MAXITROL®

(dexamethasone / neomycin / polymyxin B)
1 mg/mL/g dexamethasone/3,500 IU neomycin sulfate/ 6,000 IU polymyxin B sulfate.

Eye drops, suspension and Eye ointment

Summary of Product Characteristics (SmPC)

Version 2.0

1 NAME OF THE MEDICINAL PRODUCT

MAXITROL® Eye drops, suspension, Eye ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Eye Drops, Suspension

1 mL of suspension contains 1 mg of dexamethasone, 3,500 (International Units) IU of neomycin sulfate and 6,000 IU of polymyxin B sulfate. *

Excipients with known effects: Benzalkonium Chloride 0.04 mg/ml.

Eye Ointment

1 g of ointment contains 1 mg of dexamethasone, 3,500 IU of neomycin sulfate and 6,000 IU of polymyxin B sulfate. *

Excipients with known effects: methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), wool fat. *

For the full list of excipients, see section 6.1.

**Information might differ in some countries. Refer to the currently approved local product labeling.*

3 PHARMACEUTICAL FORM

Eye Drops, Suspension

Eye Ointment

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

General

- For the short term treatment of steroid responsive inflammatory conditions of the eye for which a corticosteroid is indicated and where a bacterial infection or a risk of bacterial ocular infection exists. [1]
- The use of a combination drug with an anti-infective component is indicated where the risk of infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye. [1]
- The two particular anti-infective drugs in this product are active in combination against common bacterial eye pathogens including *Staphylococcus aureus,*

Haemophilus influenzae, Klebsiella/Enterobacter species, and Pseudomonas aeruginosa (See Section 5.1). [1]

- This product does not provide adequate coverage against: *streptococci,* including *Streptococcus pneumoniae*. [1]
- Inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroids use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. Also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns; or penetration of foreign bodies. [1]

Eye Drops

- Following surgery and injuries where an antibiotic effect is desired and where a reduction of the inflammatory reaction is also required. [1]
- Eye infections requiring simultaneous antibacterial treatment and anti-inflammatory treatment with a glucocorticosteroid. [1]

Eye Ointment

- Eye inflammations, which are sensitive to glucocorticoids, are accompanied by bacterial infection, or are at risk of bacterial infection of the eye, such as conjunctivitis, inflammation of the eyelids/eyeball, inflammation of the cornea and anterior portion of the eye, chronic inflammation of the anterior iris. [1]

4.2 Posology and Method of Administration

Posology

General

- For ocular use only. [1]
- If more than 1 topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Ointments should be administered last. [1]

Adults and Elderly

Eye Drops [1]

- 1 to 2 drops in the conjunctival sac 4 to 6 times daily. In severe disease, drops may be used hourly, being tapered to discontinuation as the inflammation subsides.

- Shake the bottle well before use.
- Remove the loose collar from the cap when the bottle is first opened. After cap is removed, if tamper evident snap collar is loose, remove before using product. [Only applicable for Eye Drop containing a snap collar]
- In order to prevent contamination of the dropper tip and the suspension, caution should be exercised to ensure that the dropper tip does not touch the eyelids, the surroundings of the eye, or any other surfaces.
- Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions.

Eye Ointment [1]

- Apply a small amount into the conjunctival sac(s) up to 3 or 4 times daily.
- Do not let the tip of the tube touch your eye.

Pediatric population[1]

- Safety and effectiveness of Dexamethasone-Neomycin-Polymyxin Eye Drops, Eye Ointment in pediatric subjects have not been established

Geriatric population [1]

- Posology is the same as in adults.

Hepatic and renal impairment [1]

- Dexamethasone-Neomycin-Polymyxin Eye Drops Eye Ointment has not been studied in these subject populations. However, due to low systemic absorption of the active substances after topical administration of this product, dose adjustment is not necessary.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients. [1]
- Herpes simplex keratitis. [1]
- Vaccinia, varicella, and other viral infection of cornea or conjunctiva. [1]
- Fungal diseases of ocular structures or untreated parasitic eye infections. [1]
- Mycobacterial ocular infections. [1]

4.4 Special Warnings and Precautions for Use

- Sensitivity to topically administered aminoglycosides, such as neomycin, 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. [1]
- Additionally, topical use of neomycin may lead to a skin sensitization. [1]
- Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitized to topical neomycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered. [1]
- Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic neomycin or when applied topically to open wounds or damaged skin. Nephrotoxic and neurotoxic reactions have also occurred with systemic polymyxin B. Although these effects have not been reported following topical ocular use of this product, caution is advised when used concomitantly with systemic aminoglycoside or polymyxin B therapy. [1]
- Prolonged use of ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual field defects, and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy, intraocular pressure should be checked routinely and frequently. *[FOR COUNTRIES THAT HAVE PEDIATRIC USE INCLUDED OR APPROVED IN THE LOCAL LABEL:]* <This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults.> *[FOR COUNTRIES THAT HAVE PEDIATRIC USE EXCLUDED OR CONTRA-INDICATED IN THE LOCAL LABEL:]* <This is especially important in pediatric patients, as the risk of corticosteroid-induced ocular hypertension may be greater in children and may occur earlier than in adults. *[TRADENAME]* is not approved for use in pediatric patients.>

  The risk of corticosteroid-induced raised intraocular pressure and/or cataract formation is increased in predisposed patients (e.g. diabetes). [1]

- 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. [1],[2]
- Corticosteroids may reduce resistance to and aid in the establishment of non-susceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection.
- Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued. [1]
- As with other anti-infectives, prolonged use of antibiotics such as neomycin and polymyxin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy. [1]
- 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). [1]
- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids. [1]
- Contact lens wear is discouraged during treatment of an ocular inflammation or infection. [1]
- [Dexamethasone-Neomycin-Polymyxin B Eye Drops] contains benzalkonium chloride which may cause eye irritation and is known to discolor soft contact lenses. Avoid contact with soft contact lenses. However, if the healthcare provider considers contact lenses use appropriate, patients must be instructed to remove contact lenses prior to application of [Dexamethasone-neomycin-polymyxin B Eye Drops] and wait at least 15 minutes before reinsertion. [Only applicable for eye drops containing benzalkonium chloride] [1]
- This product contains methylparahydroxybenzoate and propylparahydroxybenzoate which may cause allergic reactions (possibly delayed). [Only applicable to products containing methylparahydroxybenzoate and propylparahydroxybenzoate, i.e. Eye Ointment] [1]

- This product contains wool fat which may cause local skin reactions (e.g. contact dermatitis) [Only applicable to products containing wool fat, i.e. Eye Ointment] [1]

4.5 Interaction with other Medicinal Products and Other Forms of Interaction

- Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems. [1]
- CYP3A4 inhibitors including ritonavir and cobicistat may increase systemic exposure resulting in increased risk of 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. [2]

4.6 Pregnancy and Lactation

Fertility [1]

There are no available data on the use of neomycin or polymyxin B affecting male or female fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility. Dexamethasone was free of adverse effects on fertility in a chorionic gonadotropin primed rat model.

Pregnancy [1]

There are no or limited amount of data from the use of dexamethasone, neomycin or polymyxin B in pregnant women.

Aminoglycoside antibiotics, such as neomycin, do cross the placenta after intravenous dosing in pregnant women. Non-clinical and clinical systemic exposure to aminoglycosides has been shown to induce ototoxicity and nephrotoxicity. At the low dose administered via this topical product, neomycin is not expected to cause ototoxicity or nephrotoxicity from in utero exposure. In a rat study where animals were orally administered neomycin at up to 25 mg/kg bw/day, no evidence of maternal toxicity, fetotoxicity or teratogenicity was observed. Prolonged or repeated corticoid use during pregnancy has been 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 (See Section 4.4).

Studies in animals have shown reproductive toxicity after systemic and ocular administration of dexamethasone (See Section 5.3). There is no data available regarding the safety of polymyxin B in pregnant animals.

[Dexamethasone-Neomycin-Polymyxin B Eye Drops, Eye Ointment] is not recommended during pregnancy.

Lactation [1]
It is unknown whether topical ophthalmic dexamethasone, neomycin or polymyxin B are excreted in human milk.

Aminoglycosides are excreted in human milk after systemic administration. No data is available on the passage of dexamethasone and polymyxin B into human breast milk. However, it is likely that the amount of dexamethasone, neomycin and polymyxin B would not be detectable in human milk and would not be capable of producing clinical effects in the infant following appropriate maternal use of this topical product.

A risk to the breastfed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

4.7 Effects on Ability to Drive and Use Machines

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs after instillation, the patient must wait until the vision clears before driving or using machinery. [1]

4.8 Undesirable Effects

Tabulated list of adverse reactions [Clinical studies]

The following adverse reactions have been reported during clinical studies with [Dexamethasone-Neomycin-Polymyxin B Eye Drops, Eye Ointment] and are classified according to the following 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. [1]

System Organ Classification	**MedDRA Preferred Term**
Eye disorders	*Uncommon*: keratitis, intraocular pressure increased, eye pruritus, ocular discomfort, eye irritation

Tabulated list of adverse reactions [Post-Marketing Surveillance]

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data. Within each System Organ Class adverse reactions are presented in order of decreasing seriousness. [1]

System Organ Classification	**MedDRA Preferred Term**
Immune system disorders	hypersensitivity
Nervous system disorders	headache
Eye disorders	ulcerative keratitis, vision blurred, photophobia, mydriasis, eyelid ptosis, eye pain, eye swelling, foreign body sensation in eyes, ocular hyperaemia, lacrimation increased
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome

Other side effects reported with the individual components of Dexamethasone-Neomycin-Polymyxin B Eye Drops, Eye Ointment] are listed in the product information for [Dexamethasone Eye Drops and/or Eye Ointment]. [3]

4.9 Overdose

Due to the characteristics of this preparation, no additional toxic effects are expected with an acute ocular overdose of this product, nor in the event of accidental ingestion of the contents of 1 bottle/tube. [1]

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Dexamethasone and anti-infectives. ATC code: S01CA01. [1]

Mechanism of action [1]

Dexamethasone

The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects.

Polymyxin B

A cyclic lipopeptide that penetrates the cell wall of Gram-negative bacilli to destabilize the cytoplasmic membrane. It is generally less active against Gram-positive bacteria.

Neomycin

An aminoglycoside antibiotic that primarily exerts its effect on bacterial cells by inhibiting polypeptide assembly and synthesis on the ribosome.

Mechanism of resistance [1]

Resistance of bacteria to polymyxin B is of chromosomal origin and is uncommon. A modification of the phospholipids of the cytoplasmic membrane appears to play a role**.**

Resistance to neomycin occurs by several different mechanisms including (1) alterations of the ribosomal subunit within the bacterial cell; (2) interference with the transport of neomycin into the cell, and (3) inactivation by an array of adenylating, phosphorylating, and acetylating enzymes. Genetic information for production of inactivating enzymes may be carried on the bacterial chromosome or on plasmids.

Breakpoints [1]

Each milliliter of Dexamethasone-Neomycin-Polymyxin B Eye Drops contains 6,000 IU polymyxin B sulfate and 3,500 IU neomycin sulfate and each gram of Dexamethasone-Neomycin-Polymyxin B Eye Ointment contains 6,000 IU polymyxin B sulfate and 3,500 IU neomycin sulfate. The breakpoints and the *in vitro* spectrum as mentioned below consider the dual formulation activity of either polymyxin B or neomycin. The breakpoints listed here are based upon acquired resistance for specific species found in ocular infections and the ratio in IU of polymyxin B to neomycin in Dexamethasone-Neomycin-Polymyxin B Drops, Eye Ointment: Resistance breakpoints: >5:2.5 to >40:20 depending upon the bacterial species.

Susceptibility [1]

The information listed below provides guidance on the approximate probabilities on the susceptibility of microorganisms to polymyxin B or neomycin in Dexamethasone-Neomycin-Polymyxin B Eye Drops, Eye Ointment. The presentation below lists bacterial species recovered from external ocular infections of the eye.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Expert advice should be sought, as necessary, when the local prevalence of resistance is such that the utility of the combination of polymyxin B or neomycin as in Dexamethasone-Neomycin-Polymyxin B Eye Drops, Eye Ointment in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive microorganisms
Bacillus cereus
Bacillus megaterium
Bacillus pumilus
Bacillus simplex
Corynebacterium accolens
Corynebacterium bovis
Corynebacterium macginleyi
Corynebacterium propinquum
Corynebacterium pseudodiphtheriticum
Staphylococcus aureus (methicillin susceptible - MSSA)
Staphylococcus capitis
Staphylococcus epidermidis (methicillin susceptible - MSSE)
Staphylococcus pasteuri

Staphylococcus warneri *Streptococcus mutans* Aerobic Gram-negative microorganisms *Haemophilus influenzae* *Klebsiella pneumoniae* *Moraxella catarrhalis* *Moraxella lacunata* *Pseudomonas aeruginosa* *Serratia species*
SPECIES FOR WHICH ACQUIRED RESISTANCE MIGHT BE A PROBLEM *Staphylococcus epidermidis* (methicillin resistant - MRSE) *Staphylococcus hominis* *Staphylococcus lugdunensis*
INHERENTLY RESISTANT ORGANISMS Aerobic Gram-positive microorganisms *Enterococcus faecalis* *Staphylococcus aureus* (methicillin resistant - MRSA) *Streptococcus mitis* *Streptococcus pneumoniae* Anaerobic Bacteria *Propionibacterium acnes*

Pharmacodynamics [1]

Dexamethasone is one of the most potent corticosteroids with a relative anti-inflammatory potency greater than prednisolone or hydrocortisone.

PK/PD relationship [1]

A pharmacodynamic/pharmacokinetic relationship after topical ocular administration has not been established.

Clinical Studies [1]

No recent clinical trials have been conducted with Dexamethasone-Neomycin-Polymyxin B Eye Drops/Ear Drops.

Pediatric Population [1]

The safety and efficacy of Dexamethasone-Neomycin-Polymyxin B Eye Drops/Ear Drops have not been studied in children. For information concerning posology, precautions, and warnings for pediatric subjects see Sections 4.2 and 4.4, respectively.

5.2 Pharmacokinetic Properties

Absorption [1]

Dexamethasone - Following topical instillation into the conjunctival sac, corticosteroids such as dexamethasone are absorbed into the aqueous humor, and systemic absorption could occur. However, because topical ophthalmic corticosteroid dosage is less than when the drugs are given systemically, there is usually no clinical evidence of systemic absorption. Oral bioavailability of dexamethasone ranged from 70-80% in normal subjects and patients.

Neomycin - Studies in rabbit suggest neomycin slowly absorbs into the aqueous humor after topical administration. Absorption increases if the cornea is abraded. Oral absorption of neomycin was low with a mean of 2.5%.

Polymyxin B – It is suggested that polymyxin B is not absorbed from the conjunctival sac. Systemically administered polymyxin B does not distribute into the aqueous humor of the eye, even in the presence of inflammation. Systemic absorption was undetectable after ocular administration. Polymyxin B is not absorbed orally, and is typically administered topically or intravenously.

Distribution [1]

Dexamethasone - The volume of distribution at steady state after intravenous administration of dexamethasone was 0.58 L/kg. In vitro, no change in human plasma protein binding was observed with dexamethasone concentrations from 0.04 to 4 μg/mL, with a mean plasma protein binding of 77.4%.

Neomycin – Volume of distribution for neomycin is 0.25 L/kg with low plasma protein binding of 20%.

Polymixin B - Polymixin B has a small volume of distribution (0.07 - 0.2 L/kg) in seriously ill patients. Polymixin B is moderately bound in plasma proteins in normal subjects (56%); however, that percent increases up to 90% in seriously ill patients; where the plasma protein

to which polymixin B binds, α1-glycoprotein, may increase up to 5-fold in blood serum due to stress.

Biotransformation [1]

Dexamethasone – After oral dosing, 60% of the dose is recovered as 6β-hydroxydexamethasone and 5-10% recovered as an additional metabolite, 6β-hydroxy-20-diydrodexamethasone.

Neomycin – Negligible metabolism occurs with neomycin.

Polymixin B – Not known.

Elimination [1]

Dexamethasone - After intravenous administration, the systemic clearance was 0.125 L/hr/kg. The half-life has been reported as 3-4 hours but was found to be slightly longer in males. This observed difference was not attributed to changes in systemic clearance but to differences in volume of distribution and body weight. After i.v. bolus administration, 2.6% of the parent drug was recovered unchanged in the urine.

Neomycin – Systemically absorbed neomycin is principally excreted unchanged in feces (97%) and urine (1%).

Polymyxin B – Polymyxin B total clearance is 0.27-0.81 mL/min/kg in seriously ill patients (e.g. sepsis), with <1% of an intravenous dose recovered in the urine as unchanged drug suggesting nonrenal pathway of elimination, and produces a long half-life in plasma. Polymixin B does not appear to be substrates or inhibitors of major cytochrome P450s.

5.3 Preclinical Safety Data

Non-clinical data revealed no special hazard for humans from topical ocular exposure to Dexamethasone, Neomycin or Polymixin B based on conventional repeated-dose toxicity studies, genotoxicity or carcinogenicity studies. Effects in non-clinical reproductive and developmental studies with 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. [1]

There is little to no data available regarding the safety of neomycin and Polymixin B in non-clinical reproductive and developmental studies. [1]

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Eye drops

Sodium chloride

Polysorbate 20 (E432)

Benzalkonium chloride

Hypromellose (hydroxypropylmethylcellulose, E464)

Concentrated hydrochloric acid and/or sodium hydroxide (to adjust pH)

Purified water

Eye ointment

Methyl p-hydroxybenzoate (E218)

Propyl p-hydroxybenzoate (E216)

Wool fat

White soft petrolatum

**Information might differ in some countries. Refer local labeling.*

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

Eye drops

2 years*

Discard 4 weeks after first opening.

Eye ointment

4 years*

Discard 4 weeks after first opening.

**Information might differ in some countries. Refer to the currently approved local product labeling.*

6.4 Special Precautions for Storage

Eye drops

Do not store above 25°C.

Do not refrigerate.

Store the bottle upright.

Keep the bottle tightly closed.

Eye ointment

Do not store above 25 °C.

Do not refrigerate.

Keep the tube tightly closed.

** Information might differ/be more restricted in some countries, depending on local requirements and/or climate zone classification. Refer to the currently approved local labeling.*

6.5 Nature and Contents of Container

Eye drops

Plastic tamper-evident bottle, consisting of a LDPE dropper container and a polypropylene tamper-evident screw cap.

The following pack sizes are available: carton containing 1 bottle, volumes ranging from 2.5 mL to 15 mL.

Eye ointment

Epoxy-phenolic lined aluminium tube with a polyethylene nozzle and screw cap.

Carton contains 1 tube of 3.5 g ointment.

** Information might differ in some countries or for different fill sizes / presentations. Refer to the currently approved local labeling.*

6.6 Instructions for Use and Handling <and Disposal>

[No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

**Information might differ in some countries. Refer local labeling.*

7 SUPPLIER

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