SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product
Lotel (Loteprednol Etabonate ophthalmic Gel 0.5%w/w)

2. Qualitative and quantitative composition
The ophthalmic gel contains 0.5%w/w Loteprednol etabonate.

Excipient with known effect: Benzalkonium Chloride USP-NF (0.003%w/w)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form
Ophthalmic Gel. White to off white gel.

4. Clinical particulars
4.1 Therapeutic indications
Loteprednol is a corticosteroid indicated for the 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

Loteprednol 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
Loteprednol 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

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids, including Loteprednol, 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 renewal of the medication order should be made by a physician 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 infection or enhance existing infection.

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.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with loteprednol.

Lotel contains benzalkonium chloride

This medicinal product contains benzalkonium chloride.

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. Lottel 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.

4.5 Interaction with other medicinal products and other forms of interaction

Since loteprednol etabonate is not detected in plasma following the topical administration of Loteprednol, 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

Pregnancy

There are no adequate and well-controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses ≥1.2 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses ≥ 30 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses ≥3 times the RHOD.
Maternal toxicity was observed in rats at doses ≥ 304 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 30 times the RHOD.
The background risk of major birth defects and miscarriage for the indicated population is unknown Animal Data Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at doses ≥ 0.1 mg/kg (1.2 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption).

Spina bifida (including meningocele) was observed at doses ≥ 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at doses ≥ 0.4 mg/kg (4.9 times the RHOD).
At 3 mg/kg (36 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at doses ≥ 6 mg/kg (73 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.
Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at doses ≥ 5 mg/kg (30 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at doses ≥ 50 mg/kg (304 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (608 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at doses of ≥ 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.
A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At doses ≥ 0.5 mg/kg (3 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (30 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (304 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.
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 human.

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 (≥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 https://pv.pharmacyboardkenya.org

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 anti-inflammatory activity designed to be active at the site of action. Its anti-inflammatory 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 Loteprednol 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, Loteprednol 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 ≥10 mm Hg was lower in the Loteprednol treated patients. In many patients treated with Loteprednol 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 ≥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
Loteprednol etabonate is lipid soluble and can penetrate into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds 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 the inactive carboxylic acid metabolites, PJ-91 and PJ-90. The systemic exposure to loteprednol etabonate following ocular administration of Loteprednol has not been studied in humans.

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. Loteprednol etabonate was not genotoxic in vitro in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or in vivo in the single dose mouse micronucleus assay.
Treatment of female and male rats with doses ≥ 25 mg/kg/day of loteprednol etabonate (152 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused preimplantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (30 times the RHOD).

6. Pharmaceutical particulars
6.1 List of excipients
Benzalkonium Chloride USP-NF
Disodium Edetate BP
Boric Acid BP
Tyloxapol USP
Glycerol BP
Propylene Glycol BP
Sodium Chloride BP
Polycarbophil USP
Sodium Hydroxide BP (Pellets)
Hydrochloric Acid BP
Water for Injections IP/BP/IH/USP.

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

6.3 Shelf life
24 Months.
Discard any unused contents 28 days after first opening the bottle.

6.4 Special precautions for storage
Store below 30°C.

6.5 Nature and contents of container
5 ml solution in a vial in a carton along with pack insert.

6.6 Special precautions for disposal and other handling
No special requirements.

7. Marketing authorization holder
Ajanta Pharma Limited
Ajanta House,
Charkop, Kandivli (West),
Mumbai- 400 067, India
Manufacturing Site Address:
Ajanta Pharma Limited
Mirza, Palashbari Road, Vill-Kokjhar,
Kamrup, Assam. India
E-mail: info@ajantapharma.com

8. Marketing authorization number(s)
CTD10079

9. Date of first authorization/renewal of the authorization
24/12/2022

10. Date of revision of the text
16/09/2023

11. Dosimetry
Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals
Not Applicable