SCHEDULING STATUS

S4

PROPRIETARY NAME (AND DOSAGE FORM)

TOBRADEX* Eye Drops, suspension

TOBRADEX* Eye Ointment

COMPOSITION

TOBRADEX Eye Drops contains 1 mg dexamethasone and 3 mg tobramycin per ml, with 0,01 % (m/v) benzalkonium chloride as preservative.

Excipients: disodium edetate, hydroxy ethyl cellulose, sodium chloride, sodium sulphate anhydrous, tyloxapol and purified water. Small amounts of sulphuric acid or sodium hydroxide are added to adjust pH.

TOBRADEX Eye Ointment contains 1 mg dexamethasone and 3 mg tobramycin per gram, with 0,5 % (m/m) chlorobutanol as preservative.

Excipients: liquid paraffin and white soft paraffin.

PHARMACOLOGICAL CLASSIFICATION

A.15.3. Combination antibiotics and corticosteroids.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

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 s*pecies

Rickettsia species

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.

CONTRA-INDICATIONS

Hypersensitivity to dexamethasone, tobramycin or any component of **TOBRADEX**.

Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and many other viral diseases of the cornea and conjunctiva. Mycobacterial infection of the eye. Fungal diseases of ocular structures The use of **TOBRADEX** is always contra-indicated 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.

WARNINGS AND SPECIAL PRECAUTIONS

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 subcapsular 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 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 treatment such as **TOBRADEX**.

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 such as **TOBRADEX** to the eyes of patients with bacterial, viral and fungal conjunctivitis 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 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 steroids such as **TOBRADEX** and topical NSAIDs 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 such as **TOBRADEX** may suppress the host response and thus increase the hazard of secondary ocular infection.

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 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 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.

Hyper-sensitivity to topically applied aminoglycosides may occur in some patients.

If a hyper-sensitivity reaction does occur, discontinue use of **TOBRADEX**.

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.

Contact lens wear is not recommended during treatment of an ocular inflammation or infection.

Effects on ability to drive and use machines

Temporarily blurred vision or other visual disturbances with use of **TOBRADEX** may affect the ability to drive or use machines. If blurred vision occurs with application, the patient must wait until the vision clears before driving or using machinery.

TOBRADEX Eye Drops 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 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.

INTERACTIONS

No specific interaction studies were performed.

Concomitant use of topical steroids and topical NSAIDs may delay corneal healing.

PREGNANCY AND LACTATION

Pregnancy

The safety of **TOBRADEX** during pregnancy has not yet been established.

Lactation

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 breast-feeding their infants.

DOSAGE AND DIRECTIONS FOR USE

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 SPECIAL PRECAUTIONS.

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.

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 **WARNINGS & SPECIAL PRECAUTIONS**.

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.

SIDE EFFECTS

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.

System Organ Classification	**Adverse reactions**
Eye disorders	*Uncommon:* intraocular pressure increased, eye pain, eye pruritus, ocular discomfort, eye irritation *Rare*: keratitis, eye allergy, vision blurred, dry eye, ocular hyperaemia
Gastro-intestinal disorders	*Rare:* dysgeusia

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

Frequencies cannot be estimated from the available data.

System organ classification	**Adverse reactions**
Immune system disorders	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	rash, swelling face, pruritus

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

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

Infections and Infestations

Less frequent: eye infection (exacerbation or secondary).

Endocrine Disorders

Less frequent: adrenal suppression.

Eye Disorders

Less frequent: reduced visual acuity, glaucoma, visual field defects, subcapsular cataract, increased ocular pressure.

General Disorders and Administration Site Conditions

Less frequent: impaired healing.

Injury, Poisoning and Procedural Complications

Less frequent: optic nerve injury, corneal perforation.

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

Infections and Infestations

Less frequent: eye infection (secondary)

Immune System Disorders

Less frequent: hypersensitivity (local)

Eye Disorders

Less frequent: eye irritation (burning and stinging upon instillation), ocular hyperaemia, blurred vision, eyelid oedema, eyelid pruritus, eye pain (periorbital).

Skin and Subcutaneous Tissue Disorders

Less frequent: erythema (periorbital).

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

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See the Side-effects above. Discontinue use immediately.

Treatment is symptomatic and supportive.

IDENTIFICATION

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

TOBRADEX Eye Ointment is a white to off-white sterile homogenous

ointment.

PRESENTATION

TOBRADEX Eye Drops: Low density polyethylene DROP-TAINER*

dispenser containing 5 ml.

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

STORAGE INSTRUCTIONS

Keep in cool place, below 25 °C.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

TOBRADEX* Eye Drops: X/15.3/91

TOBRADEX* Eye Ointment: X/15.3/92

NAME AND BUSINESS ADDRESS OF THE APPLICANT

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2090

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