1.5.5 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

LOTEMAX® OPHTHALMIC GEL

Loteprednol etabonate 0,5 % eye gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram contains;

Loteprednol etabonate 5 mg (0,5 % *w/w*) as the active ingredient

Benzalkonium chloride 0,003 % *w/w* as the preservative

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye gel

LOTEMAX OPHTHALMIC GEL is a sterile, white to off-white gel.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LOTEMAX OPHTHALMIC GEL is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

4.2 Posology and method of administration

Posology

Apply one to two drops of LOTEMAX OPHTHALMIC GEL into the conjunctival sac of the affected eye(s) four times daily beginning the day after surgery and continuing throughout the first two weeks of the post-operative period.

Method of administration

Invert the closed bottle and shake once to fill the tip before instillation.

This product is sterile when packaged. To avoid contamination, patients should be advised not to let the applicator tip touch the surface of the eye, fingers, or any other surface.

To reduce systemic absorption, it is recommended to compress the lacrimal sac at the medial canthus for at least 2 minutes during and following instillation.

Paediatric population

The safety and effectiveness of LOTEMAX OPHTHALMIC GEL have been established in paediatric patients from birth to 11 years of age (see section 5.1).

Elderly population

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

4.3 Contraindications

LOTEMAX OPHTHALMIC GEL is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia,

varicella, and also in mycobacterial infections of the eye and fungal diseases of ocular structures.

LOTEMAX OPHTHALMIC GEL is also contraindicated in individuals with known or suspected hypersensitivity to loteprednol etabonate or any other ingredients of this preparation (see section 6.1) and to other corticosteroids.

4.4 Special warnings and precautions for use

For ophthalmic use only.

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

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

Contact lens wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX OPHTHALMIC GEL.

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 LOTEMAX OPHTHALMIC GEL is used for 10 days or longer, intraocular pressure should be monitored even though it may be difficult in children and uncooperative patients.

Cataracts

Prolonged 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 casing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a medical doctor only after examination of the patient with the aid of magnification, such as 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 the infection or enhance existing infections.

Viral infections

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

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.

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.

Concurrent administration of cycloplegics may increase the risk of raised intraocular pressure.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety of LOTEMAX OPHTHALMIC GEL in pregnancy has not been established.

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 OPHTHALMIC GEL 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 OPHTHALMIC GEL should not breastfeed their babies.

Fertility

There is no human data on the influence of loteprednol etabonate on male and female fertility.

4.7 Effects on ability to drive and use machines

LOTEMAX OPHTHALMIC GEL may cause ocular adverse reactions. If abnormal or blurred vision occurs at instillation, patients should wait until their vision clears before driving or using machinery.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions associated with ophthalmic steroids include elevated intraocular pressure, which may be associated with 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.

The most common adverse reactions reported in the clinical trials with LOTEMAX OPHTHALMIC GEL (2 – 5 %) were anterior chamber inflammation, eye pain, and foreign body sensation.

Tabulated summary of adverse reactions

Treatment-related adverse reactions from clinical trials with loteprednol etabonate ophthalmic gel:

System Organ Class	Frequency	Adverse reactions
Eye disorders	Common (≥1/1 00 to <1/10)	Eye pain, eye lid oedema (in paediatric patients)

	Uncommon (≥1/1 000 to <1/100)	Anterior chamber inflammation, increased lacrimation, photophobia, eye irritation, eye pruritis, foreign body sensation, dry eye, IOP increased, macular oedema, anterior chamber cell, blurred vision, ocular hyperaemia, ocular discomfort, anterior chamber flare, eyelids pruritis, eye swelling, photopsia, punctate keratitis, pupillary disorder
Skin and subcutaneous tissue disorders	Uncommon (≥1/1 000 to <1/100)	Facial rash
Gastrointestinal disorders	Uncommon (≥1/1 000 to <1/100)	Dry mouth

Adverse reactions from spontaneous reporting:

System Organ Class	**Frequency**	**Adverse reactions**
Immune system disorders	Frequency unknown	Hypersensitivity

Nervous system disorders	Frequency unknown	Headache
Eye disorders	Frequency unknown	Eye irritation, ocular hyperaemia, blurred vision, eye swelling, increased lacrimation, eye pruritis, dry eye, photophobia
Gastrointestinal disorders	Frequency unknown	Nausea

Paediatric population

In a paediatric study of patients between birth and 11 years of age, eyelid oedema was observed in 1,9 % of 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 **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

You can also report side effects directly to the company, using the following e-mail address: PV-SouthAfrica@bausch.com.

4.9 Overdose

There is hardly a possibility to acutely overdose loteprednol etabonate ophthalmic products since the conjunctival sac has limited capacity and excess volume of medicine administered spill out of the eye surface.

There is also virtually no danger expected due to accidental oral ingestion, based on the low bioavailability evidenced in initial human PK studies. Loteprednol etabonate is well-tolerated after the oral ingestion of 40 mg. Systemic safety evaluation in this trial included physical examination, vital sign determination, electrocardiography, and blood/urine sampling for blood chemistry, haematology, and urine analysis. There were no serious, severe, or clinically significant adverse events. All subjects completed the study as planned.

Treatment is supportive and symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 15.2 Ophthalmic preparations with 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 collagen, 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.

Clinical efficacy and safety

Adult studies

In two randomized, multicentre, double-masked, parallel-group, vehicle-controlled studies in 813 subjects with post-operative inflammation, LOTEMAX OPHTHALMIC GEL was more effective compared to its vehicle in resolving anterior chamber inflammation and pain following cataract surgery. Primary endpoints were complete resolution of anterior chamber cells (cell count of 0) and no pain at post-operative day 8.

In these studies, LOTEMAX OPHTHALMIC GEL had a statistically significant higher incidence of subjects with complete clearing of anterior chamber cells (31 % vs 14-16 %) and were pain-free at post-operative day 8 (73-76 % vs 42-46 %).

Paediatric study

The safety and effectiveness of LOTEMAX OPHTHALMIC GEL were evaluated in a paediatric study of patients from birth to less than 11 years of age (mean age of 3 years) undergoing cataract surgery.

Patients were randomized to receive ether LOTEMAX OPHTHALMIC GEL (54 patients) or prednisolone acetate ophthalmic suspension 1 % (53 patients) four times daily for 14 days.

At Day 14, percentages of patients with complete clearing of anterior chamber inflammation were 57 % in the LOTEMAX OPHTHALMIC GEL group and 63 % in the prednisolone group.

5.2 Pharmacokinetic properties

Loteprednol etabonate is lipid soluble and can penetrate into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compound so that it will undergo a predictable transformation to an inactive metabolite. Based upon in vivo and in vitro preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites, PJ-91 and PJ-90. The systemic exposure to loteprednol etabonate following ocular administration of LOTEMAX has not been established in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride (preservative)

Boric acid

Edetate disodium dihydrate

Glycerin

Polycarbophil

Propylene glycol

Sodium chloride

Sodium hydroxide (for pH adjustment)

Tyloxapol

Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

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 25 °C.

Discard any remaining eye gel within 28 days of first opening the dropper bottle.

6.5 Nature and contents of container

LOTEMAX OPHTHALMIC GEL is supplied in a fill weight of 5 g in a 10 ml white, low density polyethylene plastic bottle with a white controlled drop tip and pink 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

Soflens (Pty) Ltd

254 Hall Street

Centurion

0157

South Africa

Tel: +27 10 025 2100

Manufactured by:

Bausch & Lomb Incorporated

8500 Hidden River Parkway

Tampa, Florida 33637

USA

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