SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LOTEFORTE 0.5% Ophthalmic Suspension
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml suspension contains:
Active substance(s):
Loteprednol etabonate..... 5 mg
Excipient(s) with known effect:
Benzalkonium chloride (as a preservative)..... 0.1 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Ophthalmic suspension.
White to off-white suspension without any foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

It is indicated for the treatment of steroid responsive 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, cyclitis, selected infective conjunctivitis, when the inherent hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation. It is also indicated for the treatment of postoperative inflammation following ocular surgery.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
Treatment of steroid-responsive conditions
Instill 1 to 2 drops into the conjunctival sac of the affected eye(s) 4 times per day. During initial treatment within the first week, if necessary, the dosage may be increased up to 1 drop per hour. Care should be taken not to terminate the treatment early. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Treatment of post-operative inflammation
Instill 1 to 2 drops into the conjunctival sac of the operated eye(s) 4 times per day, beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period.

The duration of treatment should not exceed 2 weeks.

Method of administration:
Instill into the conjunctival sac of the affected eye. Shake the bottle vigorously before using. The suspension in the bottle is sterile and since it may become contaminated during use, the dropper tip should not be contacted with any surface while the medicine is instilled into the eye. Discard any unused product after 28 days from the first opening date.

Additional information on special populations:
Renal / Hepatic impairment:
There are no reports of topical ophthalmic use in this population.

Pediatric patients:
Efficacy and safety have not been established in pediatric patients.

Geriatric patients:
There are no reports of topical ophthalmic use in this population.

4.3 Contraindications
As with other ophthalmic corticosteroids, LOTEFORTE 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 corticosteroids, 'red eye' with unknown diagnosis and infection caused by amoeba. Using LOTEFORTE is contraindicated for breastfeeding mothers.

It is also contraindicated in individuals with known 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 retinopathy (CSR) 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. The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

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

Ocular steroids can increase the severity or prolong the course of many viral eye infections (including herpes simplex). Extreme caution should be exercised when using a corticosteroid in the treatment of patients with a history of herpes simplex.

Ophthalmic use only. At the time of initial prescription and at the time of renewal after 14 days, the patient should be examined by the physician using a slit lamp and, if necessary, fluorescein staining. 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, although this may be difficult in children and uncooperative patients.

Long-term treatment with topical steroids may cause corneal fungal infections. Fungal invasion

should be considered in any persistent corneal ulcer that has been or is being treated with steroids. When appropriate, fungal cultures should be obtained.

To prevent contamination, the tip of the dropper should not be brought into contact with any surface. If pain develops, or redness, itching, or inflammation becomes severe, the patient should contact the physician immediately.

As with all ophthalmic preparations containing benzalkonium chloride, LOTEFORTE should not be administered while wearing a soft contact lens.

LOTEFORTE contains a preservative (benzalkonium chloride) which may cause eye irritation.

Contact with soft contact lenses should be avoided. Patients should remove contact lenses before using this medicine and put them back 15 minutes afterwards. This medication is known to discolor soft contact lenses.

4.5 Interactions with other medicinal products and other forms of interaction
Since loteprednol etabonate is not detected in plasma following the topical administration of loteprednol etabonate, 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 LOTEFORTE 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.

Additional information on special populations
No interaction studies have been performed.

Pediatric population
No interaction studies have been performed.

4.6 Pregnancy, lactation and fertility
General recommendation
Pregnancy category is C.

Women of childbearing potential / Birth control (Contraception)
There are insufficient data regarding the use of LOTEFORTE in women of childbearing potential and/or the need for contraception in women using LOTEFORTE.

Pregnancy
LOTEFORTE should not be used during pregnancy unless clearly necessary.
There are insufficient data regarding its use in pregnant women.
Studies on animals have shown reproductive toxicity (see section 5.3).
The potential risk for humans is unknown.

Lactation

It is not known whether topical corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk. Systemic steroids appear in human milk and could suppress growth. Using LOTEFORTE is contraindicated for breastfeeding mothers.

Fertility
There is no clinical data indicating that loteprednol etabonate affects fertility in humans.

4.7 Effects on the ability to drive and use machines
There are no studies on the effects of topical ophthalmic use on driving or operating machinery. If transient blurred vision occurs at instillation, the patient should be advised to wait until this subsides before driving or operating machinery.

4.8 Undesirable effects
Frequencies are defined 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); not known (cannot be estimated from the available data).

Infections and infestations
Uncommon: Pharyngitis
Rare: Urinary tract infection, urethritis

Neoplasms benign and malignant (including cysts and polyps)
Rare: Breast neoplasm

Psychiatric disorders
Rare: Nervousness

Nervous system disorders
Common: Headache
Rare: Migraine, taste perversion, dizziness, paresthesia

Eye disorders
Common: Corneal defect, eyelid erythema, eye discharge, ocular discomfort, dry eye, epiphora, foreign body sensation in eyes, conjunctival hyperemia, itching
Uncommon: Abnormal vision, chemosis, keratoconjunctivitis, conjunctivitis, iritis, eye irritation, eye pain, conjunctival papillae, photophobia, uveitis
Unknown: Vision blurred (see section 4.4)

Ear and labyrinth disorders
Rare: Tinnitus

Respiratory, thoracic and mediastinal disorders
Uncommon: Rhinitis
Rare: Cough

Gastrointestinal disorders
Rare: Diarrhea, nausea, vomiting

Skin and subcutaneous tissue disorders
Rare: Face edema, urticaria, rash, dry skin, eczema

Musculoskeletal, connective tissue, and bone 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, randomized 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 prednisolone and 0.5% (3/583) among patients receiving placebo.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose and treatment
No case of ocular overdose has been reported. Symptomatic and supportive treatment should be applied in case of overdose.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group : Ophthalmologicals, antiinflammatory agents, corticosteroids
ATC Code : S01BA14

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. There is no generally accepted explanation for the mechanism of action of ocular corticosteroids. However, corticosteroids are thought to act by the induction of phospholipase A2 inhibitory proteins, collectively called lipocortins. It is postulated that these proteins control the biosynthesis of potent mediators of inflammation such as prostaglandins and leukotrienes by inhibiting the release of arachidonic acid from membrane phospholipids. Arachidonic acid is released from membrane phospholipids by phospholipase A2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate belongs to a new class of corticosteroids designed to have potent anti-inflammatory activity at the site of action. Its anti-inflammatory effect is similar to other potent corticosteroids used in ophthalmology, while its effect on intraocular pressure is lower. Animal studies show that loteprednol etabonate has a binding affinity for corticosteroid receptors 4.3 times greater than dexamethasone. Bioactive molecules in this new class of steroids can be predicted to be transformed into non-toxic substances through *in vivo* transformation, as their

chemical structures and enzymatic pathways in the body are known. Cortienic acid is an inactive metabolite of hydrocortisone, and cortienic acid analogs have no corticosteroid activity. One of these metabolites, cortienic acid etabonate, is used to synthesize loteprednol, an ester derivative.

5.2. Pharmacokinetic properties

General properties

Loteprednol etabonate is structurally similar to other corticosteroids. However, it does not have a ketone group at position 20. Its lipid solubility is quite high and therefore its penetration into cells is strong.

Absorption:

Limited systemic absorption is observed with loteprednol etabonate (<1 ng/ml).

Distribution:

Administration of loteprednol etabonate has been shown to result in low levels of radioactivity in the blood, reaching peak concentration in 1 to 2 hours.

Biotransformation:

Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds and is extensively metabolized to inactive carboxylic acid metabolites in *in vivo* and *in vitro* preclinical metabolism studies.

Elimination:

Since systemic absorption of LOTEFORTE (<1 ng/ml) combination is limited, elimination data for topical use have not been reported. No information on special populations.

5.3 Preclinical safety data

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 fetal 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 multi-dose rabbit ocular studies.

Carcinogenicity:

No carcinogenicity studies are available for loteprednol etabonate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Tyloxapol
Benzalkonium chloride
Povidone
Disodium edetate
Hydrochloric acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities

Due to the absence of incompatibility studies, this medicinal product must not be mixed with

other medicinal products.

6.3 Shelf life
24 months.

6.4 Special precautions for storage
Store at room temperature below 25°C, in an upright position. Do not freeze.
Keep out of the reach and sight of children and in its original package.
Do not use this medicine after the expiry date stated on the box.
Once opened, it should be used within 28 days, provided it is stored below 25°C.

6.5 Nature and contents of the container
The primary packaging material of LOTEFORTE 0.5% Ophthalmic Suspension is an opaque white low-density polyethylene bottle of 5 mL with a dropper and a white screw cap. Each cardboard box includes one bottle and a package leaflet.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
34303 No:1 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORIZATION NUMBER

2018/189

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization : 05.04.2018
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT