

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **TOBRADEX**[®]

Tobramycin and Dexamethasone Ophthalmic Suspension, USP
0.3% / 0.1% w/v

Tobramycin and Dexamethasone Ophthalmic Ointment, USP
0.3% / 0.1% w/w

Antibacterial and Corticosteroid

Novartis Pharmaceuticals Canada Inc.
385 Bouchard Blvd.
Dorval, Quebec
H9S 1A9
www.novartis.ca

Date of Revision:
June 1, 2018

Submission Control No: 214254

TOBRADEX is a registered trademark

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....3
SUMMARY PRODUCT INFORMATION3
INDICATIONS AND CLINICAL USE.....3
CONTRAINDICATIONS4
WARNINGS AND PRECAUTIONS.....4
ADVERSE REACTIONS.....7
DRUG INTERACTIONS8
DOSAGE AND ADMINISTRATION8
OVERDOSAGE9
ACTION AND CLINICAL PHARMACOLOGY9
STORAGE AND STABILITY.....9
DOSAGE FORMS, COMPOSITION AND PACKAGING9

PART II: SCIENTIFIC INFORMATION11
PHARMACEUTICAL INFORMATION.....11
CLINICAL TRIALS12
MICROBIOLOGY12
TOXICOLOGY16
REFERENCES18

PART III: PATIENT MEDICATION INFORMATION19

PART III: PATIENT MEDICATION INFORMATION25

Pr **TOBRADEX**[®]

Tobramycin and Dexamethasone Ophthalmic Suspension, USP
Tobramycin and Dexamethasone Ophthalmic Ointment, USP

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Topical ophthalmic	Suspension/ tobramycin 0.3% w/v and dexamethasone 0.1% w/v	Benzalkonium chloride as preservative. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>
	Ointment/ tobramycin 0.3% w/w and dexamethasone 0.1% w/w	Chlorobutanol as preservative. <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

TOBRADEX[®] (tobramycin and dexamethasone ophthalmic suspension and ointment) is indicated 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 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, thermal burns or penetration of foreign bodies.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of TOBRADEX and other antibacterial drugs, TOBRADEX should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria (See **MICROBIOLOGY**).

Pediatrics (< 18 years of age):

The safety and effectiveness of TOBRADEX have not been established in pediatric patients.

CONTRAINDICATIONS

TOBRADEX is contraindicated in:

- Patients who are hypersensitive to tobramycin, dexamethasone or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Patients with known or suspected hypersensitivity to other aminoglycosides. Partial cross-allergenicity to other aminoglycosides has been established.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral diseases of the cornea and conjunctiva.
- Fungal diseases of the eye or untreated parasitic eye infections.
- Mycobacterial ocular infections, including tuberculosis 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.
- After uncomplicated removal of a corneal foreign body.

WARNINGS AND PRECAUTIONS

General

FOR TOPICAL OCULAR USE ONLY. NOT FOR INJECTION INTO THE EYE.

NOT FOR OTIC USE.

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.

Patients should be advised to inform their physicians of any prior use of corticosteroids.

Sensitivity to topically applied aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalized reactions, such as erythema, itching, urticaria, skin rash, anaphylaxis, anaphylactoid reactions or bulbous reactions. If hypersensitivity develops during use of TOBRADEX, treatment should be discontinued.

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.

If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration. Serious adverse reactions, including neurotoxicity, ototoxicity and nephrotoxicity, have occurred in patients receiving systemic aminoglycoside therapy.

Infections:

Prolonged use of corticosteroids may suppress the host response, and aid in the establishment of secondary ocular bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection.

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. If fungal infection occurs, corticosteroid therapy should be discontinued.

Delayed Healing:

Topical ophthalmic corticosteroids may slow corneal wound healing.

Concomitant use of topical ophthalmic corticosteroids and topical NSAIDs may increase the potential for, and severity of, healing problems (see **DRUG INTERACTIONS**).

Driving and Using Machinery:

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

Susceptibility/Resistance**Development of Drug Resistant Bacteria:**

Prescribing TOBRADEX in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and risks the development of drug-resistant bacteria.

Potential for Microbial Overgrowth:

Prolonged use of antibacterials such as tobramycin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

Endocrine and Metabolism

Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ophthalmic dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat) (see **DRUG INTERACTIONS**). In these cases, treatment should not be discontinued abruptly, but progressively tapered. The combination of CYP3A4 inhibitors with TOBRADEX should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

Ophthalmologic

Prolonged or intensive use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision, and posterior subcapsular cataract formation. This risk is higher in patients with diabetes. In patients with diseases causing thinning of the cornea or sclera, perforation has been

known to occur with the use of topical corticosteroids. If treatment exceeds 9 days, intraocular pressure should be routinely and frequently monitored.

Contact lens wear is not recommended during treatment of ocular inflammation or infection. TOBRADEX suspension contains the preservative benzalkonium chloride, which may cause eye irritation and is known to bind to, and discolour, soft contact lenses. Avoid contact of TOBRADEX suspension with soft contact lenses. In the event patients are allowed to wear contact lenses, they must be instructed to remove contact lenses prior to application of TOBRADEX suspension and wait at least 15 minutes before re-insertion.

Sexual Function/Reproduction

Studies have not been performed to evaluate the effect of topical ocular administration of TOBRADEX on human fertility.

Special Populations

Pregnant Women:

There are no adequate and well-controlled studies with TOBRADEX in pregnant women. Studies in animals have shown reproductive toxicity after systemic administration of dexamethasone and tobramycin (see **TOXICOLOGY, Reproduction and Teratology**).

Tobramycin does cross the placenta into the fetus after intravenous dosing in pregnant women. Tobramycin is not expected to cause ototoxicity from *in utero* exposure. Prolonged or repeated corticosteroid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation.

TOBRADEX should be given to a pregnant woman only if the potential benefit to the mother outweighs the potential risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Nursing Women: It is not known whether topical TOBRADEX therapy results in tobramycin or dexamethasone excretion in human milk. Tobramycin is excreted in human milk after systemic absorption. No data is available on the passage of dexamethasone into human breast milk, but the molecular weight of dexamethasone is small enough to allow for transfer. Systemic corticosteroids could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects.

Because many drugs are excreted in human milk, a decision should be made either to discontinue breast-feeding or discontinue/abstain from TOBRADEX therapy, taking into account the importance of TOBRADEX therapy to the mother and the potential risk to the infant.

Pediatrics (< 18 years of age):

The safety and effectiveness of TOBRADEX have not been established in children. Pediatric patients are at a greater risk for corticosteroid-induced ocular hypertension, and it may occur earlier in children than in adults. Pediatric patients are also at a greater risk for developing Cushing's syndrome and/or adrenal suppression associated with intensive or long-term

continuous therapy with dexamethasone. TOBRADEX is not indicated for use in pediatric patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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.

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.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

In safety evaluations of TOBRADEX suspension and ointment involving 40 healthy volunteers, 10 to 25% of subjects experienced a 5-7 mmHg rise in IOP (see **CLINICAL TRIALS**).

Post-Market Adverse Drug Reactions

Additional adverse reactions identified through spontaneous reporting and subsequent clinical trials are listed below. Reliable estimates of the frequencies of spontaneous reactions cannot be determined because they are reported voluntarily from a population of uncertain size.

Eye disorders: erythema of eyelid, eyelid edema, lacrimation increased, mydriasis, dry eye, eye allergy, eye irritation, eye pain, eye pruritus, keratitis, ocular discomfort, ocular hyperemia, vision blurred;

Gastrointestinal disorders: abdominal discomfort, nausea, dysgeusia;

Immune system disorders: anaphylactic reaction, hypersensitivity;

Nervous system disorders: dizziness, headache;

Skin and subcutaneous tissue disorders: erythema multiforme, pruritus, rash, swelling face.

DRUG INTERACTIONS

Overview

No specific drug interaction studies have been performed with TOBRADEX.

Drug-Drug Interactions

Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for, and severity of, healing problems.

CYP3A4 inhibitors including ritonavir and cobicistat may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome (see **WARNINGS AND PRECAUTIONS, Endocrine and Metabolism**).

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

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.

Each drop (approximately 0.037 mL) of TOBRADEX suspension contains 111 mcg tobramycin and 37 mcg dexamethasone.

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.

Each one-half inch ribbon (approximately 33 mg) contains 0.099 mcg tobramycin and 0.033 mcg dexamethasone.

Administration

Suspension:

Shake well before use. After cap is removed: if tamper evident snap collar is loose, remove before using product.

Suspension and Ointment:

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

OVERDOSAGE

Overdosage in the use of topical ophthalmic preparations is a remote possibility. An ocular overdose may be flushed from the eye(s) with warm water.

Accidental ingestion of the contents of one bottle (5 mL size) or tube (3.5 g size) would result in ingestion of up to 15 mg tobramycin and 5 mg dexamethasone. Tobramycin is poorly absorbed from the gastrointestinal tract.

Discontinue medication when heavy or protracted use is suspected.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

STORAGE AND STABILITY

Store TOBRADEX Suspension in an upright position at room temperature.

Store TOBRADEX Ointment at 2°C - 25°C.

Keep out of the reach and sight of children.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Suspension:

TOBRADEX Suspension is a sterile, isotonic aqueous suspension containing:

Actives: tobramycin 0.3% w/v (3 mg/mL) and dexamethasone 0.1% w/v (1 mg/mL)

Preservative: benzalkonium chloride 0.01% w/v

Inactives: tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sodium hydroxide and/or sulfuric acid (to adjust pH) and purified water.

TOBRADEX Suspension is available as a sterile ophthalmic suspension in DROP-TAINER* dispensers of 5 mL. Shake well before use. Tamper evidence is provided by a closure with an extended skirt that locks to the bottle finish on application and breaks away from the closure on opening. After cap is removed: if tamper evident snap collar is loose, remove before using product.

Ointment:

TOBRADEX Ointment is a sterile ophthalmic ointment containing:

Actives: tobramycin 0.3% w/w (3 mg/g) and dexamethasone 0.1% w/w (1 mg/g)

Preservative: chlorobutanol 0.5% w/w

Inactives: mineral oil and petrolatum base.

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

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

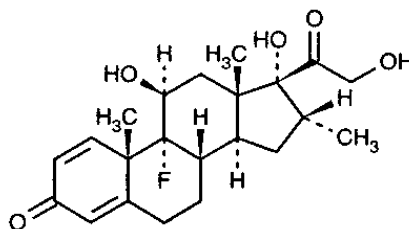
Drug Substance: Dexamethasone

Proper name: Dexamethasone

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

Molecular formula and molecular mass: C₂₂H₂₉FO₅; 392.47

Structural formula:



Physicochemical properties: 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 250°C with decomposition.

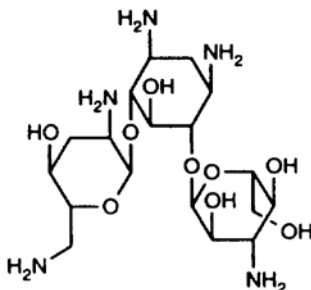
Drug Substance: Tobramycin

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

Molecular formula and molecular mass: C₁₈H₃₇N₅O₉; 467.54

Structural formula:



Physicochemical properties: 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.

CLINICAL TRIALS

Safety evaluations of Tobramycin-Dexamethasone Ophthalmic Suspension and Tobramycin-Dexamethasone Ophthalmic Ointment, USP, 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.

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.

Incidence of Microorganisms Cultured from Conjunctivas and Eyelid Margins*

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

	# 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
<i>Citrobacter sp.</i>	167		1	5	19	19	73	93	98	98	99
<i>Enterobacter sp.</i>	1126	1	4	15	36	39	81	91	97	99	99
<i>Escherichia coli</i>	2117		1	4	18	21	58	78	92	97	98
<i>Herellea</i>	206		4	8	25	26	76	91	97	99	100
<i>Klebsiella sp.</i>	1244	3	5	20	47	50	86	94	97	99	99
<i>Klebsiella - Enterobacter</i>	721		3	22	48	54	83	94	97	98	99
<i>Paracolons</i>	113			2	4	4	12	28	51	68	81
<i>Proteus mirabilis</i> (indole -)	1675			1	5	8	37	60	81	96	99
<i>Proteus sp.</i> (indole +)	1213		2	4	16	20	51	71	83	92	96
<i>Pseudomonas</i>	2880	6	18	40	63	70	91	96	97	98	99
<i>Pseudomonas</i> (gentamicin resistant)	153		12	18	27	30	35	46	59	71	80
<i>Salmonella sp.</i>	123			2	13	13	42	70	85	94	96
<i>Serratia sp.</i>	546				3	5	28	53	73	88	94
<i>Shigella sp.</i>	194				2	3	75	96	98	100	
<i>Staphylococcus aureus</i>	2013	11	28	42	70	73	87	93	96	99	99
<i>Streptococcus faecalis</i>	448			1	2	2	3	4	14	38	61
<i>Streptococcus pyogenes</i>	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 and Mutagenicity

None conducted.

Reproduction and Teratology

Corticosteroids have been shown to be teratogenic in animal studies. Dexamethasone animal studies resulted in reproductive and developmental abnormalities, including fetal abortions, cleft palate, CNS effects, brain defects, and heart defects following high dose systemic administration. 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 (equivalent to human doses of 16 and 32 mg/kg/day) and have revealed no evidence of impaired fertility or harm to the fetus.

REFERENCES

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.

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

Pr **TOBRADEX**[®]

Tobramycin and Dexamethasone Ophthalmic Suspension, USP

Read this carefully before you start taking **TOBRADEX**[®] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TOBRADEX**.

What is TOBRADEX used for?

TOBRADEX is used to treat inflammatory conditions of the eye where there is or may also be an eye infection.

Some of the conditions TOBRADEX may be used to treat include:

- Chronic inflammation of the uvea (a structure of the eye, including the iris i.e. the coloured part of the eye).
- Eye injuries caused by chemicals, radiation or heat burns.
- Eye injuries caused by foreign objects.

Antibacterial drugs like TOBRADEX treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, TOBRADEX should be used exactly as directed. Misuse or overuse of TOBRADEX could lead to the growth of bacteria that will not be killed by TOBRADEX (resistance). This means that TOBRADEX may not work for you in the future. Do not share your medicine.

How does TOBRADEX work?

TOBRADEX contains:

- Dexamethasone, a corticosteroid.
- Tobramycin, an aminoglycoside antibiotic.

Dexamethasone blocks some substances that inflame the body. Tobramycin blocks bacterial growth and reduces infections. Together, they treat the eye.

What are the ingredients in TOBRADEX?

Medicinal ingredients: tobramycin 0.3% w/v and dexamethasone 0.1% w/v

Non-medicinal ingredients:

Preservative: benzalkonium chloride

Others: edetate disodium, hydroxyethyl cellulose, sodium chloride, sodium hydroxide and/or sulfuric acid (to adjust pH), sodium sulfate, tyloxapol, and purified water.

TOBRADEX comes in the following dosage forms:

Eye drop suspension and eye ointment

Do not use TOBRADEX if you:

- Are allergic (*hypersensitive*) to tobramycin, dexamethasone or any of the other

ingredients in TOBRADEX suspension (see **What are the ingredients in TOBRADEX?**).

- Are allergic to other aminoglycoside antibiotics.
- Have herpes simplex keratitis (inflamed cornea of the eye caused by the herpes simplex virus).
- Have smallpox, chickenpox or any other viral infection of the eye.
- Have a fungal infection of the eye.
- Have a parasitic infection of the eye.
- Have a mycobacterial infection of the eye, including tuberculosis.
- Have an active untreated eye infection.
- Recently had a simple removal of an object from the eye.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TOBRADEX. Talk about any health conditions or problems you may have, including if you:

- Have used other corticosteroids before in the past.
- Develop an allergic reaction. Signs may include skin redness, itching and rash. You should stop taking TOBRADEX.
- Are taking another aminoglycoside antibiotic.
- Develop an eye infection or your infection gets worse. You should stop taking TOBRADEX.
- Have problems with your metabolism. Talk to your doctor if you experience swelling and weight gain around the trunk and in the face as these are usually the first signs of problems with your metabolism. This risk is especially important in patients treated with medicines containing ritonavir or cobicistat, medicines used in the treatment of HIV.
- Are taking a nonsteroidal anti-inflammatory drug (NSAID). Taking TOBRADEX and an NSAID at the same time may slow healing of the eye.
- Have diabetes. You may be at a higher risk of developing increased pressure in the eyes, vision problems or cataracts.
- Have a disease causing thinning of the eye. Small tears (*perforations*) have occurred.
- Wear contact lenses. Contact lens wear is not recommended during treatment of eye inflammation or an eye infection.
- Are pregnant, may be pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed.
- Are under 18 years of age. TOBRADEX has not been tested in children under 18 years of age.

Other warnings you should know about:

Taking TOBRADEX for a long time increases the risk of developing:

- High eye pressure.
- Glaucoma.
- Vision problems.
- Cataracts.
- An eye infection.
- Problems with your metabolism. Talk to your doctor if you experience swelling and

weight gain around the trunk and in the face as these are usually the first manifestations of the syndrome. These risks are especially important in patients treated with medicines containing ritonavir or cobicistat.

Your doctor should check your eye pressure regularly.

TOBRADEX contains the preservative benzalkonium chloride. Benzalkonium chloride discolours soft contact lenses and may cause eye irritation. If you must wear contact lenses, remove them before applying TOBRADEX, Wait at least 15 minutes before putting your lenses back in.

Your vision may become blurry right after using TOBRADEX. Do not drive or use machines until your vision clears.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drug interaction studies have not been done with TOBRADEX.

The following may interact with TOBRADEX:

- Nonsteroidal anti-inflammatory drugs (NSAIDs).
- Ritonavir or cobicistat (medicine used in the treatment of HIV).

How to take TOBRADEX:

SHAKE WELL BEFORE USE.

After removing the cap: if the security snap collar is loose, remove it before using TOBRADEX.

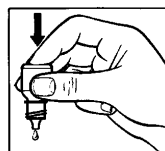
Usual adult dose:

1 to 2 drops in the conjunctival sac of the affected eye(s) every 4 hours. During the first 24 to 48 hours, 1 to 2 drops can be applied every 2 hours. As your condition improves, you may reduce the frequency as directed by your doctor or pharmacist.

How to use:



1



2

1. Wash your hands.
2. Get the TOBRADEX bottle and a mirror.
3. Shake well before use.
4. Hold the bottle, pointing down, between your thumb and fingers.
5. Tilt your head back.
6. Pull down your lower eyelid with a clean finger until there is a “v” pocket between your eyelid and your eye. The drop will go in here (picture 1).
7. Bring the bottle tip close to the eye. Do this in front of a mirror if it helps.
8. Do not touch your eye, eyelid, surrounding areas or other surfaces with the dropper, to

avoid contaminating the suspension.

9. Gently press on the base of the bottle to release one drop at a time. Do not squeeze the bottle. It is designed so that a gentle press on the bottom is all that it needs (picture 2).
10. If you miss, wipe up and try again.
11. Close the bottle immediately after use.

Overdose:

If you apply too much TOBRADEX, rinse it out with warm water. Do not apply more TOBRADEX until it is time for your next regular dose.

If you think you have taken too much TOBRADEX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take TOBRADEX, take it as soon as you remember. However, if it is close to your next regular dose, skip your missed dose and follow your regular schedule. Do not use a double dose to make up the missed dose.

What are possible side effects from using TOBRADEX?

These are not all the possible side effects you may feel when taking TOBRADEX. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Possible side effects include:

- Eyelid redness or swelling
- Increased tearing
- Pupil dilation
- Dry eye
- Eye allergy
- Eye irritation, pain, itching, inflammation, discomfort or redness
- Blurred vision
- Upset stomach, nausea or metallic taste in the mouth
- Dizziness
- Headache
- Abdominal discomfort
- Skin itching or rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Allergic reaction: swelling of the face, lips or tongue; difficulty breathing; hives; skin redness, serious skin reactions (erythema multiforme), itching or blisters			✓
Infection			✓
Increased eye pressure and/or glaucoma, vision problems, or cataracts		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.</p> <p>3 ways to report:</p> <ul style="list-style-type: none"> • Online at MedEffect; • By calling 1-866-234-2345 (toll-free); • By completing a Consumer Side Effect Reporting Form and sending it by: <ul style="list-style-type: none"> - Fax to 1-866-678-6789 (toll-free), or - Mail to: Canada Vigilance Program Health Canada, Postal Locator 1908C Ottawa, ON K1A 0K9 <p>Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.</p> <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>

Storage:

Store at room temperature in an upright position and tightly closed.

Keep out of reach and sight of children.

If you want more information about TOBRADEX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last Revised: June 1, 2018

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION**

Pr **TOBRADEX**[®]

Tobramycin and Dexamethasone Ophthalmic Ointment, USP

Read this carefully before you start taking **TOBRADEX**[®] and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **TOBRADEX**.

What is TOBRADEX used for?

TOBRADEX is used to treat inflammatory conditions of the eye where there is or may also be an eye infection.

Some of the conditions TOBRADEX may be used to treat include:

- Chronic inflammation of the uvea (a structure of the eye, including the iris i.e. the coloured part of the eye).
- Eye injuries caused by chemicals, radiation or heat burns.
- Eye injuries caused by foreign objects.

Antibacterial drugs like TOBRADEX treat only bacterial infections. They do not treat viral infections. Although you may feel better early in treatment, TOBRADEX should be used exactly as directed. Misuse or overuse of TOBRADEX could lead to the growth of bacteria that will not be killed by TOBRADEX (resistance). This means that TOBRADEX may not work for you in the future. Do not share your medicine.

How does TOBRADEX work?

TOBRADEX contains:

- Dexamethasone, a corticosteroid.
- Tobramycin, an aminoglycoside antibiotic.

Dexamethasone blocks some substances that inflame the body. Tobramycin blocks bacterial growth and reduces infections. Together, they treat the eye.

What are the ingredients in TOBRADEX?

Medicinal ingredients: tobramycin 0.3% w/w and dexamethasone 0.1% w/w

Non-medicinal ingredients:

Preservative: chlorobutanol

Others: mineral oil, petrolatum base

TOBRADEX comes in the following dosage forms:

Eye drop suspension and eye ointment

Do not use TOBRADEX if you:

- Are allergic (*hypersensitive*) to tobramycin, dexamethasone or any of the other ingredients in TOBRADEX suspension (see **What are the ingredients in**

TOBRADEX?).

- Are allergic to other aminoglycoside antibiotics.
- Have herpes simplex keratitis (inflamed cornea of the eye caused by the herpes simplex virus).
- Have smallpox, chickenpox or any other viral infection of the eye.
- Have a fungal infection of the eye.
- Have a parasitic infection of the eye.
- Have a mycobacterial infection of the eye, including tuberculosis.
- Have an active untreated eye infection.
- Recently had a simple removal of an object from the eye.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take TOBRADEX. Talk about any health conditions or problems you may have, including if you:

- Have used other corticosteroids before in the past.
- Develop an allergic reaction. Signs may include skin redness, itching and rash. You should stop taking TOBRADEX.
- Are taking another aminoglycoside antibiotic.
- Develop an eye infection or your infection gets worse. You should stop taking TOBRADEX.
- Have problems with your metabolism. Talk to your doctor if you experience swelling and weight gain around the trunk and in the face as these are usually the first signs of problems with your metabolism. This risk is especially important in patients treated with medicines containing ritonavir or cobicistat, medicines used in the treatment of HIV.
- Are taking a nonsteroidal anti-inflammatory drug (NSAID). Taking TOBRADEX and an NSAID at the same time may slow healing of the eye.
- Have diabetes. You may be at a higher risk of developing increased pressure in the eyes, vision problems or cataracts.
- Have a disease causing thinning of the eye. Small tears (*perforations*) have occurred.
- Wear contact lenses. Contact lens wear is not recommended during treatment of eye inflammation or an eye infection.
- Are pregnant, may be pregnant or planning to become pregnant.
- Are breastfeeding or planning to breastfeed.
- Are under 18 years of age. TOBRADEX has not been tested in children under 18 years of age.

Other warnings you should know about:

. Taking TOBRADEX for a long time increases the risk of developing:

- High eye pressure
- Glaucoma.
- Vision problems.
- Cataracts.
- An eye infection.
- Problems with your metabolism.

If you take TOBRADEX for a long time, your doctor should check your eye pressure regularly.

Your vision may become blurry right after using TOBRADEX. Do not drive or use machines until your vision clears.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Drug interaction studies have not been done with TOBRADEX.

The following may interact with TOBRADEX:

- Nonsteroidal anti-inflammatory drugs (NSAIDs).
- Ritonavir or cobicistat (medicines used in the treatment of HIV).

How to take TOBRADEX:

Usual adult dose:

Apply one-half inch ribbon into the conjunctival sac of the affected eye(s) up to 3 or 4 times a day. TOBRADEX ointment may be used with TOBRADEX suspension at bedtime.

How to use:



1. Wash your hands.
2. Tilt your head back.
3. Place a finger on your cheek just under your eye and gently pull down until a “v” pocket is formed between your eyeball and lower eyelid.
4. Place a small amount of TOBRADEX in the “v” pocket. Do **not** let the tip of the tube touch your eye, to avoid contaminating the ointment.
5. Look down before closing your eye.
6. Replace the cap of the tube.

Overdose:

If you apply too much TOBRADEX, rinse it out with warm water. Do not apply more TOBRADEX until it is time for your next regular dose.

If you think you have taken too much TOBRADEX, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take TOBRADEX, take it as soon as you remember. However, if it is close to your next regular dose, skip your missed dose and follow your regular schedule. Do not use a double dose to make up the missed dose.

What are possible side effects from using TOBRADEX?

These are not all the possible side effects you may feel when taking TOBRADEX. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

Possible side effects include:

- Eyelid redness or swelling
- Increased tearing
- Pupil dilation
- Dry eye
- Eye allergy
- Eye irritation, pain, itching, inflammation, discomfort or redness
- Blurred vision
- Upset stomach, nausea or metallic taste in the mouth
- Dizziness
- Headache
- Abdominal discomfort
- Skin itching or rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN Allergic reaction: swelling of the face, lips or tongue; difficulty breathing; hives; skin redness, serious skin reactions (erythema multiforme), itching or blisters			✓
Infection			✓
Increased eye pressure and/or glaucoma, vision problems, or cataracts		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 1908C
Ottawa, ON
K1A 0K9Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at 2°C-25°C.

Keep out of reach and sight of children.

If you want more information about TOBRADEX:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.novartis.ca, or by calling 1-800-363-8883.

This leaflet was prepared by Novartis Pharmaceuticals Canada Inc.

Last Revised: June 1, 2018