PRODUCT MONOGRAPH

Pr **TOBRADEX®**

Tobramycin (0.3%) & Dexamethasone (0.1%)

Ophthalmic Suspension and Ointment

Antibiotic - Corticosteroid (Ophthalmic)

:

Alcon Canada Inc
2145 Meadowpine Blvd
Mississauga, Ontario
L5N 6R8

Date of Preparation:
February 28, 1990

4HN854865

PRODUCT MONOGRAPH

Pr TOBRADEX®

Tobramycin (0.3%) & Dexamethasone (0.1%)
Ophthalmic Suspension and Ointment

Antibiotic - Corticosteroid (Ophthalmic)

ACTIONS

Dexamethasone, a potent corticosteroid, suppresses the inflammatory response to chemical, immunological, or mechanical irritants.

The bactericidal activity of tobramycin is accomplished by specific inhibition of normal protein synthesis in susceptible bacteria.

INDICATIONS

For steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial infection or a risk of bacterial ocular infection exist.

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, thermal burns or penetration of foreign bodies.

CONTRAINDICATIONS

Vaccinia, varicella, Herpes simplex and other viral diseases of the cornea and conjunctiva; Tuberculosis of the eye; Fungal diseases of the eye; Acute purulent untreated infections of the eye which, like other diseases caused by microorganisms, may be masked or enhanced by the presence of the steroid.

Hypersensitivity to a component of the medication. Partial cross-allergenicity to other aminoglycosides has been established.

The use of this combination is always contraindicated after uncomplicated removal of a corneal foreign body.

WARNINGS

NOT FOR INJECTION INTO THE EYE.

Sensitivity to topically applied aminoglycosides may occur in some patients. If a sensitivity reaction to tobramycin occurs, discontinue use.

Prolonged use of corticosteroids may result in glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation.

Prolonged use may suppress the host response, and thus increase the hazard of secondary ocular infections. Extended ophthalmic use of corticosteroid drugs may cause increased intraocular pressure in certain individuals, and in those diseases causing thinning of the cornea, perforation has been known to occur. If treatment exceeds 9 days, intraocular pressure should be routinely monitored.

PRECAUTIONS

General:

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application; fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use. As with other antibiotics, prolonged use may result in overgrowth of nonsusceptible organisms. As with all steroids, healing may be delayed if used in the uncomplicated removal of foreign bodies.

Ophthalmic examinations are recommended during long term therapy. If there is no improvement after 5 or 7 days of therapy, or if the condition worsens, the medication should be discontinued.

If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. Patients should be advised to inform their physicians of any prior use of corticosteroids. Patients should be advised regarding the use of contact lenses while on therapy.

Pregnancy:

Animal reproduction studies have not been conducted with TOBRADEX (Tobramycin-Dexamethasone Ophthalmic Suspension or Ointment). It is not known whether TOBRADEX ophthalmic preparations can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TOBRADEX ophthalmic preparations should be given to a pregnant woman only if clearly needed.

Nursing Mothers:

It is not known whether TOBRADEX ophthalmic preparations are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TOBRADEX Ophthalmic Suspension or Ointment is administered to a nursing woman.

Pediatric Use:

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component or the combination. Exact incidence figures are not available.

The most frequent adverse reactions to topical ocular tobramycin are localized ocular toxicity and hypersensitivity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Other adverse reactions have not been reported from ocular tobramycin therapy

The reactions due to the steroid component, in decreasing order of frequency are: elevation of intraocular pressure (IOP) with possible development of glaucoma and infrequent optic nerve damage, posterior capsule cataract formation, and delayed wound healing.

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.

SYMPTOMS AND TREATMENT OF OVERDOSE

There is no known treatment of overdosage since overdosage in the use of topical ophthalmic preparations is a remote possibility. Discontinue medication when heavy or protracted use is suspected.

DOSAGE AND ADMINISTRATION

Suspension:

One to two drops instilled into the conjunctival sac every four hours. During the initial 24 to 48 hours, the dosage may be increased to one or two drops every two 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 one-half inch ribbon into the conjunctival sac(s) up to three or four times daily or may be used adjunctively with drops at bedtime.

Special Instructions:

Patients should be instructed to avoid contamination of the dispensing tip.

PHARMACEUTICAL INFORMATION

CHEMISTRY:

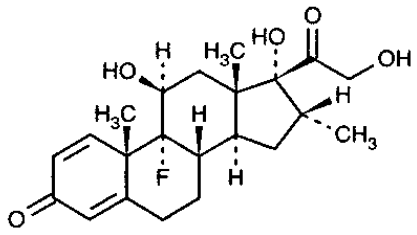
Tradename: TOBRADEX®

Drug Substance - Dexamethasone:

Proper Name: Dexamethasone

Chemical Name: 9-fluoro-11β,-17, 21-trihydroxy -16α-methylpregna-1,4-diene-3,20-dione

Structural Formula:



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

Molecular Weight: 392.47

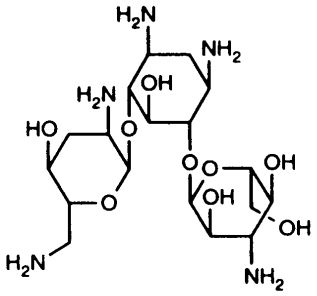
Description: Dexamethasone is a white to practically white crystalline powder, and is practically insoluble in water, sparingly soluble in alcohol, and slightly soluble in chloroform. The melting point is about 250EC with decomposition.

Drug Substance - Tobramycin:

Proper name: Tobramycin

Chemical Name: 0-3-amino-3-deoxy-α-D-glucopyranosyl-(1 | 4)-0-[2,6-diamino-2,3,6-trideoxy-α-D-ribohexopyranosyl-(1 | 6)]-2-deoxy-L-streptamine.

Structural Formula:



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

Molecular Weight: 467.54

Description: Tobramycin is a white to off-white hygroscopic powder, which is freely soluble in water. The pH of a 10% aqueous solution is approximately 10.

Composition:

TOBRADEX® (Tobramycin-Dexamethasone Ophthalmic Suspension) is a sterile, isotonic aqueous suspension containing tobramycin 3.0 mg/mL, and dexamethasone 0.1% with benzalkonium chloride 0.01% as a preservative. Also contains tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sodium hydroxide and/or sulfuric acid (to adjust pH) and purified water.

TOBRADEX® (Tobramycin-Dexamethasone Ophthalmic Ointment) is a sterile ophthalmic ointment containing tobramycin 3.0 mg/g and dexamethasone 0.1% with chlorobutanol 0.5%, as a preservative, in a mineral oil and petrolatum base.

DOSAGE FORM

Availability:

Pr TOBRADEX® Ophthalmic Suspension is available as a sterile ophthalmic suspension in DROP-TAINER® dispensers of 5 mL. Shake well before use.

Pr TOBRADEX® Ophthalmic Ointment is available as a sterile ophthalmic ointment in 3.5 g ophthalmic ointment tube.

Storage:

Store TOBRADEX suspension in an upright position.

Store TOBRADEX suspension and ointment at room temperature.

Special Instructions:

Patients should be instructed to avoid contamination of the dispensing tip.

MICROBIOLOGY

The gram positive bacteria against which tobramycin is active include *Staphylococci*, including *Staphylococcus aureus* and *Staphylococcus epidermis* (coagulase-positive and coagulase-negative) and including penicillin-resistant strains, *Streptococcus pneumoniae*, other alpha hemolytic streptococci, Group A beta-hemolytic and non-hemolytic streptococci.

The gram negative bacteria against which tobramycin is active include most strains of *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis* (indole-negative), and indole-positive Proteus species, as well as *Haemophilus* spp, *Moraxella* spp. and *Acinetobacter calcoaceticus (Herellea vaginacola).* 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.

The table on the following page details the bacterial species found in the normal (non-infected) eyes of over 10,000 individuals by ocular location (conjunctiva versus eyelids) and by age.

CLINICAL PHARMACOLOGY

Safety evaluations of Tobramycin-Dexamethasone Ophthalmic Suspension and Ointment, using human volunteers, demonstrated that the combination drug is well tolerated. Several subjects (10 - 25%) experienced a 5-7 mm Hg rise in intraocular pressure in the treated eye.

Incidence of Microorganisms Cultured from Conjunctivas and Eyelid Margins*

	1-18 years		20-35 years		40-90 years	
	Percent positive (range)**		**Percent positive (range)**		**Percent positive (range)**	
Microorganisms	Conjunctivas	Eyelids	Conjunctivas	Eyelids	Conjunctivas	Eyelids
Staphylococcus epidermidis	56-73	62-81	61-78	63-76	54-83	62-82
Staphylococcus aureus	35-38	32-45	30-41	31-44	31-45	31-47
Diphtheroids	21-23	20-24	32-39	33-43	21-34	28-43
Streptococcus viridans	1.1-2.1	0.7-2.5	0.3-0.7	0.3-0.8	0.5-5.0	0.5-5.0
Diplococcus pneumoniae	5.0-9.0	5.0-9.0	0.9-2.7	0.5-1.3	0.4-0.8	0.2-1.2
Escherichia coli	0.1-0.2	0.2-0.4	0.2-2.7	0.3-1.5	0.4-3.0	0.5-4.0
Klebsiella pneumoniae	0.6-3.0	0.6-3.0	0.3-3.0	0.3-1.3	0.2-1.2	0.2-2.2
Klebsiella ozenae	--	--	--	--	0.2-0.6	0.2-0.6
Proteus vulgaris	0.1-0.2	0.1-0.2	0.1-0.2	0.1-0.3	0.6-3.0	0.9-4.0
Proteus morgani	0.1-0.2	0.1-0.2	0.1-0.2	0.1-0.6	0.3-3.0	0.3-3.0
Proteus mirabilis	0.1-0.2	0.1-0.2	0.1-0.4	0.2-0.9	0.7-2.4	0.7-2.4
Proteus rettgeri	--	--	--	--	0.5-0.9	0.5-0.9
Neisseria catarrhalis	0.9-3.0	0.2-0.6	0.1-1.3	0.2-1.5	0.2-1.2	0.2-1.2
Neisseria sicca	0.5-0.9	0.9-2.0	0.2-2.0	0.2-3.0	0.2-1.1	0.5-1.1
Neisseria flava	--	--	0.1-0.7	0.2-0.9	0.3-1.2	0.3-1.2
Bacillus subtilis	0.6-1.3	0.5-1.3	0.7-2.3	0.8-4.0	0.2-1.8	0.6-2.6
Bacillus cereus	--	--	--	--	0.2-1.2	0.2-1.5
Bacillus megaterium	--	--	--	--	0.4-1.1	0.3-1.5
Sarcina	0.8-1.2	0.9-1.2	0.5-1.0	0.5-1.5	0.2-1.8	0.2-2.4
Micrococcus tetragenus	0.7-1.2	0.6-1.2	0.5-2.0	0.7-3.2	0.4-4.0	0.8-4.1

* From 1,024 young people 1-18 years old, 1786 adults 20-35 years old, and 7461 patients awaiting ocular surgery, 1952-1968. None had infected eyes. Ages 1-18 drawn from children awaiting surgery, those accompanying parents to clinic, and visiting high school students; ages 20-35 years drawn from graduate students and from some of the personnel at the Columbia-Presbyterian Medical Center, 1957-1962.
** Figures given are from the years showing the lowest and the highest incidence for each microorganism.
Source: *Microbiology of the Eye.* Deborah Locatcher-Khorazo and Beatrice Carrier Seegal. C.V. Mosby Co. 1972.

In vitro Susceptibility of Microorganisms to Tobramycin
Cumulative Percent of Strains Inhibited in Broth or Agar Dilution Studies
MIC (Φg/mL)

	# strains	<0.06	0.06-0.12	0.13-0.25	0.26-0.5	0.51-0.78	0.79-1.56	1.6-3.12	3.2-6.25	6.3-12.5	12.5-25
Citrobacter sp.	167		1	5	19	19	73	93	98	98	99
Enterobacter sp.	1126	1	4	15	36	39	81	91	97	99	99
Escherichia coli	2117		1	4	18	21	58	78	92	97	98
Herellea	206		4	8	25	26	76	91	97	99	100
Klebsiella sp. *Klebsiella -*	1244	3	5	20	47	50	86	94	97	99	99
Enterobacter	721		3	22	48	54	83	94	97	98	99
Paracolons	113			2	4	4	12	28	51	68	81
Proteus mirabilis (indole -)	1675			1	5	8	37	60	81	96	99
Proteus sp. (indole +)	1213		2	4	16	20	51	71	83	92	96
Pseudomonas	2880	6	18	40	63	70	91	96	97	98	99
Pseudomonas (gentamicin resistant)	153		12	18	27	30	35	46	59	71	80
Salmonella sp.	123			2	13	13	42	70	85	94	96
Serratia sp.	546				3	5	28	53	73	88	94
Shigella sp.	194				2	3	75	96	98	100	
Staphylococcus aureus	2013	11	28	42	70	73	87	93	96	99	99
Streptococcus faecalis	448			1	2	2	3	4	14	38	61
Streptococcus pyrogenes	177	7	13	15	18	18	27	43	65	87	95

* (Providencia, Bethesda-Ballerup, Arizona sp)
Data from published sources: 10^3 - 10^5 cells/mL inoculum in broth or agar dilution assays

TOXICOLOGY

Toxicology studies conducted with tobramycin-dexamethasone ophthalmic suspension and ointment are summarized in the following table:

Test	Suspension Dosage	Ointment Dosage	Observations
Acute Toxicity			
Rabbit: Ocular irritation	0.7 mL/eye over 6 hours	0.6 mL/eye over 6 hours	moderate conjunctival congestion, minimal conjunctival discharge
Long Term Toxicity			
Rabbit: 30 day ocular irritation	0.3 mL/eye/day for 2 days; 0.2 mL/eye/day for 31 days	0.25 mL/eye/day for 2 days; 0.15 mL/eye/day for 31 days	Minimal-moderate conjunctival congestion; minimal ocular discharge; nasal discharge; nasal congestion; loose stool; pulmonary congestion; suppression of weight gain. Two instances of bilateral lens changes for each dosage form.
Monkey: 3 month ocular toxicity	0.18 mL/eye/day for 1 week; 0.24 mL/eye/day for 3 months	0.15 mL/eye/day for 1 week; 0.20 mL/eye/day for 3 months	minimal conjunctival congestion; sporadic instances of minimal corneal cloudiness and fluorescein staining; loose stool; transient diarrhea.

Note: Each mL Tobramycin-Dexamthasone contains:
1.0 mg dexamethasone
3.0 mg tobramycin

Note: Ointment single dose = 10 mm strip = 0.05 mL

Carcinogenicity, Mutagenicity, Reproduction and Teratology

None conducted.

BIBLIOGRAPHY

1. Davis SD, Sarff LD, Hyndiuk RA. Corticosteroids in experimentally induced pseudomonas keratitis. Arch Ophthal 1978; 96: 126.

2. Kupferman A and Leibowitz HM. Topically applied steroid in corneal disease. V. Dexamethasone alcohol. Arch Ophthalmol 1974; 92: 326-330.

3. Leibowitz HM and Kupferman A. Pharmacology of topically applied dexamethasone. Trans Am Acad Oph Otol 1974; 78: 856.

4. Leibowitz HM and Kupferman A. Bioavailability and therapeutic effectiveness of topically administered corticosteroids. By invitation, Boston MA. Trans Am Acad Oph Otol 1975; 79.

5. Leibowitz HM and Kupferman A. Drug interaction in the eye. Concurrent corticosteroid - antibiotic therapy for inflammatory keratitis. Arch Ophthalmol 1977; 95: 682.

6. Leibowitz HM and Kupferman A. Topically administered corticosteroids. Effect on antibiotic treated keratitis. Arch Ophthalmol 1980; 98: 1287.

7. Locatcher-Khorazo D, and Seegal BC. Microbiology of the eye. CV Mosby Co St Louis, 1977.

8. Maxwell E, and Aijian KM. Maxitrol suspension and ointment; clinical evaluation of two new antibiotic-steroid preparations. Current Therapeutic Research 1964; 6: 130-133.

9. Neu, H.C. Tobramycin: an overview. J. Infect. Dis. 1976; 134: 513-519.