NOVARTIS

Regulatory Affairs

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

Core Data Sheet (CDS) - Rationale

Version 3.0

NOTICE

The Novartis Core Data Sheet (CDS) displays the company's current position on important characteristics of the product, including the Core Safety Information according to ICH E2C.

The Novartis CDS contains all relevant information relating to indications, dosage regimen, pharmacology and Core Safety Information which Novartis requires to be listed for the product in all countries where the product is registered.

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1 Tradename(s)

MAXITROL® Eye drops, suspension, Eye ointment

2 Description and composition

Pharmaceutical form(s)

Eye drops, suspension

Eye ointment

Active substance(s)

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.

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

Eye drops, suspension

Excipients with known effects: 1 mL of eye drop suspension contains 0.04 mg of benzalkonium chloride.

Other excipients: sodium chloride , Hypromellose ((hydroxypropylmethylcellulose) polysorbate 20,), hydrochloric acid and/or sodium hydroxide (to adjust pH), purified water.

Eye ointment

Excipients with known effects: methyl parahydroxybenzoate, propyl parahydroxybenzoate and wool fat.

Other excipients: white soft petrolatum.

Information might differ in some countries.

3 Indications

Maxitrol is indicated for:

- 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 11 Clinical pharmacology) [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, suspension

- 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 Dosage regimen and administration

Dosage regimen

Adults and elderly

Eye drops, suspension

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 [1].

Eye ointment

Apply a small amount into the conjunctival sac(s) up to 3 or 4 times daily [1].

Special populations

Renal and hepatic impairment [1]

No studies have been performed in patients with renal and hepatic impairment. No dosage regimen adjustment is required for patients with renal and hepatic impairment.

Pediatric patients (below 18 years) [1]

The safety and efficacy of Maxitrol in pediatric subjects have not been established.

Geriatric patients *(*65 years of age or above) [1]

No dosage regimen adjustment is required in patients 65 years of age or above.

Method of administration

- 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].

Eye drops, suspension [1]

- 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, it should be removed before using the product.
- 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]

Do not let the tip of the tube touch your eye.

5 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]

6 Warnings and precautions

- 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.

- 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.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 8 Interactions). 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 8 Interactions) [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].

Special excipients

- Maxitrol Eye drops, suspensionMaxitrol Eye drops contains benzalkonium chloride which may cause eye irritation and may possibly discolor soft contact lenses. Contact lenses must be removed before administration of Maxitrol Eye drops and reinserted at least 15 minutes later.

Maxitol Eye ointment:

- This product contains methylparahydroxybenzoate and propylparahydroxybenzoate which may cause allergic reactions (possibly delayed) [1].
- This product contains wool fat which may cause local skin reactions (e.g., contact dermatitis) [1].

7 Adverse drug reactions

Tabulated summary of adverse drug reactions from clinical trials

Adverse drug reactions from clinical trials (Table 7-1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): 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) [1].

Table 7-1 Adverse drug reactions in clinical trials

System organ classification	Adverse drug reaction	Frequency category
Eye disorders	Keratitis, intraocular pressure increased, eye pruritus, ocular discomfort, eye irritation	Uncommon

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Maxitrol via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness [1].

Table 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

System organ classification	Adverse drug reaction
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

8 Interactions

- 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 of dexamethasone resulting in increased risk of adrenal suppression/Cushing's syndrome (see Section 6 Warnings and precautions). 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].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary [1]

There are no adequate and well-controlled studies with Maxitrol in pregnant women to inform a product associated risk.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 6 Warnings and precautions).

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

Maxitrol Eye drops and Eye Ointment is not recommended during pregnancy.

9.2 Lactation

Risk summary [1]

It is not known if topical ophthalmic dexamethasone, neomycin or polymyxin B are transferred into 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.

9.3 Females and males of reproductive potential

There are no data regarding the effects of topical ocular administration of Maxitrol on human or animal fertility. There is limited clinical data to evaluate the effect of dexamethasone on male or female fertility. In rats, dexamethasone caused male reproductive toxicity at clinically relevant doses after dermal administration.

10 Overdosage

Due to the characteristics of this preparation, no additional toxic effects are expected with an acute ocular overdose of this product or in the event of accidental ingestion of the contents of one bottle or tube [1].

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

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

Mechanism of action (MOA)

Dexamethasone

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

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

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

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 [1].

Breakpoints
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 [1].

Susceptibility

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 [1].

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*

Pharmacokinetics (PK)

Absorption

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 [1].

Distribution

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 [1].

Biotransformation/metabolism

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

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.

12 Clinical studies

Maxitrol Eye drops, suspension and Eye Ointment are well-established products.

13 Non-clinical 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. For reproductive toxicity, see Section 9 Pregnancy, lactation and females and males of reproductive potential[1].

14 Pharmaceutical information

Incompatibilities

Not applicable

Special precautions for storage

Eye drops, suspension: Do not refrigerate. Store the bottle upright.
Keep the bottle tightly closed.

Eye ointment
Do not refrigerate. Keep the tube tightly closed.
Maxitrol Eye drops and Eye Ointment must be kept out of the reach and sight of children.
Information might differ in some countries.

Instructions for use and handling

No special requirements [1].

Special precautions for disposal

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

15 References

1. CCDS Supporting Document: TDOC-0051329 v.1.0. This is the supporting document for the previous CCDS version (TDOC-0051679 v.1.0) 22-Jan-2018
2. Clinical Overview (CO) (TDOC-0054749): Changes to Core Data Sheet (CDS) / Product Information for Dexamethasone and Dexamethasone-containing products. 22-Jan-2018
3. Dexamethasone CCDS Supporting Document (TDOC-0051106 v1.0). 22-Jan-2018

16 CDS history table

Version	Effective date	GLC/PSB approval date	SLC Tracking No.	Section keyword	Refs.	Author GLM/GPRD/GPRM
2.0	22-Jan-2018	28-Nov-2017	NA	-	TDOC-0051659	Betty Lan
3.0	21-Jul-2023	06-Jun-2023	NA	CDS converted from Alcon to Novartis template. Section 4: updated text in Method of administration. Section 9: Conversion to PLLR format. added optional information under the 9.3 Section.		Vinay Thandra Katiana Francois