SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Tobramycin 3 mg/ml + Dexamethasone 1 mg/ml eye drops, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml suspension contains 3 mg tobramycin and 1 mg dexamethasone.

Excipients with known effect: contains Benzalkonium chloride 0.1 mg/ml

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Eye drops, suspension

Milky white suspension

pH – 5.2 to 6.1

Osmolality – 270 to 330 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

This product is indicated for reduction of intraocular inflammation and ocular surface bacterial contamination after cataract surgery in adults and children aged 2 years and older.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Adults

One drop instilled into the conjunctival sac(s) every 4 to 6 hours while the patient is awake. During the initial 24 to 48 hours, the dosage may be increased to one drop every two hours while the patient is awake. Dosing should continue for 14 days not to exceed a maximum of 24 days. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Use in the Elderly

Clinical studies have indicated dosage modifications are not required for use in the elderly.

Paediatric population

Tobramycin/dexamethasone may be used in children 2 years of age and older at the same dose as in adults. Currently available data is described in section 5.1. The safety and efficacy in children younger than 2 years of age have not been established, and no data is available. Shake the bottle well before use.

Method of administration

Ocular use.

Shake the bottle well before use. 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.

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 the active substances or to any of the excipients listed in section 6.1.
- Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and other viral disease of the cornea and conjunctiva.
- Mycobacterial infections 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
- Untreated purulent infection of the eye.

4.4 Special warnings and precautions for use

This product is for topical use only and not for injection or oral use.

Prolonged use of topical ophthalmic corticosteroids (i.e., longer than the maximum duration used in clinical trials [24 days]) 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.

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 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, 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).

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.

Caution should be exercised when prescribing this medicine 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.

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.

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 or fungal infection and mask the clinical signs of infection.

Sensitivity to topically applied aminoglycosides may occur in some patients. 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 used concomitantly.

Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy 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, perforation has been known to occur with topical corticosteroids.

The preservative in this product, benzalkonium chloride, has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the 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 and wait at least 15 minutes before reinsertion.

Paediatric population:

From the limited data available, there is no difference in the adverse event profile of benzalkonium chloride in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

4.5 Interaction with other medicinal products and other forms of interaction

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

In case of concomitant therapy with other topical ophthalmic medicinal products, see section 4.2.

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 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

There are no adequate data from the use of this product in pregnant women. Subcutaneous administration of tobramycin to pregnant animals has not revealed any teratogenic effects. High systemic doses of aminoglycoside antibiotics have been associated with ototoxicity. However, after ocular, topical administration, systemic levels are expected to be very low and tobramycin is not expected to cause direct or indirect harmful effects on reproduction.

Topical administration of corticosteroids to pregnant animals can cause abnormalities in foetal development, including cleft palate. The clinical relevance is not known. Further, animal and clinical data indicate that administration of pharmacological doses of glucocorticoids during pregnancy may increases the risk for intra-uterine growth retardation, adult cardiovascular and/or metabolic disease and/or impaired neurobehavioral development.

Treatment during pregnancy, and especially during the first three months, should only take place after a careful benefit-risk assessment. Therefore, women should inform their physician if pregnancy occurs. So far, use in humans has not generated any suspicion of embryotoxic effects. However, during long-term treatment growth disorders in the unborn child cannot be ruled out. Treatment towards the end of

pregnancy may inhibit the body's own production of glucocorticoids necessitating treatment after birth.

Therefore, this product should only be used during pregnancy when the potential benefit justifies the potential risk.

Lactation

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. this product should not be used during the breastfeeding unless the potential benefit outweighs the potential risk.

Fertility

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

4.7 Effects on ability to drive and use machines

Although no specific studies have been conducted, according to its pharmacodynamic properties, the product has no or negligible influence on the ability to drive and use machines.

As with any ocular medication, if transient blurred vision occurs at instillation, the patient should wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

During clinical studies involving over 1600 patients, tobramycin/dexamethasone was administered up to 6 times per day. No serious adverse reactions, either ocular or systemic, were described, related to the active substances or any components of the product. The undesirable effects observed most often during treatment with tobramycin/dexamethasone were eye pain, intraocular pressure increased, eye irritation (burning sensation after instillation) and eye pruritus occurring in less than 1% of patients.

The following adverse reactions have been described with tobramycin/dexamethasone during clinical trials or during post-marketing experience 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), very rare (< 1/10.000), not know (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness.

System organ classification	Frequency	Adverse reaction
Immune system disorders	Not known	Hypersensitivity
Nervous system disorders	Uncommon Not known	Headache Dizziness

Eye disorders	Uncommon Rare Not known	Eye pain, Eye pruritus, Ocular discomfort, Ocular hypertension, Conjunctival oedema, Increased intraocular pressure, Eye irritation Keratitis, Eye allergy, Blurred vision (see also section 4.4), Dry eye, Ocular hyperaemia Eyelid oedema, Erythema of the eyelid, Mydriasis, Lacrimation increased
Respiratory, thoracic, and mediastinal disorders	Uncommon	Rhinorrhoea, Laryngospasm
Gastrointestinal disorders	Rare Not known	Dysgeusia Nausea, Abdominal discomfort
Skin and subcutaneous tissue disorders	Not known	Rash, Swelling face, Pruritus

The following adverse reactions have been observed following use with Dexamethasone ophthalmic suspension:

System organ classification	**Frequency**	**Adverse reaction**
Endocrine disorders	Not known	Cushing's syndrome, Adrenal suppression (see section 4.4)
Nervous system disorders	Common	Headache
Eye disorders	Common	Eye irritation,* Ocular hyperaemia,* Erythema of eyelid, Abnormal sensation in eye*
Respiratory, thoracic, and mediastinal disorders	Common	Post nasal drip

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

System organ classification	**Frequency**	**Adverse reaction**
Eye disorders	Common	Ocular hyperaemia*, Eye pain*

	Uncommon	Eye pruritus,* Ocular discomfort,* Eye allergy, Eyelid oedema,* Conjunctivitis, * Glare, Increased lacrimation,* Keratitis*

*These events were also observed with tobramycin/dexamethasone postmarketing.

Prolonged use of topical ophthalmic corticosteroids may result in increased intraocular pressure with damage to the optical 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 administrated aminoglycosides may occur in some patients (See Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of benefit/risk balance of the medicinal product. Health care professionals are asked to report any suspected adverse reactions via their national reporting system Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Due to the characteristics of this preparation, no toxic effects are to be expected with an ocular overdose of this product, or in the event of accidental ingestion of the contents of one bottle.

A topical overdose of this product may be flushed from the eye(s) with lukewarm tap water.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinflammatory agents and antiinfectives in combination, corticosteroids and antiinfectives in combination. ATC Code: S01C A01

Dexamethasone

The efficacy of corticosteroids for the treatment of inflammatory conditions of the eye is well established. Corticosteroids achieve their anti-inflammatory effects through suppression of vascular endothelial cell adhesion molecules, cyclooxygenase I or II, and cytokine expression. This action culminates in a reduced elaboration of pro-inflammatory mediators and the suppression of adhesion of circulation leukocytes to the vascular endothelium, thereby preventing their migration into inflamed ocular tissue. Dexamethasone has marked anti-inflammatory activity with reduced mineralocorticoid activity compared with some other steroids, and is one of the most potent anti-inflammatory agents.

Tobramycin

Mechanism of action

Tobramycin is a potent broad-spectrum, rapidly bactericidal aminoglycoside antibiotic. It exerts its primary effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome. Tobramycin in this combination provides antibacterial protection against susceptible bacteria.

The following MIC breakpoints, separating susceptible from intermediate susceptible organisms, and intermediate susceptible from resistant organisms, are suggested: S (≤ 4 μg/ml, R (≥ 8 μg/ml). The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. The following information gives only an approximate guidance on probabilities whether bacteria will be susceptible to tobramycin in tobramycin/dexamethasone.

The breakpoint definitions classifying isolates as susceptible or resistant are useful in predicting clinical efficacy of antibiotics that are administered systemically. However, when the antibiotic is administered in very high concentrations topically directly on the site of infection, these breakpoint definitions may not be applicable. Most isolates that would be classified as resistant by systemic breakpoints are indeed successfully treated topically.

In vitro studies have shown tobramycin to be active against most strains of common ocular pathogens and common skin flora bacteria as listed in the Table below:

Categories	**Frequency of Acquired Resistance in Europe**
SENSITIVE SPECIES	
Aerobic Gram-Positive Microorganisms	
Corynebacterium species	0-3%
Staphylococcus aureus Methicillin -S [a]	0-3%
Staphylococcus epidermidis Methicillin -S [a]	0-28%
Other Coagulase-negative Staphylococci	0-40%
Aerobic Gram-Negative Microorganisms	
Acinetobacter species	0%

Citrobacter *species*	
Escherichia coli	0%
Enterobacter species	0%
Haemophilus influenzae	0%
Klebsiella species	0%
*Moraxell*a species	0%
Proteus species	0%
Pseudomonas aeruginosa	0%
MODERATELY SUSCEPTIBLE SPECIES (*in vitro*, intermediate susceptibility)	
Aerobic Gram-Negative Microorganisms	
Serratia marcescens	
INHERENTLY RESISTANT SPECIES	
Aerobic Gram-Positive Microorganisms	
Enterococcus species	50-70%
Staphylococcus aureus Methicillin –R [a]	30-40%
Staphylococcus epidermidis Methicillin –R [a]	
Streptococcus pneumoniae	
Streptococcus species	
Aerobic Gram-negative microorganisms	
Burkholderia cepacia	
Stenotrophomonas maltophilia	
Anaerobic microorganisms	
Strict anaerobic bacteria	
Others	
Chlamydia species	
Mycoplasma species	
Rickettsia species	

[a] Methicillin-susceptible (S), Methicillin-resistant (R). The beta-lactam (i.e., methicillin; penicillin) resistance phenotype is unrelated to the aminoglycoside resistance phenotype and both are unrelated to the virulence phenotypes. Some methicillin-resistant (R) *S. aureus* strains (MRSA) are susceptible to tobramycin (MIC: S ≤4); conversely some strains of methicillin–susceptible (S) *S. aureus* (MSSA) are resistant to tobramycin (MIC: S ≥8).

The frequency of methicillin resistance (R) may be up to 50 % of all staphylococci in some European countries.

Paediatric Population

The safety and efficacy of tobramycin/dexamethasone in children have been established by broad clinical experience, but only limited data are available. In a clinical study of tobramycin/dexamethasone suspension for the treatment of bacterial conjunctivitis, 29 paediatric patients, ranging in age from 1 to 17 years, were treated with 1 or 2 drops of tobramycin/dexamethasone every 4 or 6 hours for 5 or 7 days. In this study, differences in the safety profile between adult and paediatric patients were not observed.

Other information

Cross-resistance between aminoglycosides (e.g., gentamicin and tobramycin) is due to the specificity of the enzyme modifications, Adenyltransferase (ANT) and Acetyltransferase (ACC). However, cross-resistance varies between the aminoglycoside antibiotics due to the differing specificity of the various modifying enzymes. The most common mechanism of acquired resistance to aminoglycosides is antibiotic inactivation by plasmid and transposon-encoded modifying enzymes.

5.2 Pharmacokinetic properties

Dexamethasone

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. Dexamethasone is eliminated extensively as metabolites.

Systemic exposure to dexamethasone is low following topical ocular administration of this product.

Peak dexamethasone plasma concentrations following ocular administration ranged from 220 to 888 pg/ml (mean 555 $\pm$ 217 pg/ml) after administration of one drop containing the combination of tobramycin (3 mg/ml) and dexamethasone (1 mg/ml) to each eye four times per day for two consecutive days.

Tobramycin

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. Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following the 2-day topical ocular regimen of tobramycin-containing eye drops were below the limit of quantification in most subjects or low ($\leq$ 0.25 microgram/ml).

5.3 Preclinical safety data

The systemic toxicity profile of the individual active substances is well established. Preclinical effects of tobramycin and dexamethasone were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to human use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate

Hydroxyethylcellulose (E1525)

Benzalkonium chloride

Purified water

Sodium chloride

Sodium sulphate (E514)

Sulphuric acid (E513) and/or sodium hydroxide (E524) to adjust pH

Tyloxapol

6.2 Incompatibilities

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.3 Shelf life

3 years

After first opening: Use within 4 weeks

6.4 Special precautions for storage

No special storage conditions are required

6.5 Nature and contents of container

Polyethylene bottle with a low density polyethylene tip and a tamper-evident screw cap in polypropylene.

Pack size: one bottle contains 5 ml eye drops suspension.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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Lincs, NG31 9GG, UK

8 MARKETING AUTHORISATION NUMBER(S)

PL31103-0010

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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