

1. NAME OF THE MEDICINAL PRODUCT

MAXITROL® sterile ophthalmic suspension
MAXITROL® sterile ophthalmic ointment
(dexamethasone, neomycin sulfate and polymyxin B sulfate)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MAXITROL ophthalmic suspension

1 ml of suspension contains 1 mg dexamethasone, 3,500 IU neomycin sulfate and 6,000 IU polymyxin B sulfate.

Preservative: 1 ml of suspension contains 0.04 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

MAXITROL ophthalmic ointment

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

Preservative: 1 g of ointment contains 0.5 mg methylparaben and 0.1 mg propylparaben.

Excipient with known effect: 1 g of ointment contains 30 mg anhydrous liquid lanolin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

MAXITROL ophthalmic suspension

Sterile ophthalmic suspension

Opaque, white to pale yellow suspension, no agglomerates

MAXITROL ophthalmic ointment

Sterile ophthalmic ointment

A greasy, translucent to opaque and white to light yellow, homogeneous ointment, free of lumps

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

MAXITROL combines two antibiotics, neomycin sulfate and polymyxin B sulfate, offering broad spectrum antibacterial activity with the anti-inflammatory activity of a corticosteroid, dexamethasone, for combating certain microbial infections of the anterior segment of the eye(s). The suspension also contains hypromellose for maximum effectiveness and comfort.

MAXITROL is indicated for ocular inflammation when concurrent use of an antimicrobial is judged necessary.

4.2 Posology and method of administration

MAXITROL ophthalmic suspension

Posology

1 to 2 drops topically in the conjunctival sac(s). In mild disease, drops may be used up to 4 to 6 times daily. In severe disease, drops may be used hourly, being tapered to discontinuation as the inflammation subsides.

Use in children

The safety and efficacy of MAXITROL ophthalmic suspension in children have not been established.

Use in geriatric population

No dosage adjustment is needed.

Use in patients with hepatic or renal impairment

MAXITROL ophthalmic suspension has not been studied in patients with hepatic or renal impairment.

However, due to low systemic absorption of the active substances after topical administration of MAXITROL ophthalmic suspension, dose adjustment is not necessary.

Method of administration

For ocular use.
Shake well before use.

After cap is removed, if tamper evident snap collar is loose, remove before using product.

To prevent contamination of the dropper tip and suspension, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip. Keep the bottle tightly closed when not in use.

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.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. Eye ointments should be administered last.

MAXITROL ophthalmic ointment

Posology

Apply a small amount into the conjunctival sac(s) up to 3 or 4 times daily or, may be used adjunctively with drops at bedtime.

Use in children

The safety and efficacy of MAXITROL ophthalmic ointment in children have not been established.

Use in geriatric population

No dosage adjustment is needed.

Use in patients with hepatic or renal impairment

MAXITROL ophthalmic ointment has not been studied in patients with hepatic or renal impairment. However, due to low systemic absorption of the active substances after topical administration of MAXITROL ophthalmic ointment, dose adjustment is not necessary.

Method of administration

For ocular use.

To prevent contamination of the tube tip and ointment, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the tube tip. Keep the tube tightly closed when not in use.

If more than one topical ophthalmic product is being used, the products must be administered at least 5 minutes apart. 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. Hypersensitivity to the antibiotic component occurs at a higher rate than for other components.
- The use of MAXITROL is always contraindicated after uncomplicated removal of a corneal foreign body.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infections of cornea or conjunctiva.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections.

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, urticaria, skin rash, anaphylaxis, anaphylactoid reactions or bullous reactions. If hypersensitivity develops during use of this medicine, treatment should be discontinued.
- Additionally, topical use of neomycin may lead to a skin sensitisation.

- Cross-hypersensitivity to other aminoglycosides can occur, and the possibility that patients who become sensitised to topical neomycin 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 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.
- 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, for 10 days or longer, intraocular pressure should be checked routinely and frequently, 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 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 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.
- Corticosteroids may suppress the host response and thus reduce resistance to and aid in the establishment of non-susceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection or enhance existing infection.
- Fungal infection should be suspected in patients with persistent corneal ulceration. If fungal infection occurs, corticosteroids therapy should be discontinued. The possibility of persistent fungal infections of the cornea should be considered after prolonged steroid dosing.
- As with other anti-infectives, prolonged use of antibiotics such as neomycin and polymyxin B may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, discontinue use and institute alternative therapy.
- Topical ophthalmic corticosteroids may slow corneal wound healing. Topical non-steroidal anti-inflammatory drugs (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.
- Contact lens wear is discouraged during treatment of an ocular inflammation or infection.
- MAXITROL ophthalmic suspension contains benzalkonium chloride which may cause eye irritation 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 MAXITROL ophthalmic suspension and wait at least 15 minutes before reinsertion.
- MAXITROL ophthalmic ointment contains methylparaben and propylparaben which may cause allergic reactions (possibly delayed).
- MAXITROL ophthalmic ointment contains anhydrous liquid lanolin which may cause local skin reactions (e.g. contact dermatitis).
- Employment of steroid medication in the treatment of herpes simplex requires great caution.
- The initial prescription and renewal of the medication order beyond 20 ml or 8 g should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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.
- 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

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 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.

MAXITROL is not recommended during pregnancy.

Breast-feeding

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 suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue or abstain from MAXITROL therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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.

4.7 Effects on ability to drive and use machines

MAXITROL has no or negligible influence on the ability to drive and use machines.

However, 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.

4.8 Undesirable effects

Tabulated summary of adverse reactions

The following adverse reactions are classified according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), or not known (cannot be estimated from the available data; data from post-marketing surveillance). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience.

System Organ Class	Adverse reactions
Immune system disorders	<i>Uncommon</i> : hypersensitivity
Nervous system disorders	<i>Not known</i> : headache
Eye disorders	<i>Uncommon</i> : keratitis, intraocular pressure increased, vision blurred, photophobia, mydriasis,

	eyelid ptosis, eye pain, eye swelling, eye pruritus, ocular discomfort, foreign body sensation in eyes, eye irritation, ocular hyperaemia, lacrimation increased <i>Not known: ulcerative keratitis</i>
Skin and subcutaneous tissue disorders	<i>Not known: Stevens-Johnson syndrome</i>

Description of selected adverse reactions

- Sensitivity to topically administered aminoglycosides may occur in some patients. Additionally, topical use of neomycin may lead to skin sensitisation (see section 4.4).
- Prolonged topical ophthalmic corticosteroids may result in increased intraocular pressure with possible development of glaucoma and damage to the optic nerve, reduced visual acuity and visual field defects, posterior subcapsular cataract formation and delayed wound healing (see section 4.4).
- The development of secondary infections has occurred after the use of combinations containing corticosteroids or antimicrobials (see section 4.4).
- Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation (see section 4.4).

4.9 Overdose

An ocular overdose of MAXITROL may be flushed from the eye(s) with lukewarm water.

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 or tube.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-inflammatory agents and anti-infectives in combination – corticosteroids and anti-infectives in combination. ATC code: S01CA01.

Mechanism of action

MAXITROL has a dual effect: suppression of inflammation symptoms by the corticosteroid component dexamethasone, and an anti-infective effect due to the presence of two antibiotics, polymyxin B and neomycin. Corticosteroids suppress the inflammatory response to a variety of agents and may delay or slow healing. Since corticosteroids may inhibit the body's defence mechanisms against infection, a concomitant antimicrobial drug may be used when this inhibition is considered to be clinically significant in a particular case.

Dexamethasone

Dexamethasone is a synthetic glucocorticoid with potent anti-inflammatory activity. The exact mechanism of anti-inflammatory action of dexamethasone is unknown. It inhibits multiple inflammatory cytokines and produces multiple glucocorticoid and mineralocorticoid effects. The anti-infective component in the combination is included to provide action against specific organisms susceptible to either agent.

Polymyxin B

A cyclic lipopeptide that penetrates the cell wall of Gram-negative bacilli to destabilise 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.

The compatibility of ingredients of the three drugs in the same formulation has the added assurance that the appropriate dosage of drugs is administered in the correct volume resulting in greater patient compliance and convenience when a decision to administer both a corticosteroid and an antimicrobial is made. The relative potency of corticosteroids depends on the molecular structure, concentration and release from the vehicle.

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.

Breakpoints

Each millilitre of MAXITROL ophthalmic suspension and each gram of MAXITROL ophthalmic 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 International Units of polymyxin B to neomycin in MAXITROL: Resistance breakpoints: >5:2.5 to >40:20 depending upon the bacterial species.

Susceptibility

The information listed below provides guidance on the approximate probabilities on the susceptibility of microorganisms to polymyxin B or neomycin in MAXITROL. 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 MAXITROL in at least some types of infections is questionable.

<p>COMMONLY SUSCEPTIBLE SPECIES</p> <p><u>Aerobic Gram-positive microorganisms</u></p> <p><i>Bacillus cereus</i> <i>Bacillus megaterium</i> <i>Bacillus pumilus</i> <i>Bacillus simplex</i> <i>Corynebacterium accolens</i> <i>Corynebacterium bovis</i> <i>Corynebacterium macginleyi</i> <i>Corynebacterium propinquum</i> <i>Corynebacterium pseudodiphtheriticum</i> <i>Staphylococcus aureus</i> (methicillin susceptible - MSSA) <i>Staphylococcus capitis</i> <i>Staphylococcus epidermidis</i> (methicillin susceptible - MSSE) <i>Staphylococcus pasteurii</i> <i>Staphylococcus warneri</i> <i>Streptococcus mutans</i></p> <p><u>Aerobic Gram-negative microorganisms</u></p> <p><i>Haemophilus influenzae</i> <i>Klebsiella pneumoniae</i> <i>Moraxella catarrhalis</i> <i>Moraxella lacunata</i> <i>Pseudomonas aeruginosa</i> <i>Serratia species</i></p>
<p>SPECIES FOR WHICH ACQUIRED RESISTANCE MIGHT BE A PROBLEM</p> <p><i>Staphylococcus epidermidis</i> (methicillin resistant - MRSE) <i>Staphylococcus hominis</i> <i>Staphylococcus lugdunensis</i></p>

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive microorganisms

Enterococci faecalis

Staphylococcus aureus (methicillin resistant - MRSA)

Streptococcus mitis

Streptococcus pneumoniae

Anaerobic Bacteria

Propionibacterium acnes

Pharmacodynamics

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

Corticosteroids have an anti-inflammatory as well as a vasoconstrictive effect. They suppress the inflammatory response and symptoms in various disorders without basically curing these disorders.

PK/PD relationship

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

Clinical studies

No recent clinical trials have been conducted with MAXITROL.

Paediatric population

The safety and efficacy of MAXITROL have not been studied in children. For information concerning posology, precautions and warnings for paediatric subjects, see sections 4.2 and 4.4 respectively.

5.2 Pharmacokinetic properties

Absorption

Dexamethasone

Following topical instillation into the conjunctival sac, corticosteroids such as dexamethasone are absorbed into the aqueous humour, 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 humour 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 humour 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

Dexamethasone

After intravenous administration, the volume of distribution at steady state 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 is found to be 0.25 l/kg with low plasma protein binding of 20%.

Polymyxin B

Polymyxin B has a small volume of distribution (0.07 - 0.2 l/kg) in seriously ill patients. Polymyxin 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 polymyxin B binds, α 1-glycoprotein, may increase up to 5-fold in blood serum due to stress.

Biotransformation

Dexamethasone

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

Neomycin

Negligible metabolism occurs with neomycin.

Polymyxin 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 unchanged parent drug was recovered in the urine.

Neomycin

Systemically absorbed neomycin is principally excreted unchanged in faeces (97%) and urine (1%) with a plasma half-life of 2 hours.

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 non-renal pathway of elimination, and produces a long half-life in plasma. Polymyxin 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 polymyxin 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MAXITROL ophthalmic suspension

Polysorbate 20 (E432), sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), benzalkonium chloride, hypromellose (E464) and purified water.

MAXITROL ophthalmic ointment

Methylparaben (E218), propylparaben (E216), anhydrous liquid lanolin and white petrolatum.

6.2 Incompatibilities

Not applicable.

6.3 Special precautions for storage

Do not use this medicine after the expiry date which is stated on the packaging.

Discard 4 weeks after first opening.

Keep this medicine out of the sight and reach of children.

6.4 Nature and contents of container

MAXITROL ophthalmic suspension

Sterile DROP-TAINER® dispenser containing 5 ml.

MAXITROL ophthalmic ointment

Tube containing 3.5 g ointment.

Not all presentations may be registered/marketed.

6.5 Special precautions for disposal

No special requirements.

Manufactured by:

ALCON-COUVREUR

B-2870 Puurs (Belgium) for Novartis Pharma AG, Basel, Switzerland

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