PROFESSIONAL INFORMATION: MYDEX® OPHTHALMIC SUSPENSION

SCHEDULING STATUS **S4**

1. NAME OF THE MEDICINE

MYDEX 3 mg/ml, 1 mg/ml ophthalmic suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 1 mg dexamethasone and 3 mg tobramycin.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sterile ophthalmic suspension.

White homogenous suspension without lumps or foreign suspending particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MYDEX ophthalmic suspension 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 in section 4.4

Method of administration

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

- Hypersensitivity to dexamethasone, tobramycin or to any of the excipients of MYDEX listed in section 6.1.
- Epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella and 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 MYDEX is always contraindicated after uncomplicated removal of a corneal foreign body.
- MYDEX should not be used in the treatment of mechanical lacerations and abrasions of the eye.
- MYDEX will delay healing and promote the development and spread of infection.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Prolonged use of topical ophthalmic corticosteroid containing medicines such as MYDEX, 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 MYDEX 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 MYDEX.

The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes).

IF MYDEX 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 corticosteroid containing medicines such as MYDEX 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 medicines containing steroids such as MYDEX.

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

Concomitant use of topical medicines containing steroids such as MYDEX and topical NSAIDs may delay corneal healing.

MYDEX 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 corticosteroid containing medicines such as MYDEX may suppress the host response and thus increase the hazard of secondary ocular infection.

Medicines containing corticosteroids such as MYDEX may cause progression of the dendritic keratitis (herpes simplex infection), resulting in irreversible clouding of the cornea.

In acute purulent conditions of the eye, corticosteroid containing medicines such as MYDEX 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 corticosteroid containing medicines such as MYDEX. The possibility of fungal invasion must be considered in any persistent corneal ulceration where MYDEX treatment has been used. If fungal infection occurs, corticosteroid therapy should be discontinued.

MYDEX should not be used for injection into the eye.

Hypersensitivity 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, urticaria, skin rash, anaphylaxis, anaphylactoid reactions, or bullous reactions. If a hypersensitivity reaction does occur, discontinue use of MYDEX treatment.

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 MYDEX 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.

MYDEX 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 MYDEX 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 MYDEX, cannot be excluded, regular ophthalmological examination is required.

Caution should be exercised in the use of benzalkonium chloride preserved topical medicine such as MYDEX 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 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

Pregnancy

The safety of tobramycin and dexamethasone as contained in MYDEX during pregnancy has not yet been established. MYDEX is not recommended during pregnancy.

Breastfeeding

It is not known whether tobramycin and dexamethasone as contained in MYDEX, are excreted in human milk following topical ocular administration; therefore, caution should be observed when it is administered to mothers breastfeeding their infants.

4.7 Effects on ability to drive and use machines

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

Adverse reactions

Adverse reactions and their frequencies are reported in Tables 1 to 3 by system organ class and by frequency.

Table 1: Tabulated summary of adverse reactions

The following undesirable effects have been reported.

System Organ Class	Undesirable effects
Immune system disorders	
Frequency unknown:	Anaphylactic reaction, hypersensitivity.
Endocrine disorders	
Frequency unknown:	Cushing's syndrome, adrenal suppression (see section 4.4).
Nervous system disorders	
Less Frequent:	Headache.
Frequency unknown:	Dizziness.
Eye disorders	
Less frequent:	Eye pain, eye pruritus, ocular discomfort, ocular hypertension, conjunctival oedema, increased

	intraocular pressure, eye irritation, keratitis, eye allergy, vision blurred, dry eye, ocular hyperaemia.
Frequency unknown:	Eyelid oedema, erythema of the eyelid, mydriasis, lacrimation increased.
Respiratory, thoracic and mediastinal disorders	
Less Frequent:	Rhinorrhoea, laryngospasm.
Gastrointestinal disorders	
Less frequent:	Dysgeusia.
Frequency unknown:	Nausea, abdominal discomfort.
Skin and subcutaneous tissue disorders	
Frequency unknown:	Erythema multiforme, 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.

Table 2: Tabulated summary of adverse reactions: Dexamethasone

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

System Organ Class	Undesirable effects
Infections and infestations	
Less Frequent:	Eye infection (exacerbation or secondary).
Endocrine disorders	
Less Frequent:	Cushing's syndrome, adrenal suppression (see section 4.4).
Nervous system disorders	
Frequent:	Headache.
Eye disorders	
Frequent:	Eye irritation*, ocular hyperaemia*, erythema of eyelid, abnormal sensation in eye*.

Less frequent:	Reduced visual acuity, glaucoma, visual field defects, subcapsular cataract, increased ocular pressure.
Respiratory, thoracic and mediastinal disorders	
Frequent:	Post-nasal drip.
General disorders and administration site conditions	
Less frequent:	Impaired healing.
Injury, poisoning and procedural complications	
Less frequent:	Optic nerve injury, corneal perforation.

Table 3: Tabulated summary of adverse reactions: Tobramycin

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-dexamethasone containing ophthalmic medicines.

System Organ Class	Undesirable effects
Infections and infestations	
Less Frequent:	Eye infection (secondary).
Immune system disorders	
Less Frequent:	Hypersensitivity (local).
Eye disorders	
Frequent:	Ocular hyperaemia*, eye pain*.
Less frequent:	Eye irritation (burning and stinging upon instillation), ocular hyperaemia, blurred vision, eyelid oedema, eyelid pruritus, eye pain (periorbital), ocular discomfort*, eye allergy, conjunctivitis*, glare, increased lacrimation*, keratitis*.
Skin and subcutaneous tissue disorders	
Less Frequent:	Erythema (periorbital).

*These adverse reactions were also observed during post marketing.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of MYDEX is important. It allows continued monitoring of the benefit/risk balance of MYDEX. Healthcare professionals are asked to report any suspected adverse reactions. Suspected adverse reactions can be reported to Gen-Eye (Pty) Ltd via email: pharmacovigilance@gen-eye.co.za or telephonically on 011 312 3812. Suspected adverse reactions can also be reported 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.

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

Category and class: A.15.3 Combination antibiotics and corticosteroids

Dexamethasone is a potent corticosteroid with an anti-inflammatory potency approximately 25 times that of hydrocortisone. Therapeutic concentrations are attained in the aqueous humor 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 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 as contained MYDEX were below the limit of quantification in most subjects or low (≤ 0,25 microgram/ml).

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 dexamethasone as contained in MYDEX. 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 as contained in MYDEX, to each eye four times per day for two consecutive days.

5.3 Preclinical safety data

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 observed 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 shown to induce teratogenicity in rats or rabbits. The ocular administration of 0,1 % dexamethasone resulted in foetal anomalies in rabbits. Dexamethasone had no adverse effects on female fertility in a chorionic gonadotropin primed rat model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate dihydrate
Sodium chloride
Tyloxapol
Benzalkonium chloride
Hydroxypropyl methylcellulose E4 premium
Sodium sulphate anhydrous
Purified water
Sulfuric acid 25 % *w/w* (for pH adjustment)
Sodium Hydroxide 10N (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened: 2 years
After first opening: 28 days

6.4 Special precautions for storage

Store at or below 30 °C. Do not refrigerate.

Keep the container well-closed and in the outer carton.

Protect from light.

Discard 28 days after first opening.

6.5 Nature and contents of container

Opaque white sterile 5 ml dropper bottle with a white sterile capillary plug and white sterile cap, containing

5 ml suspension.

The dropper bottle is contained in an outer cardboard carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gen-Eye (Pty) Ltd[1]
Royal Palm Business Estate
Unit 7, 646 Washington Street
Halfway House, Midrand, 1685
Gauteng, South Africa

8. REGISTRATION NUMBER

46/15.3/0196

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Not applicable

[1] Company Registration Number.: 2009/009360/07

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