Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

OCTUDEX (Eye drops, suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml eye drop contains:

Tobramycin 3,0 mg

Dexamethasone 1,0 mg

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

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Eye drops, White to off suspension filled in 5 ml plastic bottle with white colour cap.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

OCTUDEX is 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

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.

Method of administration

OCTUDEX is for ocular use only.

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 solution, care must 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

- *Hypers*ensitivity to dexamethasone, tobramycin or any component of **OCTUDEX** as listed in section 6.1.
- Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and many viral diseases of the cornea and conjunctiva (except herpes zoster keratitis).
- Mycobacterial infection of the eye caused by, but not limited to, acid-fast bacilli such as *Mycobacterium tuberculosis, Mycobacterium leprae*, or *Mycobacterium avium*.

- Fungal diseases of ocular structures or untreated parasitic eye infections
- The use of **OCTUDEX** is always contra-indicated after uncomplicated removal of a corneal foreign body.
- **OCTUDEX** should not be used in the treatment of mechanical lacerations and abrasions of the eye. **OCTUDEX** will delay healing and promote the development and spread of infection.
- Untreated purulent infection of the eye.

4.4. Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Prolonged use of **OCTUDEX** 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 containing therapy such as **OCTUDEX** 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 **OCTUDEX**.

IF **OCTUDEX** 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 **OCTUDEX** 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 (see section 4.3).

In those diseases causing thinning of the cornea or sclera, perforations have been reported with the use of the topical medicines containing steroids such as **OCTUDEX**.

Corneal ulceration may be aggravated when **OCTUDEX** is applied. It is important that corneal ulcers are correctly diagnosed before treatment with **OCTUDEX** is initiated.

Concomitant use of topical medicines containing steroids such as **OCTUDEX** and topical NSAIDs may delay corneal healing. **OCTUDEX** 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 medicines containing such as **OCTUDEX** may suppress the host response and thus increase the hazard of secondary ocular infection.

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

Medicines containing corticosteroids such as **OCTUDEX** may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection. (see section 4.3)

Medicines containing corticosteroids 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 **OCTUDEX** may mask progression of infection until sight is lost or enhance existing infection

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Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of corticosteroids containing medicines such as **OCTUDEX**. The possibility of fungal

invasion must be considered in any persistent corneal ulceration where **OCTUDEX** treatment has been used.

If fungal infection occurs, corticosteroid therapy should be discontinued.

OCTUDEX should not be used for injection into the eye.

Hyper-sensitivity to topically applied aminoglycosides may occur in some patients. Severity of hypersensitivity reactions may vary from local effects to generalised reactions such as erythema, itching, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If a hyper-sensitivity reaction does occur, discontinue use of **OCTUDEX**.

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 been reported in patients receiving systemic

aminoglycoside therapy. Caution is advised when used concomitantly with systemic aminoglycosides.

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

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.

It is advisable that the intraocular pressure be checked frequently. This is especially important in paediatric patients receiving dexamethasone-containing medicines, as the risk of steroid-induced ocular hypertension may be greater in children below 6 years of age and may occur earlier than a steroid response in adults. The frequency and duration of treatment should

be carefully considered, and the intraocular pressure should be monitored from the outset of treatment, recognising the risk for earlier and greater steroid-induced intraocular pressure increases in the 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 ocular 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 be progressively discontinued. Caution should be exercised when prescribing **OCTUDEX** Eye Drops 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.

OCTUDEX contains benzalkonium chloride(as preservative) 0,01 *% w/v* which may cause eye irritation, especially if you have dry eyes or disorders of the cornea and it is known to discolour soft contact lenses .Avoid contact with soft contact lenses.

If patients are allowed to wear contact lenses, they must be instructed to remove lenses prior to application of **OCTUDEX** 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 **OCTUDEX**, cannot be excluded, regular ophthalmological examination is required.

Caution should be exercised in the use of benzalkonium chloride preserved topical medicine such as **OCTUDEX** 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 reported with topical ocular dosing.

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

Dexamethasone is metabolised via cytochrome P450 3A4 (CYP3A4).

CYP3A4 inhibitors (including ritonavir and cobicistat); may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided.

4.6. Fertility, pregnancy and lactation

Pregnancy

OCTUDEX is not recommended during pregnancy.

The safety of tobramycin and dexamethasone during pregnancy has not yet been reported. There are no or limited amount of reported data from the topical ocular use of tobramycin and dexamethasone in pregnant women. 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 corticoid use during pregnancy has been reported to be associated with an increased risk of intra-uterine growth retardation. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism.

Studies in animals have reported reproductive toxicity after systemic administration of tobramycin and dexamethasone. These effects were reported at exposures considered

sufficiently in excess of the maximum human ocular dosage delivered from the maternal use of the product (see section 5.3).

Breastfeeding

Tobramycin is reported to be excreted in human milk after systemic administration. It is not known whether dexamethasone and tobramycin are excreted in human milk following topical ocular administration. Therefore, caution should be observed when **OCTUDEX** is administered to mothers breastfeeding their infants.

4.7. Effects on ability to drive and use machines

OCTUDEX may cause dizziness. Patients should be advised not to drive until they know how **OCTUDEX** affects them. Temporarily blurred vision or other visual disturbances with use of **OCTUDEX** 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.

4.8. Undesirable effects

No serious ophthalmic or systemic adverse reactions related to tobramycin and dexamethasone were reported in clinical studies. The most frequently reported adverse reactions with tobramycin and dexamethasone were eye pain, intraocular pressure increased, eye irritation (burning upon instillation) and eye pruritus

System Organ Classification	***Less Frequent***	**Frequency unknown**

Eye disorders:	Intraocular pressure increased, eye pain, eye pruritus, ocular discomfort, eye irritation	keratitis, eye allergy, vision blurred, dry eye
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			erythema multiforme,

subcutaneous tissue disorders:			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		impaired healing	

site conditions:			
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 tobramycin and dexamethasone

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)	

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

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the '**6.04 Adverse Drug Reaction Reporting form'**, found online under SAHPRA's publication: https://www.sahpra.org.za/Publications/index/8.

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.

A topical overdose of tobramycin & dexamethasone may be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A.15.3. Combination antibiotics and corticosteroids.

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

5.2. Pharmacokinetic properties

Tobramycin:

Animal studies have reported that tobramycin is absorbed into the cornea following ocular

administration. Following systemic administration to patients with normal renal function, a plasma half-life of approximately 2 hours has been reported. Tobramycin is reported to be eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following the 2-day topical ocular regimen of tobramycin & dexamethasone were reported to be below the limit of quantification in most subjects or low (≤ 0,25 microgram/ml).

Dexamethasone:

Following ocular administration, dexamethasone is reported to be absorbed into the eye with maximum concentrations in the cornea and aqueous humour attained within 1-2 hours. The plasma half-life of dexamethasone is reported to be approximately 3 hours. Dexamethasone is reported to be eliminated extensively as metabolites. Systemic exposure to dexamethasone is low following topical ocular administration of tobramycin & dexamethasone. Peak dexamethasone plasma levels after the last topical dose ranged from 220 to 888 pg/ml (mean 555 ± 217pg/ml) after administration of one drop of tobramycin & dexamethasone to each eye four times per day for two consecutive days.

5.3 Preclinical safety data

Reported non-clinical data revealed no special hazard for humans from topical ocular exposure to tobramycin or dexamethasone based on conventional repeated-dose topical ocular toxicity studies, genotoxicity or carcinogenicity studies. Effects in non-clinical reproductive and developmental studies with tobramycin and dexamethasone were reported only at exposures considered sufficiently in excess of the maximum human ocular dosage indicating little relevance to clinical use for low-dose short-term courses of therapy.

Tobramycin has not been reported to induce teratogenicity in rats or rabbits. The ocular administration of 0,1 % dexamethasone resulted in fetal anomalies in rabbits. No adverse

effects on female fertility in a chorionic gonadotropin primed rat model were reported with dexamethasone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, disodium edetate, hydroxy ethyl cellulose, sodium chloride, sodium sulphate anhydrous and tyloxapol.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store at or below 25 ^{o}C.

Do not refrigerate.

Protect from light

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

6.5 Nature and contents of container

OCTUDEX ophthalmic suspension is available in a 5 ml natural LDPE dropper bottle plugged with a 13 mm natural LDPE sterile plug and capped with a 13 mm white opaque HDPE pilfer proof sterile cap for dropper bottle.

6.6 Special precautions for disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets)

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill Ext.1

Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

51/15.3/1074

9. DATE OF FIRST AUTHORISATION

19 July 2022

10. DATE OF REVISION OF THE TEXT

19 July 2022