Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lotemax 0.5% w/v eye drops, suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The suspension contains 0.5%w/v loteprednol etabonate (5 mg/ml).
Each drop contains 0.19 mg loteprednol etabonate.

Excipient with known effect: Benzalkonium Chloride (0.01%)
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye-drops, suspension.
Milky-white.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of post-operative inflammation following ocular surgery.

4.2 Posology and method of administration

Posology

Adults and elderly
One to two drops four times daily beginning 24 hours after surgery and continuing throughout the post-operative period.

The duration of treatment should not exceed 2 weeks.

Paediatric Population
Lotemax should not be used in the paediatric age group until further data become available.

Method of administration
Ocular use

Shake the bottle vigorously before using the eye drops.

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. The bottle should be closed immediately after use.

4.3 Contraindications

Lotemax is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures; untreated purulent acute infections which, similar to other infectious diseases, can be masked and worsened by corticoids, 'red eye' with unknown diagnosis and infection caused by amoeba.
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other corticosteroids.

4.4 Special warnings and precautions for use

Prolonged use of corticosteroids may result in ocular hypertension or glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and in posterior subcapsular cataract formation. Steroids should be used with caution in the presence of glaucoma.

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.

Prolonged use of corticosteroids may suppress the host response and may increase the possibility of secondary ocular infections. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Long term treating with corticosteroids can cause fungal disease. Fungal disease should be considered in the differential diagnosis when a corneal ulcer persists.

In general patients should not wear contact lenses after cataract surgery, unless contact lens wearing is medically indicated.

If signs and symptoms fail to improve after two days, the patient should be re-evaluated. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Lotemax contains benzalkonium chloride
This medicinal product contains 0.0152 mg benzalkonium chloride in each dosage unit (2 drops) which is equivalent to 0.20 mg/ml.

Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the
contact lenses. Patients should remove contact lenses before using this medicine and put them back 15minutes afterwards.

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

4.5 Interaction with other medicinal products and other forms of interactions

Since loteprednol etabonate is not detected in plasma following the topical administration of Lotemax, it is not expected to affect the pharmacokinetics of systemically administered medicinal products. However, the low potential of ocular loteprednol etabonate eye drops 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

<u>Pregnancy</u>

For Lotemax no clinical data on exposed pregnancies are available. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown and Lotemax should not be used in pregnancy unless clearly necessary.

Breastfeeding

It is not known whether loteprednol etabonate is excreted in human milk. Excretion of loteprednol etabonate in breast milk has not been investigated in animal studies. Therefore, the use of loteprednol etabonate is contraindicated in lactating women.

Fertility
There are no clinical data concerning the loteprednol etabonate influence on the fertility in humans.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

If there are any transient effects on vision, the patient should be advised to wait until these subside before driving or operating machinery.

4.8 Undesirable effects

Reactions associated with ophthalmic steroids include elevated intraocular pressure in steroid responsive patients, which may be associated with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.
Ocular adverse reactions occurring in patients treated with loteprednol etabonate ophthalmic suspension in clinical studies included the following:

All undesirable effects have been classified as follows very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), or very rare (<1/10,000), not known (cannot be estimated from the available data).

Eye disorders

Common: Corneal defect, eye discharge, ocular discomfort, dry eye, epiphora, foreign body sensation in eyes, conjunctival hyperaemia and ocular itching.

Uncommon: Abnormal vision, chemosis, keratoconjunctivitis, conjunctivitis, iritis, eye irritation, eye pain, conjunctival papillae, photophobia and uveitis.

Not known: Vision blurred (see also section 4.4).

Some of these events were similar to the underlying ocular disease being studied

Non-ocular events possibly related to treatment occurring in patients included:

Infections and infestations

Uncommon: Pharyngitis

Rare: Urinary tract infection and urethritis

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Rare: Breast neoplasm

Psychiatric disorders

Rare: Nervousness

Nervous system disorders

Common: Headache

Rare: Migraine, taste perversion, dizziness, paresthesia

Ear and labyrinth disorders

Rare: Tinnitus

Respiratory, thoracic and mediastinal disorders

Uncommon: Rhinitis

Rare: Cough

Gastrointestinal disorders

Rare: Diarrhoea, nausea and vomiting

Skin and subcutaneous tissue disorders

Rare: Face oedema, urticaria, rash, dry skin and eczema

Musculoskeletal and connective tissue disorders

Rare: Twitching

General disorders and administration site conditions

Common: Instillation site burning

Uncommon: Asthenia

Rare: Chest pain, chills, fever and pain

Investigations

Rare: Weight gain

In a summation of controlled, randomised studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (^{3}10 mmHg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

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

Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

4.9 Overdose

No case of overdose has been reported. Acute overdosage is unlikely to occur via the ophthalmic route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroid, ATC code: S01BA14

Mechanism of action
Corticosteroids suppress the inflammatory response to inciting agents of mechanical, chemical or immunological nature. No generally accepted explanation of this steroid property has been advanced.

Pharmacodynamic effect
Loteprednol etabonate is a new class of corticosteroid with potent antiinflammatory activity designed to be active at the site of action. Its antiinflammatory activity is similar to the most powerful steroid used in ophthalmology but with less intraocular pressure. Animal studies have shown that loteprednol etabonate has a binding affinity to steroid receptors that is 4.3 times greater than dexamethasone. This new class of steroids consists of bioactive molecules whose *in-vivo* transformation to non-toxic substances can be predicted from their chemistry and knowledge of enzymatic pathways in the body. Cortienic acid is an inactive metabolite of hydrocortisone and analogs of cortienic acid are also devoid of corticosteroid activity. Loteprednol etabonate is an ester derivative of one of these analogs, cortienic acid etabonate.

Clinical efficacy and safety
Placebo controlled studies demonstrated that Lotemax is significantly more effective than placebo for the treatment of external ocular inflammation.

Corticosteroids are capable of producing a rise in intraocular pressure in susceptible individuals. In a small study, Lotemax demonstrated a significantly longer time to produce a rise in pressure than did prednisolone acetate. The overall incidence of patients who had an intraocular pressure elevation of $\geq$10 mm Hg was lower in the Lotemax treated patients. In many patients treated with Lotemax the ultimate rise in intraocular pressure never achieved the levels seen in patients treated with prednisolone acetate. In clinical trials only 2% of all patients had an intraocular pressure elevation of $\geq$10 mm Hg. In the small percentage of patients who did show a significant rise in intraocular pressure, pressure rapidly returned to normal on discontinuation of the medicinal products.

Paediatric population
There are no data available in the paediatric population.

5.2 Pharmacokinetic properties

Results from oral and ocular administration of Lotemax in normal volunteers have shown that there are low or undetectable concentrations of either unchanged material or the metabolite. Results from a bioavailability study established that plasma concentrations of loteprednol etabonate following ocular administration of one drop in each eye of Lotemax eight times daily for 2 days or four times daily for 42 days were below the limit of quantitation (1 ng/mL) and detection (500 pg/mL) at all sampling times. In the same study, plasma cortisol concentrations were measured and no evidence of adrenal cortex suppression was observed. All cortisol measurements were within normal range. This study suggests that limited, if any, systemic absorption occurs with Lotemax.

5.3 Preclinical safety data

***Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity*.**

Embryotoxicity and teratogenic effects were observed in reproductive toxicity studies in rabbits (delayed ossification, increased incidence of meningocele, abnormal left carotid artery and limb flexures) at oral doses 35 times the maximum daily clinical dose and in rats (decreased foetal body weight and skeletal ossification, absent innominate artery, cleft palate and umbilical hernia) at oral doses greater than 60 times the maximum daily clinical dose.

Mild ocular irritation was noted with both the acute and multidose rabbit ocular studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium Edetate
Glycerol
Povidone
Purified Water
Tyloxapol
Hydrochloric Acid (pH adjuster)
Sodium Hydroxide (pH adjuster)
Benzalkonium Chloride

6.2 Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

2,5 mL: 15 months (unopened).
5 mL, 10 mL: 2 years (unopened).

Discard any unused contents 28 days after first opening the bottle.

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

6.5 Nature and contents of container

Lotemax is available in the following packaging configurations:

2.5 mL and 5 mL supplied in a white low density polyethylene bottle (7.5 mL) with a white control drop tip and a pink polypropylene cap.

10 mL supplied in a white low density polyethylene bottle (10 mL) with a white control drop tip and a pink polypropylene cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Store the container in an upright position.

7 MARKETING AUTHORISATION HOLDER

Dr. Gerhard Mann, chem.-pharm. Fabrik GmbH
Brunsbutteler Damm 165-173
13581 Berlin

Germany

8 MARKETING AUTHORISATION NUMBER

PA1245/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 November 2006

Date of last renewal: 31 March 2008

10 DATE OF REVISION OF THE TEXT

January 2021