

TOBRADEX[®]

Tobramycin and dexamethasone sterile ophthalmic suspension and ointment

Presentation

TOBRADEX (Tobramycin and Dexamethasone) Ophthalmic Suspension and Ointment are sterile, multiple dose antibiotic and steroid combinations for topical ophthalmic use.

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.

Each gram of TOBRADEX Ointment contains:

Actives: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1% (1 mg).

Preservative: Chlorobutanol 0.5%

Inactives: Mineral Oil and White Petrolatum.

Uses

Actions

Corticoids suppress the inflammatory response to a variety of agents and they probably delay or slow healing. Since corticoids may inhibit the body's defence mechanism against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant. Dexamethasone is a potent corticoid.

The antibiotic component in the combination (tobramycin) is included to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

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

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

Bacterial susceptibility studies demonstrate that in some cases microorganisms resistant to gentamicin remain susceptible to tobramycin. A significant bacterial population resistant to tobramycin has not yet emerged; however, bacterial resistance may develop upon prolonged use.

Pharmacokinetics

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

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

conjunctivitis 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.

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 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.

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 Warnings and PRECAUTIONS below.

Keep out of reach of children.

Contraindications

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and many other viral diseases of the cornea and conjunctiva. Mycobacteria 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 and Precautions

NOT FOR INJECTION INTO THE EYE.

Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction does occur, discontinue use. Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Although these effects have not been reported following topical ocular use of tobramycin, caution is advised when used concomitantly

Prolonged use of steroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual activity 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. Topical ophthalmic corticosteroids may slow corneal wound healing.

General

The possibility of fungal infections of the cornea should be considered after long-term steroid dosing and in patients with persistent corneal ulceration. As with other antibiotic preparations, prolonged use may result in overgrowth of non-susceptible organisms, including fungi. If fungal infection occurs, corticosteroids therapy should be discontinued. If superinfection occurs, appropriate therapy should be initiated. When multiple prescriptions are required, or whenever clinical judgement dictates, the

patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been conducted to evaluate the carcinogenic or mutagenic potential. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

Pregnancy - 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 foetus. 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 foetus.

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 when using TOBRADEX Ophthalmic Suspension or Ointment.

Paediatric Use

Safety and effectiveness in children have not been established.

Effects on Ability to Drive and Use Machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

Contact Lenses

Contact Lens wear should not be worn during treatment of an ocular inflammation or infection. TOBRADEX Ophthalmic Suspension contains benzalkonium chloride which may cause eye irritation and is known to discolour soft contact lenses.

Adverse Effects

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination. Exact incidence figures are not available. The most frequent adverse reactions to topical ocular tobramycin (TOBREX) are localized ocular toxicity and hypersensitivity, including lid itching and swelling, and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics. Other adverse reactions have not been reported; however, if topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. The reactions due to the steroid component are: elevation of intraocular pressure (IOP) with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.

Secondary Infection

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials, Fungal Infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroid. 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.

Post Marketing Events

No serious ophthalmic adverse events related to TOBRADEX Ophthalmic Suspension or Ointment were reported in clinical studies. The most frequently reported treatment-related adverse reactions were eye pain, intraocular pressure increased, eye irritation, and eye pruritus occurring in less than 1% of patients.

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience with TOBRADEX Ophthalmic Suspension or Ointment.

Eye Disorders

Uncommon ($\geq 0.1\%$ to $< 1\%$): intraocular pressure increased, eye pain, eye pruritus, ocular discomfort, eye irritation

Rare ($\geq 0.01\%$ to $< 0.1\%$): keratitis, hypersensitivity, vision blurred, dry eye, foreign body sensation in eyes, ocular hyperaemia

Not Known: eyelid oedema, mydriasis, lacrimation increased

Nervous System Disorders

Rare ($\geq 0.01\%$ to $< 0.1\%$): dysgeusia

Not Known: headache

Gastrointestinal Disorders

Not Known: nausea, abdominal discomfort

Skin and subcutaneous tissue disorders

Not Known: rash, swelling face, pruritus, erythema

Interactions

No interaction studies have been performed.

Overdosage

A topical overdose of TOBRADEX Ophthalmic Suspension or Ointment can be flushed from the eye(s) with lukewarm water. In New Zealand call 0800 POISON or 0800 764 766 for advice on management.

Pharmaceutical Precautions

Store at 8° to 27°C. Store suspension upright and shake well before using.

Medicine Classification

Prescription Medicine.

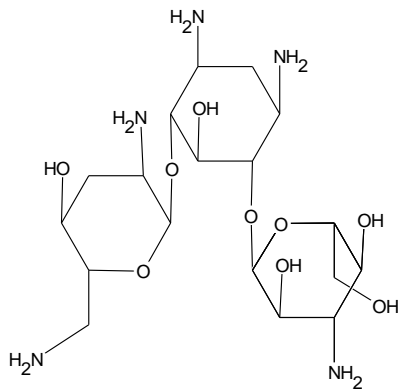
Package Quantities

Sterile ophthalmic suspension in 5 mL DROP-TAINER® dispenser.

Sterile ophthalmic ointment in 3.5 g ointment tube.

Further Information

The chemical structures for tobramycin and dexamethasone are presented below:

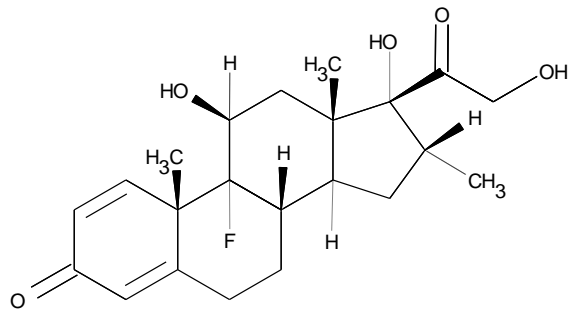


Tobramycin

Empirical Formula: $C_{18}H_{37}N_5O_9$

Chemical Name:

O-3-Amino-3-deoxy- α -D-glucopyranosyl-(1- \rightarrow 4)-
O-[2,6-diamino-2,3,6-trideoxy- α -D-ribo-hexopy-
ranosyl-(1- \rightarrow 6)]-2-deoxy-L-streptamine



Dexamethasone

Empirical Formula: $C_{22}H_{29}FO_5$

Chemical Name:

9-Fluoro-11 β ,17,21-trihydroxy-16 α -
methylpregna-1,4-diene-3,20-dione

Name and Address

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