NOVARTIS

1. NAME OF THE MEDICINAL PRODUCT

MAXITROL® sterile ophthalmic suspension

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.

3. PHARMACEUTICAL FORM

MAXITROL ophthalmic suspension
Sterile ophthalmic suspension
Opaque, white to pale yellow suspension, no agglomerates

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.

MAXITROL is indicated in 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.

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, urticarial, 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.
- Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.
- Prolonged use of ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity and visual fields 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 uncooperative patients. The risk of corticosteroid- induced ocular hypertension may be greater in children and may occur earlier than in adults. Maxitrol 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).
- 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 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.
- The initial prescription and renewal of the medication order beyond 20 ml 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, the animals

were orally administered neomycin at up to 25 mg/kg/day, no evidence of maternal toxicity, fetotoxicity or teratogenicity was observed. Prolonged or repeated corticosteroid 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.

Lactation

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

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 list of adverse reactions [Clinical Studies]

The following adverse reactions have been reported during clinical studies with Maxitrol 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), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in

order of decreasing seriousness.

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.

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 MAXITROL are listed in the product information for MAXIDEX® Eye Drops and/or Eye Ointment.

Description of selected adverse reactions

- Sensitivity to topically administered aminoglycosides may occur in some patients. Additionally, topical use of neomycin may lead to skin sensitization (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

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.

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

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 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 all three drugs is administered in the correct volume resulting in greater patient compliance and convenience when a decision to administer both a corticosteroid and antimicrobials 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.

Neomycin Sulfate is considered active against the following microorganisms: *Staphylococcus aureus, Corynebacterium diphteriae, Streptococcus viridans, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Aerobacter aerogenes,* and *Haemophilus influenzae.*

Polymyxin B Sulfate is considered active against the following microorganisms: *Pseudomonas aeruginosa, Aerobacter aerogenes, Escherichia coli, Klebsiella pneumoniae* and *Koch-Weeks bacillus.*

Pharmacodynamics
Dexamethasone is one of the most potent corticosteroid 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.

Pediatric Population
The safety and efficacy of Dexamethasone-Neomycin-Polymyxin B Eye 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
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 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 - 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

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.

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. There is little to no data available regarding the safety of neomycin and Polymixin B in nonclinical 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.

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 plastic bottle dispenser containing 5 ml.

6.5 Special precautions for disposal

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

6.6 Manufacturer

See folding box.

Novartis Pharma AG, Basel, Switzerland