

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

TOBRADEX™ (tobramycin 0.3% and dexamethasone 0.1%) Ophthalmic Suspension
TOBRADEX™ (tobramycin 0.3% and dexamethasone 0.1%) Ophthalmic Ointment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tobradex Ophthalmic Suspension

Each mL of the drops contains tobramycin 3 mg and dexamethasone 1 mg.

Tobradex Eye Ointment

Each gram of the ointment contains tobramycin 3 mg and dexamethasone 1mg.

Excipient with known effect

Tobradex Ophthalmic Suspension

Benzalkonium chloride 0.01% as a preservative.

Tobradex Eye Ointment

Chlorobutanol 0.5% as a preservative.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tobradex Eye Drops

Eye drops, suspension.

Tobradex Eye Ointment

Ointment.

4. CLINICAL PARTICULARS

4.1. Therapeutic 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 conjunctivitides is accepted to obtain a diminution in oedema 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 medicine 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.

4.2. Dose and method of administration

Ophthalmic Suspension

Shake well before use.

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 Section 4.4. Special warnings and precautions for use.

Keep out of reach of children.

Gently closing the eyelid and nasolacrimal occlusion after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic side effects.

4.3. 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 or untreated parasitic eye infections.

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

Hypersensitivity to a component of these medications. Refer to Section 6.1 for a list of excipients.

4.4. Special warnings and precautions for use

NOT FOR INJECTION INTO THE EYE.

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, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. 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.

Caution should be exercised when prescribing Tobradex Ophthalmic Suspension and Ointment to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of their potential effect on neuromuscular function.

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 and frequently monitored even though it may be difficult in children and uncooperative patients. This is especially important in paediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. Tobradex

is not approved for use in paediatric patients. The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).

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 Section 4.5 Interactions with other medicinal products and other forms of interactions). In these cases, treatment should not be discontinued abruptly, but progressively tapered.

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. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

Visual Disturbance

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

General

Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection. 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.

Hepatic and Renal Impairment

Tobradex has not been studied in these patient populations.

Paediatric use

Safety and effectiveness in children have not been established.

Contact Lenses

Contact lenses 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. Avoid contact with soft contact lenses. In case patients are allowed to wear contact lenses, they must be instructed

to remove contact lenses prior to application of Tobradex and wait at least the 15 minutes before reinsertion.

4.5 Interactions with other medicinal products and other forms of interactions

Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

CYP3A4 inhibitors (including ritonavir and cobicistat) may increase systemic exposure resulting in increased risk of adrenal suppression/Cushing's syndrome. (See Section 4.4 Special Warnings and Precautions for Use). The combination 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.

4.6 Fertility, pregnancy and lactation

Pregnancy Category C

Tobradex Ophthalmic Suspension and Ointment should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

See Section 5.2. Pre-clinical safety studies for tobramycin and dexamethasone animal reproductive studies.

Breast-feeding

It is not known whether this medicine 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. A risk to the suckling child cannot be excluded.

Fertility

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

See Section 5.2. Pre-clinical safety studies for further information in animal fertility studies.

4.7 Effects on ability to drive or 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.

4.8 Undesirable effects

Adverse reactions have occurred with steroid/anti-infective combination medicines 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 a 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. eye allergy, vision blurred (see Section 4.4 Special Warnings and Precautions for Use), dry eye, foreign body sensation in eyes, ocular hyperaemia.

Not known: eyelid oedema, erythema of eyelid, mydriasis, lacrimation increased.

Nervous System Disorders

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

Not Known: dizziness, headache.

Immune System Disorders

Not Known: anaphylactic reaction, hypersensitivity.

Gastrointestinal Disorders

Not Known: nausea, abdominal discomfort.

Skin and subcutaneous tissue disorders

Not Known: rash, swelling face, pruritus, erythema multiforme.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting>.

4.9 Overdose

A topical overdose of Tobradex Ophthalmic Suspension or Ointment can be flushed from the eye(s) with lukewarm water.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON or 0800 764 766.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination. ATC code: S01C A01.

Mechanism of action

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 medicine 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.

Pharmacodynamic effects

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 aginacola*) 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.

Clinical efficacy and safety

Not available.

5.2 Pharmacokinetic properties

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 medicines. 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.

5.3 Preclinical safety data

Pregnancy

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. Studies in animals have shown reproductive toxicity after systemic administration of corticosteroids and tobramycin. There are no adequate and well controlled studies in pregnant women.

Fertility

No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at doses of 50 and 100 mg/kg/day.

Carcinogenicity and mutagenicity

No studies have been conducted to evaluate the carcinogenic or mutagenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ophthalmic Eye drops, suspension

Benzalkonium chloride
Tyloxapol
Disodium edetate
Sodium chloride
Cetyl hydroxyethylcellulose
Sodium sulfate
Sulfuric acid and/or sodium hydroxide (to adjust pH)
Purified water.

Ophthalmic Ointment

Chlorobutanol
Liquid paraffin
White soft paraffin.

6.2 Incompatibilities

Not known.

6.3 Shelf life

24 months.

6.4 Special precautions for storage

Ophthalmic Eye drops, suspension

Store below 25° C.

Do not freeze. Store container upright. Shake well before use.

Discard container 28 days after opening.

Ophthalmic Ointment

Store below 25° C.

Discard container 28 days after opening.

6.5 Nature and contents of container

Ophthalmic Eye drops, suspension

5 mL Drop-Tainer® dispenser

Ophthalmic Ointment

3.5 g tube

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket

Auckland 1149

New Zealand.

Free Phone: 0800 354 335

9. DATE OF FIRST APPROVAL

Ophthalmic Eye drops, suspension

15 December 1988

Ophthalmic Ointment

29 June 1992

10. DATE OF REVISION OF THE TEXT

23 July 2020

Summary Table of Changes

8 Sponsor	Update to Sponsor address
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