic Ointment

Pharmacologic Category:

Antibiotic and steroid combination

Submitted:

Draft labeling to revise the Pediatric Use subsection of the Precautions section of the package insert. Alcon has included the revised labeling as both typed text and as a copy of August 1995 FPL with the proposed revisions typed onto it. Placement of the proposed text is indicated by arrows on this copy of FPL.

Following is the labeling submitted by the company. Recommended additions are shown in shading and deletions by ~~strikeout~~ lines.

TobraDex®
(Tobramycin and Dexamethasone Ophthalmic Ointment)
Sterile

DESCRIPTION: TOBRADEX® ((Tobramycin and Dexamethasone ophthalmic ointment) 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 Structure]

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 Structure]

Dexamethasone
Empirical Formula: $C_{22}\ H_{29}\ F\ O_5$
Chemical Name:
9-Fluoro-11B,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.

Reviewer's comments: *The generic name should appear in lower case letters and it should include the dosage form.*

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.

Reviewer's comments: *The sixth paragraph and the first sentence of the seventh paragraph above are written correctly in the copy of the August 1995 labeling in this submission.* (b) (4) [redacted]

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.

(b) (4)

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.

Reviewer's comments: *The copy of the August 1995 FPL has the Contraindications section written correctly.* [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~~pediatric patients 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.

Reviewer's comments: *The word "children" should be revised to "pediatric patients" in the third sentence of the second paragraph for consistency with the TobraDex Ophthalmic Solution (NDA 50-592).*

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.

Ophthalmic ointments may retard corneal wound healing.

Information for Patients: Do not touch dropper or tube tip to any surface, as this may contaminate the contents.

Contact lenses should not be worn during the use of this product.

Reviewer's comments:

1. *The precaution about ointments and corneal wound healing should be added to the General subsection.*
2. *Contact lenses should not be worn while the patient is using this product, due to the increased risk of infection (see the Warnings section). This precaution should be added to the Information for Patients subsection.*

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 below the age of 2 years have not been established.

Reviewer's comments: *Alcon has provided the following justification to extend the use of the product down to pediatric patients 2 and over:*
Safety and effectiveness of tobramycin have been established in pediatric patients down to age 2; the disease course of inflammation is similar in adult and pediatric patients; dexamethasone has similar therapeutic and safety profiles in adult and pediatric patients. This is acceptable.

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 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 (logo)
ALCON LABORATORIES, INC.
FORT WORTH, TEXAS 76134 USA
Printed in USA

Revised (b) (4) July 1997

cc:
NDA 50-616
HFD-550 Div files
HFD-550/MO/Chambers
HFD-550/MO/Ludwig
HFD-550/Clin Rev/Holmes
HFD-550/Proj Mgr/Gunter
HF-2/MedWatch

Recommendations:

A not approvable letter should be issued because there are two versions of labeling submitted here. (b) (4) [redacted] There following revisions should also be requested:

1. The generic name should appear in lower case letters and should include the dosage form before and in the first sentence of the Description section, i.e., tobramycin and dexamethasone ophthalmic ointment.
2. The typed text has (b) (4) [redacted]
3. (b) (4) [redacted]
4. The word "children" should be changed to "pediatric patients" in the second paragraph of the Warnings section.
5. The following should be added to the General subsection of the Precautions section: "Ophthalmic ointments may retard corneal wound healing."
6. The following should be added to the Information for Patients subsection of the Precautions section: "Contact lenses should not be worn during the use of this product."

Joanne M. Holmes

Wiley A. Chambers, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

050616sOrig1s011

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-616/S-011

JUL 29 1997

Alcon Laboratories, Inc.
Attention: Cheryl Beal Anderson, Pharm. D.
Manager, Regulatory Affairs
6201 South Freeway
Fort Worth, Texas 76134-2099

Dear Dr. Anderson:

Please refer to your supplemental new drug application dated April 4, 1997, received April 10, 1997, submitted under section 507 of the Federal Food, Drug, and Cosmetic Act for TobraDex® (tobramycin and dexamethasone ophthalmic ointment) Sterile Ophthalmic Ointment.

This supplemental application provides for a revision to the Pediatric Use subsection to the package insert.

We have completed our review and find the information presented is inadequate, and the supplemental application is not approvable at this time.

Under section 505(d) of the Act and 21 CFR 314.125(b)(6) of the FDA implementing regulations, the proposed labeling is misleading in that the versions you have submitted in this supplement are not identical. Please submit labeling that accurately reflects the changes proposed in this supplement.

We also have the following revisions:

1. The generic name should appear in lower case letters and should include the dosage form, i.e., tobramycin and dexamethasone ophthalmic ointment. This revision should be made at the beginning of the package insert and in the first sentence of the Description section.

2. (b) (4)

3. (b) (4)

AUG 0 5 1997

Regulatory Affairs
Cheryl Anderson, Pharm.D.

4. The word "children" should be revised to "pediatric patients" in the second paragraph of the Warnings section.

5. The following statement should be added to the General subsection of the Precautions section: "Ophthalmic ointments may retard corneal wound healing."

6. The following statement should be added to the Information for Patients subsection of the Precautions section: "Contact lenses should not be worn during the use of this product."

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the supplemental application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

If you have any questions, please contact Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

MWeintraub 7/29/97

Michael Weintraub, M.D.
Acting Director
Division of Anti-Inflammatory, Analgesic, and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

DW.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-616/S-011

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

APR 16 1997

Attention: Cheryl Beal Anderson, Pharm.D.
Manager, Regulatory Affairs

Dear Dr. Anderson:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: TobraDex Ointment (tobramycin and dexamethasone)

NDA Number: 50-616

Supplement Number: S-011

Date of Supplement: April 4, 1997

Date of Receipt: April 10, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on June 9, 1997 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Attention: Document Control Room
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

Lissante C. LoBianco 4/14/97

Lissante C. LoBianco
Acting Supervisory Consumer Safety Officer
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Original NDA 50-616/S-011
HFD-550/Div. Files
HFD-550/CSO/J. Holmes

SUPPLEMENT ACKNOWLEDGEMENT