Clean Proposed Professional Information for Medicines for Human Use:

[PRODUCT NAME]

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

[PRODUCT NAME] EYE DROPS, SUSPENSION

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

[PRODUCT NAME] Eye drops contains 1 mg dexamethasone and 3 mg tobramycin per mL.

Preservative: 0,01 % (*m/v*) benzalkonium chloride per mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.

White, homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[PRODUCT NAME] 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

Posology

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.

SHAKE WELL BEFORE USE. STORE UPRIGHT.

When removing the cap for the first time, remove and discard the tamper evident ring to prevent the ring from falling into the patient's eye.

Method of administration

[PRODUCT NAME] is for ocular use only.
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.

4.3 Contraindications

- Hypersensitivity to tobramycin and/or dexamethasone or to any of the excipients listed in section 6.1.

- 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, or untreated parasitic eye infections.
- Untreated purulent infection of the eye.
- The use of [PRODUCT NAME] is always contra-indicated after uncomplicated removal of a corneal foreign body.
- [PRODUCT NAME] should not be used in the treatment of mechanical lacerations and abrasions of the eye. [PRODUCT NAME] will delay healing and promote the development and spread of infection.

4.4 Special warnings and precautions for use

[PRODUCT NAME] is for topical use only and **not** for injection or oral use.

Prolonged use of [PRODUCT NAME] may result in ocular hypertension/glaucoma with resultant damage to the optic nerve and reduced visual acuity and visual fields defects and may also result in posterior subcapsular cataract formation. Family or personal history of glaucoma has a higher risk of corticosteroid induced rise in intraocular pressure.

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 products, as the risk of steroid-induced ocular hypertension may be greater in children 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, recognizing 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). In these cases, treatment should be progressively discontinued.

Corticosteroids such as [PRODUCT NAME] may cause progression of the dendritic keratitis (herpes simplex infection), resulting in irreversible

clouding of the cornea.

Prolonged use may also result in secondary ocular infections due to suppression of host response. Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infection.

Sensitivity 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, urticarial, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If hypersensitivity develops during use of this medicine, 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.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. Caution is advised when [PRODUCT NAME] eye drops are used concomitantly with systemic aminoglycosides.

Caution should be exercised when prescribing [PRODUCT NAME] 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.

Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy as in [PRODUCT NAME] should be discontinued.

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.

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 (see section 4.5).

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

Excipients: benzalkonium chloride
[PRODUCT NAME] contains benzalkonium chloride that has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Benzalkonium chloride may cause eye irritation and discolour soft contact lenses. Avoid contact with soft contact lenses. Contact lens wear is not recommended during treatment of an ocular infection or inflammation. If patients are allowed to wear contact lenses, they must be instructed to remove lenses prior to application of [PRODUCT NAME] 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 [PRODUCT NAME] cannot be excluded, regular ophthalmological examination is required.
Caution should be exercised in the use of benzalkonium chloride preserved topical medication such as [PRODUCT NAME] over an extended period in patients with extensive ocular surface disease.

Paediatric population

See section 5.2.

4.5 Interaction with other medicines and other forms of interaction

No clinically relevant interactions have been described with topical ocular dosing.

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

Dexamethasone is metabolized 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

The safety of [PRODUCT NAME] during pregnancy has not yet been established.

Breastfeeding

It is not known whether [PRODUCT NAME] is excreted in human milk; therefore, caution should be observed when it is administered to mothers breastfeeding their infants.

Fertility

Studies have not been performed to evaluate the effect of tobramycin on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility.

4.7 Effects on ability to drive and use machines

Temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In reported clinical studies involving over 1 600 patients, ophthalmic dexamethasone and tobramycin as in [PRODUCT NAME] was administered up to six times daily. No serious ophthalmic or systemic adverse reactions related to [PRODUCT NAME] or components of the combination were reported in clinical studies. The most frequently reported adverse reactions with [PRODUCT NAME] were eye pain, intraocular pressure increased, eye irritation (burning upon instillation) and eye pruritus occurring in less than 1 % of patients.

Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during reported clinical trials and postmarket spontaneous reports with [PRODUCT NAME].

System Organ Class	**Frequency**	
	Less Frequent	**Not known**
Immune system disorders		anaphylactic reaction, hypersensitivity.
Endocrine disorders		Cushing's syndrome, adrenal suppression (see section 4.4).



Nervous system disorders	Headache.	Dizziness.
Eye disorders	eye pain, eye pruritus, ocular discomfort, ocular hypertension, conjunctival oedema, increased intraocular pressure, eye irritation. keratitis, eye allergy, vision blurred (see also section 4.4), dry eye, ocular hyperaemia.	eyelid oedema, erythema of the eyelid, mydriasis, lacrimation increased.
Respiratory, thoracic and mediastinal disorders	rhinorrhoea, laryngospasm	
Gastrointestinal disorders	dysgeusia	nausea, abdominal discomfort.
Skin and subcutaneous tissue disorders		erythema multiforme, rash, swelling face, pruritus.

Description of selected adverse reactions

The following adverse reactions have been reportedly observed following use with dexamethasone ophthalmic suspension.

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Infections and Infestations		eye infection (exacerbation or secondary)
Endocrine disorders		adrenal suppression
Nervous system disorders	headache	
Eye disorders	eye irritation, ocular hyperaemia, erythema of eyelid, abnormal sensation in eye	reduced visual acuity, glaucoma, visual field defects, subcapsular cataract, increased ocular pressure
Respiratory, thoracic and mediastinal disorders	postnasal drip	
General disorders and administration site conditions		impaired healing
Injury, poisoning and procedural complications		optic nerve injury, corneal perforation



Description of selected adverse reactions

The following adverse reactions have been reportedly observed following use with Tobramycin ophthalmic solution:

System Organ Class	**Frequency**	
	Frequent	**Less Frequent**
Infections and Infestations		eye infection (secondary)
Immune system disorders		hypersensitivity (local)
Eye disorders	ocular hyperaemia, eye pain	eye pruritus, ocular discomfort, eye allergy, eyelid oedema, conjunctivitis, glare, increased lacrimation, keratitis, eye irritation (burning and stinging upon instillation), blurred vision
Skin and subcutaneous tissue disorders		erythema (periorbital)

These adverse reactions were also reportedly observed with [PRODUCT NAME] during post marketing.

Prolonged use of topical ophthalmic corticosteroids may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects, posterior subcapsular cataract formation and delayed wound healing.



Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (see section 4.4).

The development of secondary infection has occurred after the use of combinations containing corticosteroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long term applications of steroids.

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic tobramycin therapy (see section 4.4).

Sensitivity to topically administered aminoglycosides may occur in some patients (see section 4.4).

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 "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za



4.9 Overdose

See section 4.8 above. Discontinue use immediately.

Treatment is symptomatic and supportive.

A topical overdose of [PRODUCT NAME] may be flushed from the eye(s) with lukewarm tap 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 anti-infectives in combination.

ATC Code: S01C A01

Pharmacodynamic effects

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

Dexamethasone

Absorption

Following ocular administration, dexamethasone is 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 approximately 3 hours.

Distribution

Systemic exposure to dexamethasone is low following topical ocular administration of dexamethasone 1 mg/mL and tobramycin 3 mg/mL eye drops. Peak dexamethasone plasma levels after the last topical dose ranged from 220 to 888 pg/mL (mean 555 ± 217 pg/mL) after administration of one drop of dexamethasone 1 mg/mL and tobramycin 3 mg/mL eye drops to each eye four times per day for two consecutive days.

Biotransformation and Elimination

Dexamethasone is eliminated extensively as metabolites.

Tobramycin

Absorption

Animal studies have shown 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 observed.

Distribution

Plasma concentrations of tobramycin following the 2-day topical ocular regimen of dexamethasone 1 mg/mL and tobramycin 3 mg/mL eye drops were below the limit of quantification in most subjects or low (≤ 0,25 microgram/mL).

Biotransformation and Elimination

Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation.

Paediatric Population

The safety and efficacy of [PRODUCT NAME] in children have been established by reported broad clinical experience, but only limited data are available. In a reported study, differences in the safety profile between adult and paediatric patients were not observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium Chloride

Edetate disodium

Hydroxyethylcellulose

Sodium chloride

Sodium sulfate, anhydrous

Sodium hydroxide for pH adjustment and/or

Sulfuric acid for pH adjustment

Tyloxapol

Water for injection

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

Shelf life after opening is 4 weeks.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original container to protect from light.

Do not use more than 28 days after opening.

6.5 Nature and contents of container

[PRODUCT NAME] is available in a white LDPE bottle with a LDPE dropper on top of the bottle, sealed with a HDPE and LDPE white cap with a white tamper evident ring.

Each dropper container has a capacity of 10 mL and contains 5 mL of [PRODUCT NAME].

Pack size: 1 x 5 mL dropper container.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

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Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

To be allocated by the Authority upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by the Authority upon authorisation.

10. DATE OF REVISION OF THE TEXT