Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT
Maxitrol ophthalmic suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml suspension contains 1 mg dexamethasone, 3,500 I.U. neomycin sulphate and 6,000 I.U. polymyxin B sulphate.

Excipient(s) with known effect:
1 ml suspension contains 0.04 mg benzalkonium chloride.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Ophthalmic suspension
Opaque suspension, white to pale yellow, no agglomerates for topical ocular administration.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications

Maxitrol ophthalmic suspension is indicated in ocular inflammation when concurrent use of antimicrobial in judged necessary.

4.2 Posology and method of administration
Posology:
1 to 2 drops topically in the conjunctival sac
In cases of acute disorder, drops may be instilled hourly, being tapered to discontinuation as the inflammation subsides. In mild disorders, instill 4 to 6 times daily.

Hepatic and renal impairment
Maxitrol ophthalmic suspension 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.

Method of administration
For ocular use only. Not for injection or ingestion.
Shake the bottle well before use.
After cap is removed, if tamper evident snap collar is loose, remove before using 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.

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 special 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 the use of this product.

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 nonsusceptible bacterial, fungal, parasitic or viral infections and mask the clinical signs of infection or may suppress hypersensitivity reactions to MAXITROL ophthalmic suspension. Fungal infection should be suspected in patients with persistent corneal ulceration who have been or are receiving these drugs; 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

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 suspension.

Maxitrol ophthalmic suspension contains 0.2 mg benzalkonium chloride in each 5 ml which is equivalent to 0.04 mg/ml. Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the 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 15 minutes after instillation of the dose before reinsertion.

From the limited data available, there is no difference in the adverse event profile in children compared to adults. Generally, however, eyes in children show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children. Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. Should be used with caution in dry eye patients and in patients where the cornea may be compromised. Patients should be monitored in case of prolonged use.

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 ophthalmic suspension 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 ophthalmic suspension 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 available data 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 suspension 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 suspension have shown reproductive toxicity (see section 5.3).
MAXITROL ophthalmic suspension 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 must be made whether to discontinue/abstain from breast-feeding or to discontinue therapy with MAXITROL ophthalmic suspension 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 suspension has no or negligible influence on the ability to drive and use machines. As with any other eye drop, 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
Summary of the safety profile
In clinical trials with Maxitrol ophthalmic suspension and Maxitrol ophthalmic 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 for Maxitrol ophthalmic suspension and Maxitrol ophthalmic ointment.

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 of 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 suspension 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 suspension may be flushed from the eye(s) with lukewarm water.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: ophthalmologicals; anti-infectives

ATC code: S01CA01

Mechanism of Action

Maxitrol ophthalmic suspension 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 ophthalmic suspension 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 suspension:

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 suspension. 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 suspension 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 pneumoniae
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

Sodium chloride
Hypromellose
Polysorbate 20
Benzalkonium chloride
Hydrochloric acid and/or Sodium hydroxide (to adjust pH)
Purified water

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.

6.5 Nature and contents of container

Maxitrol ophthalmic suspension is supplied in a 5 ml , droper LDPE bottles and plugs with polypropylene caps.

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
116 23 22787

8. REGISTRATION HOLDER AND IMPORTER
NOVARTIS ISRAEL LTD
P.O.B 7126, Tel Aviv

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