NOVARTIS

Tobradex Eye Drops

Each 1,0 ml suspension contains dexamethasone 1,0 mg and tobramycin 3,0 mg

Tobradex Eye Ointment

Each 1,0 g ointment contains dexamethasone 1,0 mg and tobramycin 3,0 mg

Professional Information

Document status:	Final
Release date:	26 October 2021

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

TOBRADEX* Eye Drops, suspension

TOBRADEX* Eye Ointment

2 QUALITIVE AND QUANTITIVE COMPOSITION

TOBRADEX Eye Drops contains 1 mg dexamethasone and 3 mg tobramycin per ml

Preservative: 0,01 % (*m/v)* Benzalkonium chloride

Excipients with known effect

Benzalkonium chloride (see section 4.4)

TOBRADEX Eye Ointment contains 1 mg dexamethasone and 3 mg tobramycin per gram

Preservative: 0,5 % (*m/m*) Chlorobutanol

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

TOBRADEX Eye Drops is a white to off-white sterile suspension. TOBRADEX Eye Ointment is a white to off-white sterile homogenous ointment.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

TOBRADEX Eye Drops and TOBRADEX Eye Ointment are indicated for the reduction of ocular inflammation and prophylaxis of infection due to susceptible organisms, following intraocular surgery.

4.2 Posology and method of administration

Posology

TOBRADEX Eye Drops:

- Instil one drop into the operative eye every four hours whilst awake for three days prior to surgery and one drop immediately upon conclusion of surgery.
- Beginning at the first dressing change one day following surgery, instil two drops every two hours whilst awake for two days.
- From post-operative day three, instil one drop into the eye four times a day for one week. Thereafter, instil one drop per day for ten days as maintenance therapy.

Not more than 20 ml should be prescribed initially and the prescription should not be repeated without further evaluation as outlined under section 4.4

TOBRADEX Eye Ointment

- Apply approximately a 1,5 cm ribbon ointment strip into the operative eye three times a day, three days prior to surgery. Apply a 1,5 cm ribbon ointment strip into the eye immediately upon completing surgery.
- Beginning at the first dressing change on day one following surgery, apply a 1,5 cm ribbon ointment strip three times daily for the first nine days following surgery.

- For maintenance therapy apply a 1,5 cm ribbon ointment strip per day from day ten and continue till day twenty.
- Not more than 7 g should be prescribed initially and the prescription should not be refilled without further evaluation as outlined in section 4.4
- If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart.
- Eye ointments should be administered last.

Method of administration

For ocular use.

TOBRADEX Eye Drops:

- SHAKE WELL BEFORE USE.
- STORE UPRIGHT.
- When removing the cap for the first time, remove and discard the snap collar, in order to prevent the snap collar from falling into the patient's eye.
- To prevent contamination of the dropper tip and suspension, care should be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle.
- Keep the bottle tightly closed when not in use.
- Gently closing the eyelid (s) and nasolacrimal occlusion for at least 1 minute 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.
- In case of concomitant therapy with other topical ophthalmic medicinal products, an interval of 5 minutes should be allowed between successive applications.

- Eye ointments should be administered last.

4.3 Contraindications

- Hypersensitivity to dexamethasone, tobramycin or any component of TOBRADEX listed in section 6.1
- Herpes simplex keratitis (dendritic keratitis), vaccinia varicella and ~~many~~ other viral diseases of the cornea and conjunctiva (except herpes zoster keratitis).
- Mycobacterial infection of the eye.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- The use of TOBRADEX is always contraindicated after uncomplicated removal of a corneal foreign body.
- TOBRADEX should not be used in the treatment of mechanical lacerations and abrasions of the eye.
- TOBRADEX will delay healing and promote the development and spread of infection.

4.4 Special warnings and precautions for use

- Prolonged use of TOBRADEX may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, defects in visual acuity and fields of vision and posterior sub capsular cataract formation. Family or personal history of glaucoma has a higher risk of corticosteroid-induced rise in intraocular pressure.
- A steroid glaucoma may be produced after a week or more of treatment in patients predisposed to chronic simple glaucoma.
- Topical corticosteroid containing therapy such as TOBRADEX frequently induces intraocular hypertension in normal eyes and increases pressure in eyes with initially elevated pressure.

Glaucoma is not always reversible on cessation of corticosteroid containing treatment such as TOBRADEX.

- The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes)
- IF TOBRADEX IS USED FOR 10 DAYS OR LONGER, INTRAOCULAR PRESSURE SHOULD BE ROUTINELY MONITORED (WEEKLY FOR GLAUCOMA PATIENTS) 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.
- The local administration of corticosteroids containing medicines such as TOBRADEX to the eyes of patients with bacterial, viral and fungal conjunctivitis or parasitic infections may mask evidence of progression of infection until sight is lost.
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of the topical medicines containing steroids such as TOBRADEX.
- Corneal ulceration may be aggravated when TOBRADEX is applied. It is important that corneal ulcers are correctly diagnosed before treatment with TOBRADEX is initiated.
- Concomitant use of topical NSAIDs and topical medicines containing steroids such as TOBRADEX may delay corneal healing.
- TOBRADEX may reduce resistance to and aid in the development of bacterial, viral or fungal infections and mask the clinical signs of infection.
- *Secondary infection:* Prolonged use of corticosteroids containing medicines such as TOBRADEX may suppress the host response and thus increase the hazard of secondary ocular infection.

- Medicines containing corticosteroids such as TOBRADEX may cause progression of the dendritic keratitis (herpes simplex infection), resulting in irreversible clouding of the cornea.
- In acute purulent conditions of the eye, corticosteroids containing medicines such as TOBRADEX may mask progression of infection until sight is lost or enhance existing infection.
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of corticosteroids containing medicines such as TOBRADEX. The possibility of fungal invasion must be considered in any persistent corneal ulceration where TOBRADEX treatment has been used. If fungal infection occurs, corticosteroid therapy should be discontinued.
- TOBRADEX should not be used for injection into the eye.
- Hypersensitivity to topically administered 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 bullous reactions. If hypersensitivity develops during the use of TOBRADEX, treatment should be discontinued
- Cross-hypersensitivity to other aminoglycosides can occur and the possibility that patients who become sensitised 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. Caution is advised when used concomitantly.
- Caution should be exercised when prescribing TOBRADEX Eye Drops/Eye 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.

- Contact lens wear is not recommended during treatment of an ocular inflammation or infection.
- 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)*. In these cases, treatment should not be discontinued abruptly, but progressively tapered.

Excipients with known effect

TOBRADEX Eye Drops contains benzalkonium chloride which may cause eye irritation, especially if you have dry eyes or disorders of the cornea 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 Eye Drops and wait at least 15 minutes before reinsertion. As the possibility of adverse effects on the corneal permeability and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations such as TOBRADEX Eye Drops cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication such as TOBRADEX over an extended period in patients with extensive ocular surface disease.

4.5 Interaction with other medicines and other forms of Interaction

- No specific interaction studies were performed.
- Concomitant use of topical steroids and topical NSAIDs may delay corneal healing.
- CYP3A4 inhibitors (including ritonavir and cobicistat) may: decrease dexamethasone clearance resulting in increased effects and of adrenal suppression/Cushing's syndrome *(see section 4.4)*. 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

Women of childbearing potential/ Contraception in males and females

No information available.

Pregnancy

The safety of TOBRADEX during pregnancy has not yet been established. Tobradex is not recommended during pregnancy.

Breastfeeding

It is not known whether TOBRADEX Eye Drops or TOBRADEX Eye Ointment is excreted in human milk; therefore, caution should be observed when it is administered to mothers breastfeeding their infants.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

Temporarily blurred vision or other visual disturbances with use of TOBRADEX may affect mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision. If blurred vision occurs with application, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

a. Summary of the safety profile

The following adverse reactions have been reported during clinical trials with TOBRADEX and are classified according to the subsequent convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to<1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

System Organ Classification	**Undesirable effect**		
	Common	Uncommon	Rare
Eye disorders:		intraocular pressure increased, eye pain, eye pruritus, ocular discomfort, eye irritation	keratitis, eye allergy, vision blurred, dry eye, ocular hyperaemia

Gastrointestinal disorders:			dysgeusia

Adverse reactions identified from post-marketing surveillance include the following.

Frequencies cannot be estimated from the available data.

System Organ Classification	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
Immune system disorders:			anaphylactic reaction, Hypersensitivity,
Nervous system disorders:			dizziness, headache
Eye disorders:			eyelid oedema, erythema of eyelid, mydriasis, lacrimation increased
Gastrointestinal disorders:			nausea, abdominal discomfort
Skin and subcutaneous tissue disorders:			erythema multiforme, rash, swelling face, pruritus
Endocrine disorders			Cushing's syndrome, adrenal suppression (see section 4.4)

Side effects have occurred with steroid/antibiotic combination medicines, which can usually be attributed either to the steroid component or to the antibiotic component.

The following adverse effects may occur following use of topical ophthalmic dexamethasone:

Body System	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
Infections and Infestations:		eye infection (exacerbation or secondary)	
Endocrine disorders:		Cushing's syndrome, adrenal suppression	
Eye disorders:		reduced visual acuity, glaucoma, visual field defects, subcapsular cataract, increased ocular pressure	
General disorders and administrative site conditions:		impaired healing	
Injury and poisoning:		optic nerve injury, corneal perforation	

*The following adverse effects have been reported following use of topical ophthalmic tobramycin**:***

Doses recommended for ocular administration are significantly lower than those used systemically, and systemic effects are unlikely with TOBRADEX.

Body System	**Undesirable effect**		
	Frequent	Less frequent	Frequency not known
Infections and Infestations:		eye infection (secondary)	
Immune system disorders:		hypersensitivity (local)	
Eye disorders:		eye irritation (burning and stinging upon instillation), ocular hyperaemia, blurred vision, eyelid oedema, eyelid pruritus, eye pain (periorbital)	
Skin and subcutaneous tissue disorders:		erythema (periorbital)	

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 to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications: https://www.sahpra.org.za/

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8*).

Discontinue use immediately.

Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.15.3. Combination antibiotics and corticosteroids.

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic group: Anti-inflammatory agents and anti-infectives in combination, corticosteroids and anti-infectives in combination.

ATC code: S01C A01

Dexamethasone is a potent corticosteroid with an anti-inflammatory potency approximately 25 times that of hydrocortisone. Therapeutic concentrations are attained in the aqueous humour of the eye following application into the conjunctival sac. Topical ophthalmic steroids suppress inflammation of the outer eye and anterior segment including the lids, conjunctiva, cornea, iris and ciliary body.

Tobramycin is an aminoglycoside antibiotic, active against most Gram- negative micro-organisms.

Tobramycin acts against susceptible bacteria to inhibit protein synthesis and is bactericidal.

Inherently resistant species

Aerobic Gram-positive microorganisms

Enterococcus species

Staphylococcus aureus methicillin-resistant

Staphylococcus epidermidis methicillin-resistant

Streptococcus pneumoniae

Streptococcus species

Aerobic Gram-negative micro-organisms

Burkholderia cepacia

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Strict anaerobic bacteria

Others

Chlamydia species

Mycoplasma species

Rickettsia species

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TOBRADEX Eye Drops

Disodium edetate, hydroxyethylcellulose, sodium chloride, sodium sulphate anhydrous, tyloxapol, purified water.

Sulphuric acid or sodium hydroxide (pH adjusters).

Benzalkonium chloride (preservative).

TOBRADEX Eye Ointment

Liquid paraffin, white soft paraffin.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

After the first opening of the container, the sterile ophthalmic suspension should not be used longer than four weeks.

6.4 Special precautions for storage

Store at or below 25 °C.

Store in the original package/container.

6.5 Nature and contents of container

TOBRADEX Eye Drops: Low density polyethylene plastic bottle containing 5 ml.

TOBRADEX Eye Ointment: An eye ointment tube containing 3,5 g.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

Magwa Crescent West

Waterfall City

Jukskei View 2090

8 REGISTRATION NUMBER(S)

TOBRADEX* Eye Drops: X/15.3/91

TOBRADEX* Eye Ointment: X/15.3/92

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2017

10 DATE OF REVISION OF TEXT

26 October 2021