Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
MAXITROL ophthalmic ointment

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Ophthalmic ointment:
1 g ointment contains 1 mg dexamethasone, 3,500 I.U. neomycin sulphate (as base) and 6,000 I.U.polymyxin B sulphate.

Excipients: 1 gram ointment contains
Methyl parahydroxybenzoate 0.5 mg,
Propyl parahydroxybenzoate 0.1 mg and Anhydrous liquid lanolin 30 mg
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Ophthalmic ointment
White to very pale yellow homogeneous translucent ointment

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

Maxitrol ophthalmic ointment is indicated for the treatment of eye infections which are responsive to steroids, when an antibiotic is also needed.

4.2 Posology and method of administration
Children and Adults (including the Elderly)
Apply a small amount (1-1.5 cm) in the conjunctival sac 3 to 4 times daily, or use as a supplement to the eye drops at bedtime.

After application of the ointment, look downward for a moment before closing the eyes.
Do not touch the top of the tube to any surface as this may contaminate the contents.
For topical ophthalmic use only. Not for injection or ingestion.

Hepatic and renal impairment
Maxitrol 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 listed in section 6.1.
- Herpes simplex keratitis.
- Vaccinia, varicella, and other viral infection 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
- As with all antibacterial preparation prolonged use may lead to overgrowth of non-susceptible bacterial strains or fungi. If superinfection occurs, appropriate therapy should be initiated.

- Sensitivity to topically applied aminoglycosides may occur in some patients. Cross-sensitivity to other aminoglycosides may also occur. 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 signs of serious reactions or hypersensitivity occur, discontinue use of MAXITROL ophthalmic ointment.
- Patients using ophthalmic preparations containing neomycin sulphate should be advised to consult a physician if ocular pain, redness, swelling, or irritation worsens or persists.
- 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, intraocular pressure should be checked routinely and frequently. 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 ocular 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). In these cases, treatment should be progressively discontinued.

- In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.

- 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 or may suppress hypersensitivity reactions to substances in the product. Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs and corticosteroid therapy should be discontinued if fungal infection occurs.

- To avoid the risk of enhancement of herpetic corneal disease, frequent slit lamp examination is essential.

-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).

- 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.

- Contact lens wear is discouraged during treatment of an ocular infection. Therefore patients should be advised not to wear contact lenses during treatment with MAXITROL ophthalmic ointment.

- This product contains methylparahydroxybenzoate and propylparahydroxybenzoate which may cause allergic reactions (possibly delayed).

- This product also contains lanolin which may cause local skin reactions (e.g. contact dermatitis).

- In patients receiving systemic corticosteroids, new-onset or exacerbation of pre-existing diabetes mellitus may occur. Because of the possibility of reduced glucose tolerance/diabetes mellitus with topical ophthalmic corticosteroids, caution is recommended when administering MAXITROL eye ointment to patients with a personal or family history of diabetes.

4.5 Interactions with other medicinal products and other forms of interaction
No interaction studies have been performed.
Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.
CYP3A4 inhibitors (including ritonavir and cobicistat): may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. 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.
Concomitant and/or sequential use of an aminoglycoside (neomycin) and other systemic, oral, or topical drugs that have neurotoxic, ototoxic, or nephrotoxic effects may result in additive toxicity and should be avoided, whenever possible.

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

The possibility of a higher need for hypoglycaemic medicinal products must be taken into consideration when administering MAXITROL eye ointment to diabetic patients because the hypoglycaemic effect of these medicinal products may be reduced (see section 4.4).

4.6 Fertility, pregnancy and lactation
Fertility
There are no data available on the use of this medicine 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
There are no or limited amount of data from the use of MAXITROL ophthalmic ointment 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. 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 with some active components of MAXITROL ophthalmic ointment have shown reproductive toxicity (see section 5.3).

MAXITROL ophthalmic ointment is not recommended during pregnancy.

Lactation

It is unknown whether topical ophthalmic dexamethasone, neomycin or polymyxin B are excreted in human milk. Because systemic corticosteroids and aminoglycosides may be distributed into milk, a risk to the suckling child cannot be excluded.
A decision whether to discontinue/abstain from breast-feeding or to discontinue therapy with MAXITROL ophthalmic ointment taking into account the benefit of breast-feeding for the child and the benefit of the product to the woman.

4.7 Effects on ability to drive and use machines

MAXITROL ophthalmic ointment has no or negligible influence on the ability to drive and use machines. As with any other eye ointment, temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If transient blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

In clinical trials with MAXITROL eye ointment the most common adverse reactions were ocular discomfort, keratitis and eye irritation, occurring in 0.7% to 0.9% of patients.

Tabulated summary of adverse reactions

The following adverse reactions 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 <1/1000), very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in decreasing order of seriousness. The adverse reactions were obtained from clinical trials and post-marketing experience.

System Organ Classification	**MedDRA Preferred Term (v.18.0)**
Immune system disorders	Not known *:* hypersensitivity (systemic or ocular)
Endocrine disorders	Not known: Cushing's syndrome, adrenal suppression (see section 4.4)
Nervous system disorders	*Not known:* headache
Eye disorders	Uncommon: keratitis, intraocular pressure increased, eye pruritus, ocular discomfort, eye irritation,

	Not known: ulcerative keratitis, corneal thinning, vision, blurred (see also section 4.4), photophobia, mydriasis, eyelid ptosis, eye pain, eye swelling, foreign body sensation in eyes, ocular hyperaemia, increased lacrimation.
Skin and subcutaneous tissue disorders	Not known: Stevens-Johnson syndrome

Description of selected adverse event

Due to the steroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments (See Section Special warnings and precautions for use).

Topical ophthalmic steroid use may result in increased intraocular pressure with damage to the optic nerve, reduced visual acuity and visual field defects. Also it may lead to posterior subcapsular cataract formation (See Section Special warnings and precautions for use).

Sensitivity to topically administered aminoglycosides may occur in some patients (See Section Special warnings and precautions for use). Systemic side effects may occur with extensive use.

Corticosteroids may impair glucose tolerance, which can lead to new-onset or exacerbation of diabetes mellitus (see section 4.4).

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

No case of overdose has been reported.

Signs and symptoms of an overdosage of MAXITROL ophthalmic ointment may be similar to adverse reaction effects seen in some patients (punctuate keratitis, erythema, increased lacrimation, oedema and lid itching).

Due to the characteristics of this preparation, intended for topical use, no toxic effects are expected when administered to the eye neither at the recommended dose nor in the event of accidental ingestion of the contents of a bottle.

A topical ophthalmic overdose of MAXITROL ophthalmic ointment may be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic category: ophthalmologicals;anti-infectives

ATC code: S01 CA 01

Mechanism of Action

MAXITROL ophthalmic ointment has a dual effect: suppression of inflammation symptoms by the corticosteroidal component dexamethasone, and an anti-infective effect due to the presence of two antibiotics, polymyxin B and neomycin.

Dexamethasone is a synthetic glucorticoid with potent anti-inflammatory activity. Polymyxin B is 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 is 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.

Breakpoints

Each gram of MAXITROL eye ointment contains 6000 IU polymyxin B sulphate and 3500 IU neomycin sulphate. The breakpoints and the *in vitro* spectrum as mentioned below are based on the dual 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 ophthalmic ointment:
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 ophthalmic 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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the combination of polymyxin B or neomycin as in MAXITROL ophthalmic 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
Enterococci faecalis
Staphylococcus aureus (methicillin resistant - MRSA)
Streptococcus mitis
Streptococcus pneumonia

Aerobic Gram-negative microorganisms
Serratia species
Anaerobic Bacteria
Propionibacterium acnes

Dexamethasone is a moderately powerful corticosteroid having good penetration in ocular tissue. 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.

5.2 Pharmacokinetic properties
Dexamethasone, like other corticosteroids, is absorbed rapidly after oral administration and has a biological half-life of about 190 minutes. Sufficient absorption may occur after topical application to the skin and eye to produce systemic effects. Intraocular penetration of dexamethasone occurs in significant amounts and contributes to the effectiveness of dexamethasone in anterior segment inflammatory disease.
Polymyxin B sulphate is not absorbed from the gastrointestinal tract or through intact skin, although the intact corneal epithelium prevents penetration into the corneal stroma, therapeutic concentrations do enter the stroma after epithelial damage. Good stromal penetration occurs after epithelial abrasion following topical instillation, subconjunctival injection, or corneal bath. No significant polymyxin B penetration into the vitreous is demonstrable after parenteral or local administration of the drug.
Neomycin is poorly absorbed from the gastrointestinal tract and after topical administration an insufficient amount is absorbed to produce systemic effects. Absorption has been reported to occur from wounds and inflamed skin. After absorption neomycin is rapidly excreted by the kidneys in active form.

5.3 Preclinical safety data

Mutagenicity and Carcinogenicity

Genotoxicity studies performed with neomycin and polymyxin B, with and without metabolic activation, were negative in bacterial (Ames test) or mammalian cells (chromosomal aberration assay in CHO cells). Dexamethasone was clastogenic *in vivo* in the mouse micronucleus assay at doses in excess of those obtained following topical application. Conventional long term carcinogenicity studies with MAXITROL or its active constituents have not been performed.

Teratogenicity

Pregnant rats treated daily with high doses of neomycin produced offspring that exhibited significant ototoxicity. The teratogenic dose is far greater (> 10,000-fold) than the clinical daily exposure from MAXITROL. Dexamethasone has been found to be teratogenic in animal models. Dexamethasone induced abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development.

Local Tolerance and Systemic Effects

Systemic exposure to dexamethasone is associated with its pharmacological effects as a potent glucocorticoid. Prolonged exposure to the steroid can result in glucocorticoid imbalance. Topical ocular safety studies with dexamethasone in rabbits have shown systemic effects after 1 month of treatment. In rabbits, MAXITROL was shown to have minimal irritation potential after administration to either control or irritated eyes.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous liquid lanolin
Methylparahydroxybenzoate (E218)
Propylparahydroxybenzoate (E216)
White soft paraffin

6.2 Incompatibilities

None known

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Discard 28 days after first opening.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate. Keep away from direct sunlight.
Keep the container tightly closed.

6.5 Nature and contents of container

MAXITROL ophthalmic ointment is supplied in a 3.5 g aluminium tube with tube closure.

6.6 Special precautions for disposal and other handling

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

7. REGISTRATION NUMBER

128 53 28210

8. REGISTERATION HOLDER and IMPORTER

Novartis Israel Ltd, P.O.B 7126, Tel Aviv.

Revised on September 2020