Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Maxitrol 0.1% w/v, 6000 IU/ml, 3500 IU/ml eye drops, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml suspension contains 1 mg dexamethasone, 6000 IU polymyxin B sulphate, 3500 IU neomycin sulphate (as base).

Excipients with known effect:
0.04mg Benzalkonium Chloride

For a full list of excipients see Section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, suspension
White to pale yellow opaque suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Maxitrol Eye Drops Suspension is indicated for the short-term treatment of steroid responsive conditions of the eye when prophylactic antibiotic treatment is also required, after excluding the presence of fungal and viral disease.

4.2 Posology and method of administration

Children and Adults (including the Elderly)
Apply one or two drops to each affected eye up to six times daily or, more frequently if required.

Heptic and renal impairment
Maxitrol Eye Drops has not been studied in these subject populations.

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.
- 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, urticarial, 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 infectionor may suppress hypersensitivity reactions to MAXITROL eye drops, 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.
- 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 eye drops, suspension.
- *This medicine 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 eye drops, suspension and wait 15 minutes after instillation of the dose before reinsertion.*
- *Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye). If you feel abnormal eye sensation, stinging or pain in the eye after using this medicine, talk to your doctor.*"

4.5 Interaction 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.

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 eye drops, 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. Prolonged or repeated systemic 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 dexamethasone an active component of MAXITROL eye drops, suspension have shown reproductive toxicity in several species such as rat, hamster, dog and non-human primate. In addition to post-implantation loss, multiple abnormalities involving head, ears, limbs and palate have been reported with corticosteroids in animal studies (see section 5.3).
MAXITROL eye drops, 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/abstain from MAXITROL eye drops, suspension therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7 Effects on ability to drive and use machines

MAXITROL eye drops, 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

In clinical trials with MAXITROL eye drops and 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
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 4.4 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 4.4 Special warnings and precautions for use).

Sensitivity to topically administered aminoglycosides may occur in some patients (See Section 4.4 Special warnings and precautions for use).

Systemic side effects may occur with extensive use.

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance Website: www.hpra.ie

4.9 Overdose

No case of overdose has been reported.

Signs and symptoms of an overdosage of MAXITROL eye drops, 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 eye drops, 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 eye drops, 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 eye drops, 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 eye drops, 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 eye drops, 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 eye drops, 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*
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* 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
Neomycin
In vitro treatments of human lymphocytes with neomycin [80 micrograms/mL] have shown an increase in the frequency of chromosomal aberrations. However, neomycin has also shown to be non-mutagenic in the CHO cell chromosomal aberration assay and the Ames assay. Systemically administered neomycin was found to promote colon tumour development in rats. These concentrations are far in excess (1333-fold) to what would be the systemic exposure from topical dermal formulations.

Dexamethasone
Dexamethasone was shown to be negative in the Ames assay but positive in the in vitro chromosomal aberration assay with human peripheral lymphocytes at doses of 10 and 100 micrograms/mL and the in vivo mouse micronucleus assay at doses of 1-10 mg/kg.

Teratogenicity
Neomycin
Aminoglycoside antibiotics have been found to cause nephrotoxicity and ototoxicity in animal models. However, there have been no animal reproduction toxicity studies conducted with neomycin.

Dexamethasone
Antenatal administration of glucocorticoids to pregnant animals has been linked to cleft palate and altered neurological development that ultimately lead to complex behavioural abnormalities.

Local Tolerance and Systemic Effects
Dexamethasone
The systemic toxicity profile of dexamethasone is well established and systemic exposure may be associated with the effects of glucocorticoid imbalance.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Polysorbate 20
Benzalkonium chloride
Hypromellose
Hydrochloric acid/sodium hydroxide (for pH adjustment only)
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Unopened : 2 years
Discard 4 weeks after first opening.

6.4 Special precautions for storage

Do not store above 25°C. Do not refrigerate or freeze. Store in the original package (to protect from light). Keep the container tightly closed.

6.5 Nature and contents of container

Natural or white low density polyethylene (LDPE) bottles with a natural LDPE dispensing plug and white polypropylene (PP) closure containing 5 ml suspension.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not touch the tip of the bottle to any surface as this may contaminate the contents.
Any unused product or waste materials should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Novartis Ireland Limited
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