SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZYLOTRA 0.5% + 0.3% Eye Drops, Suspension
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml eye drop contains:
Active substance:
Loteprednol etabonate (0.5%) ..... 5 mg
Tobramycin (0.3%) ..... 3 mg
Excipient(s) with known effect:
Benzalkonium chloride ..... 0.1 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, suspension.
White-yellowish white suspension free of foreign particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYLOTRA is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection caused by susceptible bacteria or a risk of bacterial ocular infection exists.

4.2 Posology and method of administration

Posology/frequency and duration of administration
1 or 2 drops are instilled into the conjunctival sac of the affected eye every 4 to 6 hours. For the first 24 or 48 hours, the dosage may be increased to 1 drop every 1 to 2 hours. According to the observed improvement in clinical symptoms, the frequency of instillation should be reduced gradually. Care should be taken not to discontinue treatment prematurely.

Method of administration
It should be thoroughly shaken before use.
It is for ophthalmic use only. The initial treatment and re-treatment after 14 days should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

To prevent contamination, the dropper tip should not be brought into contact with any surface.
If pain, redness, itching or inflammation occurs or worsens, a doctor should be consulted.

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

Pediatric population
Two trials were conducted to evaluate the efficacy and safety of loteprednol etabonate/tobramycin combination in pediatric 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, loteprednol etabonate/tobramycin with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus loteprednol etabonate/tobramycin or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, loteprednol etabonate/tobramycin 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.

ZYLOTRA is not recommended for use in infants and young children unless necessary.

Geriatric population
There are no reports regarding topical ophthalmic use in this population.
No differences in safety and efficacy were observed between older and younger patients.

4.3 Contraindications
As with other steroid anti-infective ophthalmic combination drugs, ZYLOTRA 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. ZYLOTRA is contraindicated in individuals with known or suspected hypersensitivity to any of the ingredients of this medicinal product or to other corticosteroids.

4.4 Special warnings and precautions for use
- It is not for injection into the eyes.
- Prolonged use of corticosteroids may result in posterior subcapsular cataract formation and 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.
- Some patients may develop sensitivity to topically applied aminoglycosides. The drug should be discontinued in case of a sensitivity reaction.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. 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.
- 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.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation.

- It is for ophthalmic use only.
- The initial treatment and re-treatment after 14 days should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- If this product is used for 10 days or longer, intraocular pressure should be monitored, even though it may be difficult in children and uncooperative patients.
- In prolonged local steroid treatment, fungal infections may develop in the cornea. 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.
- As with other antibiotics, prolonged antibiotic use may result in the growth of non-susceptible organisms, including fungi. If superinfection develops, appropriate treatment should be initiated.
- Cross-sensitivity to other antibiotics from the aminoglycoside group may occur. If hypersensitivity develops with this product, the use of it should be discontinued and appropriate precautions should be taken.
- During the use of ZYLOTRA, the tip of the dropper should not be brought into contact with any surface to prevent contamination. If pain, redness, itching or inflammation occurs or worsens, a doctor should be consulted.
- The product should be used and discarded within 30 days from the date the bottle is first opened.
- When topical ocular tobramycin is administered concomitantly with systemic aminoglycoside antibiotics, caution should be exercised to monitor total serum concentrations.
- ZYLOTRA may cause eye irritation due to the benzalkonium chloride excipient it contains. Contact of the product with soft contact lenses should be avoided. Lenses should be taken out before application and then put back after waiting at least 15 minutes. Because this excipient is also known to change the color of the soft contact lenses.

4.5 Interactions with other medicinal products and other forms of interaction

There is no information available on the interaction of topically applied ZYLOTRA with systemic or ophthalmic drugs.

4.6 Pregnancy and lactation

General recommendation

The pregnancy category is C.

Women of childbearing potential/Birth control (contraception)

No effects on childbearing potential have been reported.

Pregnancy

Data obtained from animal studies are insufficient to draw conclusions with regard to the effects on pregnancy and/or embryonic/fetal development and/or birth and/or postnatal development. Potential risk for humans is unknown. Since there are no adequate controlled studies in pregnant women, ZYLOTRA should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Lactation
Since it is not known whether topical ophthalmic application of corticosteroids causes systemic absorption in detectable amounts in breast milk, caution should be exercised when using ZYLOTRA in breastfeeding mothers.

Reproductive ability/Fertility
No effects on fertility have been reported.

4.7 Effects on the ability to drive and use machines
There have been no studies investigating the effect of the drug on the ability to drive and operate machinery. However, as with all ocular medications, if temporal blurring of vision occurs after administering the medication, patients should wait until their vision becomes clear again before driving or using machines.

4.8 Undesirable effects
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 available data).

Eye disorders

Common	: Ocular injection, superficial punctate keratitis, increased intraocular pressure, burning and stinging, hypersensitivity and localized ocular toxicity, including lid itching and swelling, and conjunctival erythema
Uncommon	: Vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders
Rare	: 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, increased intraocular pressure (≥10 mmHg)
Not known	: Development of secondary infection, fungal infections

Nervous system disorders

Common	: Headache

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 the national reporting system.

4.9 Overdose and treatment
Possible clinical signs and symptoms of overdose with ZYLOTRA may be similar to the adverse reactions seen in certain patients (punctate keratitis, erythema, increased lacrimation, edema and eyelid itching).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids and antiinfectives in combination
ATC Code: S01CA

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. Corticosteroids are thought to act by the induction of phospholipase A_2 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 their common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2. Corticosteroids are capable of producing a rise in intraocular pressure.

Loteprednol etabonate is structurally similar to other corticosteroids. It is highly lipid soluble, which enhances its penetration into cells. Loteprednol etabonate is synthesized through structural modifications of prednisolone-related compounds and, based upon *in vivo* and *in vitro* preclinical metabolism studies, loteprednol etabonate undergoes extensive metabolism to inactive carboxylic acid metabolites.

The antibiotic component tobramycin is included in the combination to provide action against susceptible organisms. *In vitro* studies have demonstrated that tobramycin is active against susceptible strains of the following microorganisms: Staphylococci, including *S.aureus* and *S.epidermidis* (coagulase positive and coagulase negative), including penicillin-resistant strains; Streptococci, including some of the Group A-beta-hemolytic 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.

5.2 Pharmacokinetic properties

General properties

Absorption

Loteprednol etabonate penetrates into the aqueous humor. Results were obtained following administration of 1 drop of 0.5% loteprednol etabonate ophthalmic suspension in each eye 8 times daily for 2 days or 4 times daily for 42 days. Considering that plasma levels of loteprednol and its primary metabolite remain below the quantification limit (1 ng/ml), systemic absorption of 0.5% loteprednol etabonate is thought to be very low.

There are no data on the systemic absorption of ocular tobramycin; however, it is known that some systemic absorption may occur with ocular drugs.

Distribution

In normal volunteers, plasma levels of loteprednol etabonate and Δ^1 cortienic acid etabonate (PJ 91), its primary inactive metabolite, were below the limit of quantification (1 ng/mL) at all sampling times.

Biotransformation
The primary inactive metabolite of loteprednol etabonate is Δ^1 cortienic acid etabonate (PJ-91).

Elimination
Since systemic absorption of loteprednol etabonate/tobramycin combination is limited, elimination data for topical use have not been reported.

5.3 Preclinical safety data
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol or tobramycin.

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

Mild ocular irritation was observed in acute and multiple-dose ocular studies in rabbits.

Preclinical effects have been observed at exposures that are not strongly relevant to clinical use and are considered to higher enough than the maximum human exposure.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Glycerin
Tyloxapol
Benzalkonium chloride
Povidone
Disodium edetate
Sulfuric acid
Sodium hydroxide
Water for injection

6.2 Incompatibilities
Since no incompatibility studies have been conducted, this medicinal product should not be mixed with other medicinal products.

6.3 Shelf life
24 months.
It should be used within 30 days after the first opening of the bottle. During this period, the medicine can be stored at room temperature below 25°C.

6.4 Special precautions for storage
Keep at room temperature below 25°C.

6.5 Nature and contents of the container
ZYLOTRA is presented in an opaque, white, low-density polyethylene bottle with dropper and white screw cap, which contains 5 mL of suspension.

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 AUTHORISATION NUMBER(S)

2022/1

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF AUTHORIZATION

Date of first authorization : 14.01.2022
Date of renewal of authorization :

10. DATE OF REVISION OF THE TEXT