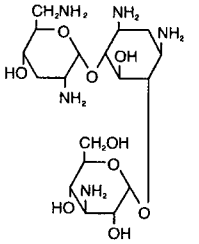
Tobraflex™

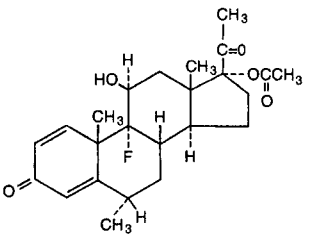
(tobramycin and fluorometholone acetate ophthalmic suspension,USP)

Sterile

DESCRIPTION: **Tobraflex™** (tobramycin and fluorometholone acetate ophthalmic suspension, USP) is a sterile, multiple dose antibiotic and steroid combination for topical ophthalmic use. The chemical structures for tobramycin and fluorometholone acetate are presented below:



Tobramycin
Empirical Formula: $C_{18}H_{37}N_5O_9$
Chemical Name:
0-3-Amino-3-deoxy-α-D-glucopyranosyl-(1->4)0-[2,6-diamino-2,3,6-trideoxy-α-D-ribo-hexopyranosyl-(1->6)]-2-deoxy-L-streptamine



Fluorometholone Acetate
Empirical Formula: $C_{24}H_{31}FO_5$
Chemical Name:
9-Fluoro-11ß, 17-dihydroxy-6α-methylpregna-1,4-diene-3,20-dione 17-acetate

Each mL contains: Active: Tobramycin 0.3% (3 mg) and Fluorometholone Acetate 0.1% (1 mg). **Preservative:** Benzalkonium Chloride 0.01%. **Inactive:** Tyloxapol, Edetate Disodium, Sodium Chloride, Hydroxyethyl Cellulose, Hydrochloric Acid and Sodium Hydroxide (to adjust pH), Purified Water. The pH range is 6.0 -7.0.

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. Clinical studies have demonstrated that Fluorometholone Acetate Suspension is a potent corticosteroid.

In clinical studies of documented steroid-responders, fluorometholone acetate demonstrated a significantly longer average time to produce a rise in intraocular pressure than dexamethasone phosphate; however, in a small percentage of individuals, a significant rise in intraocular pressure occurred within one week. The ultimate magnitude of the rise was equivalent for both drugs.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. In vitro studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, and Acinetobacter calcoaceticus (Herellea vaginacola)* and *some Neisseria species.*

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. Bacterial resistance to tobramycin may develop upon prolonged use.

No data are available on the extent of systemic absorption from **Tobraflex™** Ophthalmic Suspension; however, it is known that some systemic absorption can occur with ocularly applied drugs.

When a decision to administer both a corticoid and an antibiotic is made, the administration of such drugs in combination has the advantage of greater patient compliance and convenience, with the added assurance that the appropriate dosage of both is administered, plus assured compatibility of ingredients when both types of drug are in the same formulation and, particularly, that the correct volume of drug is delivered and retained.

INDICATIONS AND USAGE: Tobraflex™ Ophthalmic Suspension 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 anti-infective drug in this product, tobramycin, is active against the following common bacterial eye pathogens: Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae.*

Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains, *Haemophilus influenzae* and *H. aegyptius, Moraxella lacunata, and Acinetobacter calcoaceticus (Herellea vaginacola)* and some *Neisseria species.*

CONTRAINDICATIONS: Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva, Mycobacterial infection of the eye. Fungal diseases of ocular structures. Hypersensitivity to any 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.

Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye. 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. If used for more than 10 days, 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 tip to any surface, as this may contaminate the suspension. 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. No studies of impairment of fertility by fluorometholone acetate are available.

Pregnancy - Pregnancy Category C. Animal studies have not been conducted with **Tobraflex™** Ophthalmic Suspension. Fluorometholone has been shown to be embryocidal and teratogenic in rabbits when administered at low multiples of the human dose. Fluorometholone was applied ocularly to rabbits daily on days 6 to 18 of gestation, and dose-related fetal loss and fetal abnormalities including cleft palate, deformed rib cage, anomalous limbs and neural abnormalities such as encephalocele, craniorachischisis, and spina bifida were observed. Reproduction studies have been performed in rats and rabbits with tobramycin at parenteral doses up to 100 mg/kg/day with no evidence of harm to the fetus (2000X the maximum recommended human dose). There are no adequate and well-controlled studies of **Tobraflex™** Ophthalmic Suspension in pregnant women. **Tobraflex™** Ophthalmic Suspension 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 **Tobraflex™** Ophthalmic Suspension is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

Geriatic Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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® Ophthalmic Solution) are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary Infection. The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids. The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used. Secondary bacterial ocular infection following suppression of host responses also occurs.

DOSAGE AND ADMINISTRATION: 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.

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in PRECAUTIONS above.

HOW SUPPLIED: Tobraflex™ is a sterile ophthalmic suspension supplied in Alcon's DROP-TAINER® package system.

TobraFlex™ is supplied as either a 2.5 mL or a 5 mL fill in a 5 mL natural polyethylene dispenser bottle with a natural polyethylene dropper tip and a white polypropylene overcap. Tamper evidence is provided with s shrink band around the closure and neck area of the package.

2.5 mL - NDC 0065-0651-25

5 mL - NDC 0065-0651-05

STORAGE: Store upright at 36° to 77°F (2° to 25°C) and shake well before using.

Rx Only

U.S. Patent No. 5,149,693

Revised: November 2000

Alcon®
PHARMACEUTICALS

Alcon Laboratories, Inc.
Fort Worth, Texas 76134
Printed in USA

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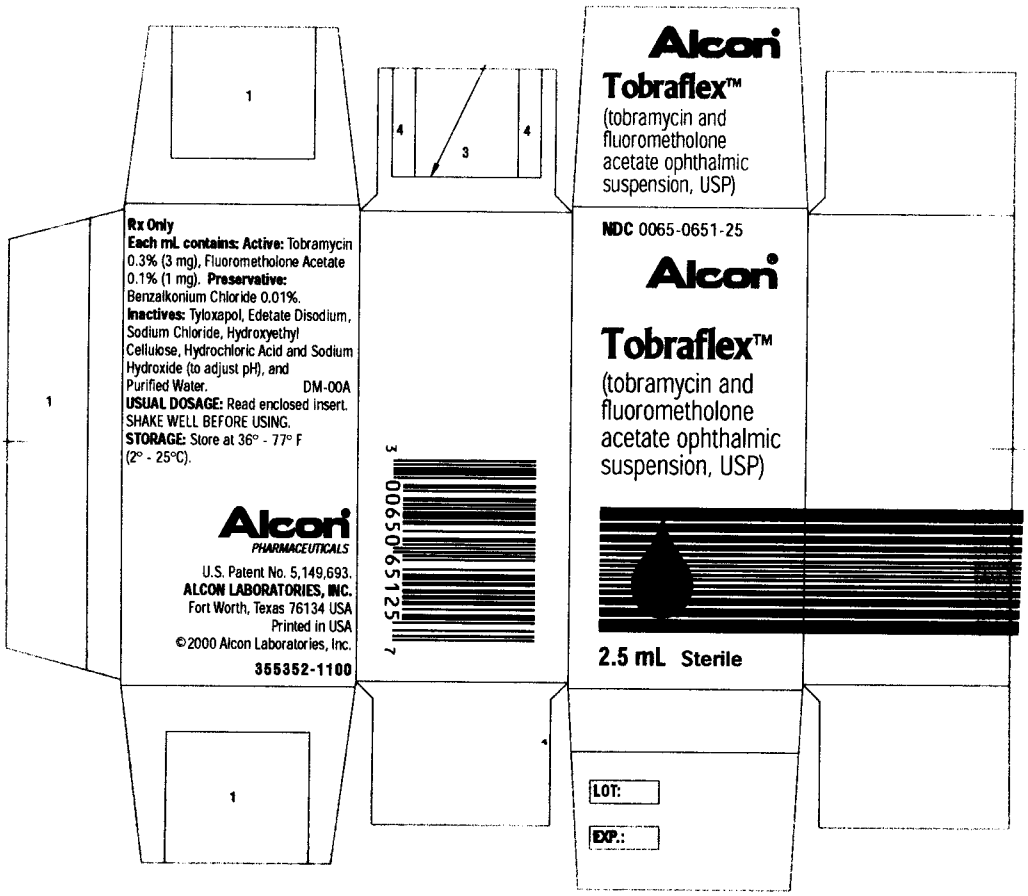
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2.5 mL Sterile
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Each mL contains: Active: Tobramycin 0.3% (3 mg), Fluorometholone Acetate 0.1% (1 mg). Preservative: Benzalkonium Chloride 0.01%.
Inactives: Tyloxapol, Edetate Disodium, Sodium Chloride, Hydroxyethyl Cellulose, Hydrochloric Acid and Sodium Hydroxide (to adjust pH), and Purified Water. DM-00A
USUAL DOSAGE: Read enclosed insert. SHAKE WELL BEFORE USING.
STORAGE: Store at 36° - 77° F (2° - 25°C).
Alcon
PHARMACEUTICALS
U.S. Patent No. 5,149,693.
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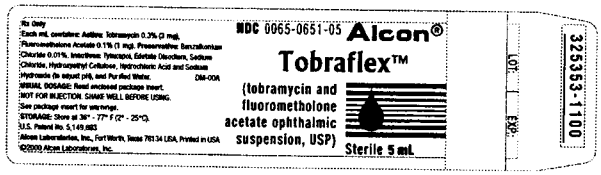
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Chloride 0.01%. Inactives: Tyloxapol, Edetate Disodium, Sodium
Chloride, Hydroxypropyl Cellulose, Hydrochloric Acid and Sodium
Hydroxide (to adjust pH), and Purified Water.
DM-00R
VIRUAL DOSAGE: Read enclosed package insert.
MOT FOR INJECTION. SHAKE WELL BEFORE USING.
See package insert for warnings.
STORAGE: Store at 36° - 77° F (2° - 25°C).
U.S. Patent No. 5,149,693
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NDC 0065-0651-05
Alcon®
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