PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LOTEMAX® CO

Loteprednol etabonate 0,5 % and tobramycin 0,3 % eye drops, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains:

Loteprednol etabonate 5 mg (0,5 % *m/v*)

Tobramycin 3 mg (0,3 % *m/v*)

Preservative: Benzalkonium chloride 0,1 mg (0,01 % *m/v*)

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye drops, suspension

LOTEMAX CO is a white to off-white, milky suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LOTEMAX CO is indicated in the treatment of superficial bacterial ocular infection or where a risk of bacterial ocular infection exists.

LOTEMAX CO is indicated in the treatment of inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, and cyclitis.

LOTEMAX CO is also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The particular anti-infective medicine in this product (tobramycin) is active against the following common bacterial eye pathogens:

Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains.

Streptococci, including some of the Group A-beta-haemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most Proteus vulgaris strains, Haemophilus influenzae,* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

4.2 Posology and method of administration

SHAKE VIGOROUSLY BEFORE USING.

Recommended dosing: Apply one or two drops of LOTEMAX CO into the conjunctival sac of the affected eye(s) every four to six hours.

During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

Prescription guideline: Not more than 20 ml should be prescribed initially, and the prescription should not be repeated without further evaluation (see section 4.4)

Handling the container: To avoid contamination, patients should be advised not to let the applicator tip touch the surface of the eye, fingers, or any other surface.

Paediatric population

Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Elderly populations

No clinical differences in safety have been observed between elderly and younger patients.

4.3 Contraindications

Hypersensitivity to tobramycin, loteprednol etabonate, other corticosteroids or any other ingredients listed in section 6.1.

LOTEMAX CO is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

For ophthalmic use only, not for injection into the eye or other tissue.

If pain develops, redness, itching or inflammation become aggravated, the patient should be advised to consult a medical doctor.

Avoidance of contact lenses

LOTEMAX CO contains benzalkonium chloride, patients should be advised not to wear soft contact lenses when using LOTEMAX CO.

Benzalkonium chloride

Benzalkonium chloride has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. LOTEMAX CO 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.

As the possibility of adverse effects on the corneal permeability, and the danger of disruption of the corneal epithelium with prolonged or repeated usage of benzalkonium chloride preserved ophthalmological preparations, cannot be excluded, regular ophthalmological examination is required. Caution should be exercised in the use of benzalkonium chloride preserved topical medication over an extended period in patients with extensive ocular surface disease.

Paediatric population

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.

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and repeats of the prescription should be made by a medical practitioner only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Viral Infections

Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of
ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).

Fungal Infections

Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal

ulceration where a steroid has been used or is in use. Fungal cultures should be taken when appropriate.

Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. Cross-sensitivity to other aminoglycoside antibiotics may also occur, and the possibility that patients who become sensitized to topical ocular tobramycin may also be sensitive to other topical and/or systemic aminoglycosides should be considered. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

Serum Concentration

Serious adverse reactions including neurotoxicity, ototoxicity and nephrotoxicity have occurred in patients receiving systemic aminoglycoside therapy. If topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, care should be taken to monitor the total serum concentration.

Caution should be exercised when prescribing LOTEMAX CO to patients with known or suspected neuromuscular disorders such as myasthenia gravis or Parkinson's disease. Aminoglycosides may aggravate muscle weakness because of their potential effect on neuromuscular function.

Prolonged use may lead to skin sensitisation or result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

Since loteprednol etabonate is not detected in significant amounts in plasma following the topical administration, it is not expected to affect the pharmacokinetics of systemically administered medicinal products. However, the low potential of ocular loteprednol etabonate to increase the intraocular pressure may be adversely affected by systemically administered medicinal products with anticholinergic activity.

In patients receiving concomitant ocular hypotensive therapy, the addition of loteprednol etabonate may increase intraocular pressure and decrease the apparent ocular hypotensive effect of these medicinal products.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. 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 side-effects.

No clinically relevant interactions for tobramycin have been described with topical ocular dosing.

Care should be exercised when tobramycin is given to patients receiving other medicines with neuromuscular blocking activity or which are ototoxic. Tobramycin and carbenicillin have been reported to have an enhanced effect. However, since an *in vitro* incompatibility with carbenicillin sodium has been demonstrated, the two antibiotics should be administered separately when both are required.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of LOTEMAX CO in pregnancy has not been established. There are no adequate and well controlled studies of tobramycin in pregnant women.

Teratogenic effects: Loteprednol etabonate has been shown to be embryotoxic and teratogenic when administered to animals. The potential risk for humans is unknown and LOTEMAX CO should not be used in pregnancy.

Breastfeeding

Systemic steroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production or cause other untoward effects. Mothers on treatment with LOTEMAX CO should not breastfeed their babies.

4.7 Effects on ability to drive and use machines

LOTEMAX CO may cause blurred vision or other visual disturbances which may affect the ability to drive or use machines. If abnormal or blurred vision occurs at instillation, patients should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

a. Summary of the safety profile

Adverse reactions have occurred with steroid/anti-infective combination medicines which can be attributed to the steroid component, the anti-infective component, or the combination.

LOTEMAX CO:

In a 42-day safety study of LOTEMAX CO, ocular adverse reactions included injection (21 %) and superficial punctate keratitis (13 %). Increased intraocular pressure was reported in 10 %

of LOTEMAX CO subjects. Nine percent (9 %) of LOTEMAX CO subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4 % include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14 % of subjects was headache; all other non-ocular reactions had an incidence of less than 5 %.

Loteprednol etabonate:

Reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with infrequent optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing and secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

In randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2 % (15/901) among patients receiving loteprednol etabonate.

Tobramycin:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and

swelling and conjunctival erythema. These reactions occur in less than 4 % of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

b. Tabulated list of adverse reactions

Adverse reactions are categorized by frequency as follows: 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).

Adverse events from LOTEMAX CO clinical trials:

System Organ Class	Frequency	Undesirable effects
Nervous system disorders	Common	Headache
Eye disorders	Common	Burning/stinging upon instillation, blurred vision, conjunctivitis, increased lacrimation, eye pain, meibomianitis, corneal staining, eyelid erythema, eyelid oedema
	Uncommon	Increased intraocular pressure, foreign body sensation, asthenopia, keratitis
Gastrointestinal disorders	Uncommon	Nausea

Skin and subcutaneous tissue disorders	Common	Rash

Adverse reactions from clinical trials with Loteprednol etabonate eye drops:

System Organ Class	**Frequency**	**Undesirable effects**
Eye disorders	Very common	Abnormal vision / blurring, burning on instillation, chemosis, discharge, dry eye, epiphora, foreign body sensation, itching, infection, photophobia
	Common	Conjunctivitis, corneal abnormalities, eyelid erythema, keratoconjunctivitis, ocular irritation / pain / discomfort, papillae, uveitis
Vascular disorders	Very common	Headache
Respiratory, thoracic and mediastinal disorders	Very common	Rhinitis and pharyngitis

Adverse reactions from clinical trials with Tobramycin eye drops:

System Organ Class	**Frequency**	**Undesirable effects**
Immune system disorders	Uncommon	Hypersensitivity

Nervous system disorders	Uncommon	Headache
Eye disorders	Common	Ocular discomfort, ocular hyperaemia
	Uncommon	Keratitis, corneal abrasion, visual impairment, vision blurred, erythema of eyelid, conjunctival oedema, eyelid oedema, eye pain, dry eye, eye discharge, eye pruritis, lacrimation increased
Skin and subcutaneous tissue disorders	Uncommon	Urticaria, dermatitis, madarosis, leukoderma, pruritis, dry skin

Adverse reactions observed from post-marketing surveillance include the following.

Frequencies cannot be estimated from the available data.

Loteprednol etabonate eye drops:

System Organ Class	**Undesirable effects**
Eye disorders	Elevated intraocular pressure with damage to the optic nerve, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection, perforation of the globe

Tobramycin eye drops:

System Organ Class	**Undesirable effects**

Infections and infestations	Eye infection (secondary)
Immune system disorders	Anaphylactic reaction, hypersensitivity (local)
Eye disorders	Eye allergy, eye irritation, ocular hyperaemia, blurred vision, eyelid oedema, eyelids pruritis, eye pain (periorbital)
Skin and subcutaneous tissue disorders	Erythema (periorbital), rash

d. Paediatric population

In paediatric studies with LOTEMAX CO, rates of incidence of adverse events were not higher than those of the adult studies.

e. Other special populations

Elderly use: No overall differences in safety have been observed between elderly and younger patients.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit-risk of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications:
https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions may also be reported directly to the Holder of the Certificate of registration at the following e-mail address: PV-SouthAfrica@bausch.com

4.9 Overdose

Overdosage of this medicine is unlikely to occur via the ophthalmic route.

In overdose, side effects can be precipitated and/or be of increased severity (see section 4.8).

Treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 15.3 Combination antibiotics and corticosteroids

Mechanism of action

Loteprednol etabonate is a corticosteroid. Corticosteroids *in vitro* inhibit the inflammatory response.

Corticosteroids inhibit the inflammatory response to a variety of inciting agents.

Corticosteroids inhibit phospholipase A_2, an enzyme early in the inflammatory cascade; this inhibition effectively eliminates both cyclooxygenase and lipoxygenase pathways of inflammation. They inhibit the oedema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collage, and scar formation associated with inflammation. While glucocorticoids are known to bind to and activate the glucocorticoid receptor, the molecular mechanisms involved in glucocorticoid/glucocorticoid receptor-dependent modulation of inflammation are not clearly established. However, corticosteroids are thought to inhibit prostaglandin production through several independent mechanisms.

Tobramycin is a basic water-soluble aminoglycoside antibiotic, active against most Gram-negative micro-organisms.

Tobramycin acts against susceptible bacteria to inhibit protein synthesis and is bactericidal.

Inherent resistant species

Aerobic Gram-positive microorganisms: *Entercoccus* species, *Staphylococcus aureus* methicillin-resistant, *Staphyloccoccus epidermidis* methicillin-resistant, *Streptococcus pneumoniae, Streptococcus* species

Aerobic Gram-negative microorganisms: *Burkholderia cepacian, Stenotrophomonas maltophilia*

Anaerobic microorganisms: Strict anaerobic bacteria

Others: *Chlamydia* species, *Mycoplasma* species*, Rickettsia* species

Paediatric population

Two trials were conducted to evaluate the safety and efficacy of LOTEMAX CO in paediatric subjects aged zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, LOTEMAX CO with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus LOTEMAX CO or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, LOTEMAX CO did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution.

There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

Therefore, LOTEMAX CO is not recommended for use in children.

5.2 Pharmacokinetic properties

Loteprednol etabonate is lipid soluble which enhances its penetration into cells. It undergoes extensive metabolism to inactive carboxylic acid metabolites. Plasma levels of loteprednol etabonate and cortienic acid etabonate its primary, inactive metabolite, were below the limit of quantification (1 ng/ml).

Animal studies have shown that tobramycin is absorbed into the cornea following ocular administration. Tobramycin is eliminated almost exclusively by glomerular filtration with little if any biotransformation. Plasma concentrations of tobramycin following a 2-day topical ocular regimen were below the limit of quantification in most subjects or low (≤0.25 microgram/ml).

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an in vivo mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride

Edetate disodium

Glycerine

Povidone

Purified water

Sodium hydroxide and/or sulfuric acid (for pH adjustment)

Tyloxapol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Before first opening: 24 months

After opening the container: 28 days

6.4 Special precautions for storage

Store upright at or below 30° C. Do not freeze.

Discard any remaining eye drops suspension within 28 days after first opening the bottle.

6.5 Nature and contents of container

LOTEMAX CO is supplied as a 5 mL fill volume in a 7,5 mL white, round, low density polyethylene plastic bottle with a white controlled drop tip and a white polypropylene cap, packed in a printed outer carton.

6.6 Special precautions for disposal and other handling

No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION

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