# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

DUPATIN 0.2% Eye Drops, Solution
Sterile

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of eye drops:
**Active substance:**
Olopatadine hydrochloride.....2.22 mg
(Equivalent to 2.0 mg olopatadine)

**Excipient(s):**
Benzalkonium chloride.....0.1 mg
Anhydrous disodium phosphate……5 mg

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Eye drops, solution
A clear, colorless to pale yellow solution free of visible particles

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications
DUPATIN is indicated for the prevention and treatment of ocular signs and symptoms of allergic conjunctivitis.

### 4.2 Posology and method of administration

**Posology/frequency and duration of administration**
DUPATIN is administered as one drop per day in the eye affected by allergic conjunctivitis.

**Method of administration**
To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

In case of concomitant therapy with other topical ocular medicines, an interval of 5-10 minutes should be allowed between successive applications.

**Additional information on special populations**

**Renal/Hepatic impairment**
Olopatadine in the form of eye drops has not been studied in patients with renal or hepatic impairment. However, no dose adjustment is expected to be necessary in patients with hepatic or renal impairment

(see section 5.2).

**Pediatric population**
The safety and efficacy in children aged under 3 years has not been established.

**Geriatric population**
No differences in safety and efficacy were observed between the elderly and younger patients.

**4.3 Contraindications**
It is contraindicated in patients with hypersensitivity to olopatadine or to any of the excipients.

**4.4 Special warning and precautions for use**
ONLY FOR OPHTALMIC ADMINISTRATION. NOT ADMINISTERED BY ORAL ROUTE OR INJECTION.

DUPATIN is an antiallergic/antihistaminic agent, and when administered topically, is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this treatment.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas, or other surfaces with the dropper tip of the bottle. Keep the bottle tightly closed when not in use.

If redness occurs in the eyes, contact lenses should not be worn.

DUPATIN should not be used to treat contact lens-related irritations. The medicine contains benzalkonium chloride as a preservative, which can be absorbed by soft contact lenses.

Patients who wear soft contact lenses and do not have redness in their eyes should be instructed to wait at least 15 minutes after instillation before re-inserting their contact lenses.

This medication contains 0.1 mg of benzalkonium chloride per mL. Benzalkonium chloride has been reported to cause eye irritation and symptoms of dry eye, and may affect the tear film and the corneal surface. It should be used with caution in patients with dry eye and in patients whose corneas may be compromised. Patients should be monitored during long-term use.

Regarding benzalkonium, based on the currently available limited data, there is no difference in the adverse event profile in children compared to adults. In general, however, the eye in children tends to react more strongly to a given irritant than the eye in adults.

This medication contains 3.35 mg of phosphate per mL. Very rare cases of corneal calcification associated with the use of phosphate-containing eye drops have been reported in some patients with severely damaged corneas.

**4.5 Interaction with other medicinal products and other forms of interaction**
No interaction studies with DUPATIN have been performed.

*In vitro* studies have shown that olopatadine does not inhibit metabolic reactions associated with cytochrome P-450 isoenzymes 1A2, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4. These results indicate that it is unlikely that olopatadine will undergo metabolic interactions with active ingredients administered

in concomitant therapy.

**Additional information regarding special populations:**
**Pediatric population:**
No interaction studies have been conducted in the pediatric population.

**4.6 Fertility, pregnancy and lactation**
**General recommendation**
Pregnancy category is C.

**Women of child-bearing potential/Contraception**
Women of child-bearing potential should use effective contraception methods during therapy.

**Pregnancy**
There are no adequate data from the use of olopatadine in pregnant women.
Animal studies are insufficient with respect to effects on pregnancy /and-or/ embryonal/fetal development/ and-or/ parturition/ and-or/ postnatal development (see section 5.3). The potential risk for humans is unknown.

DUPATIN should not be used during pregnancy unless it is absolutely necessary. It should only be used if the potential benefit during outweighs the potential fetal risk.
Caution is advised when prescribing this product to pregnant patients.

**Breast-feeding**
DUPATIN should not be used during breast-feeding.
Olopatadine has been detected in the milk of nursing rats following oral administration. It is not known whether topical ocular administration will result in systemic absorption that can pass into breast milk. Therefore, if DUPATIN is recommended to a nursing mother, the case should be kept under careful observation.

It is unknown whether olopatadine is excreted in human breast milk. The excretion of olopatadine in milk has not been studied in animals. When deciding whether to discontinue breastfeeding or to discontinue/avoid DUPATIN treatment, the benefits of breastfeeding for the child and the benefits of DUPATIN treatment for the breastfeeding mother should be considered.

**Reproductive ability / Fertility**
Studies have not been performed to evaluate the effect of topical ocular administration of olopatadine on human fertility.

**4.7 Effects on ability to drive and use machines**
As with any eye drop, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until the vision clears before driving or using machinery.

**4.8 Undesirable effects**
In clinical trials involving over 1,680 patients, olopatadine was administered as monotherapy or as an adjunct to loratadine 10 mg, at a dose of 1 drop four times daily for up to 4 months. It was anticipated that adverse effects potentially related to olopatadine use might occur in approximately 4.5% of patients; however, only 1.6% of these patients discontinued the clinical trial due to adverse effects. No serious ophthalmic or systemic adverse effects related to the treatment were reported in

the clinical trials. The most commonly reported adverse effect associated with treatment was eye pain, occurring at a frequency of 0.7%.

The following adverse reactions were assessed as administration-related and classified according to the following rule: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1000) very rare (<1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

**Infections and infestations**
Uncommon: Rhinitis

**Immune system disorders**
Not known: Hypersensitivity, swelling face

**Nervous system disorders**
Common: Headache, dysgeusia
Uncommon: Dizziness, hypoesthesia
Not known: Somnolence

**Eye disorders**
Common: Eye pain, eye irritation, dry eye, abnormal sensation in eyes
Uncommon: Corneal abrasion, corneal epithelium defect, corneal epithelium disorder, punctate keratitis, keratitis, corneal staining, eye discharge, photophobia, vision blurred, visual acuity reduced, blepharospasm, ocular discomfort, eye pruritus, conjunctival follicles, conjunctival disorder, foreign body sensation in eyes, lacrimation increased, eyelid pruritus, eyelid edema, eyelid disorder, ocular hyperemia
Not known: Corneal edema, eye edema, eye swelling, conjunctivitis, mydriasis, visual disturbance, eyelid margin crusting

**Respiratory, thoracic, and mediastinal disorders**
Common: Nasal dryness
Not known: Shortness of breath (dyspnea), sinusitis

**Gastrointestinal disorders**
Not known: Nausea, vomiting

**Skin and subcutaneous tissue disorders**
Uncommon: Dermatitis contact, skin burning sensation, dry skin
Not known: Dermatitis, erythema

**General disorders and administration site conditions**
Common: Fatigue
Not known: Asthenia, malaise

In some patients with severe corneal damage, very rare cases of corneal calcification have been reported in association with the use of phosphate-containing eye drops.

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**

No data are available in humans regarding overdose by accidental or deliberate ingestion. Olopatadine has a low order of acute toxicity in animals. Accidental ingestion of the entire contents of a bottle of DUPATIN would deliver a maximum systemic exposure of 5 mg olopatadine. This exposure would result in a final dose of 0.5 mg/kg in a 10 kg infant, assuming 100% absorption.

Prolongation of the QTc interval in dogs was observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. A 5 mg oral dose was administered twice-daily for 2.5 days to 102 young and elderly male and female healthy volunteers with no significant prolongation of QTc interval compared to placebo. The range of peak steady-state olopatadine plasma concentrations (35 to 127 ng/mL) seen in this study represents at least a 70-fold safety margin for topical olopatadine with respect to effects on cardiac repolarization.

Treatment

In the case of overdose, appropriate monitoring and management of the patient should be implemented.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Ophthalmologicals; decongestant and antiallergics; other antiallergics
ATC code: S01GX09

Olopatadine is a potent, selective antiallergic/antihistamine that exerts its effects through multiple distinct mechanisms. It is a histamine antagonist (the primary mediator of allergic reactions in humans) and prevents histamine from inducing the production of inflammatory cytokines via human conjunctival epithelial cells. Data from *in vitro* studies suggest that it may act on human conjunctival mast cells to inhibit the release of pro-inflammatory mediators. In patients with open nasolacrimal ducts, topical ocular application of DUPATIN has been recommended primarily to reduce the nasal signs and symptoms of seasonal allergic conjunctivitis. It does not cause a significant change in pupil diameter.

### 5.2 Pharmacokinetic properties

**General characteristics**

Absorption

Olopatadine, like other topically applied medicinal products, is systemically absorbed. However, the systemic absorption of topically applied olopatadine is at its lowest level in the range of plasma concentrations from values below the limit of quantification (<0.5 ng/mL) up to 1.3 ng/mL. These concentrations are 50 to 200 times lower than the following well-tolerated oral doses.

Distribution:

Compared to healthy adults, in patients with severe renal impairment (mean creatinine clearance 13 mL/min), renal dysfunction alters the pharmacokinetics of olopatadine, increasing the peak plasma concentration by 2.3-fold. In patients undergoing hemodialysis (without urinary output of ), plasma olopatadine concentrations following a 10 mg oral dose were lower on the day of hemodialysis compared to non-hemodialysis days, indicating that olopatadine can be removed by hemodialysis.

Studies comparing the pharmacokinetics of a 10 mg oral dose of olopatadine in young adults (mean age 21 years) and the elderly (mean age 74 years) show no significant differences in plasma concentrations (AUC), protein binding, or urinary excretion of the unchanged parent drug and metabolites.

A renal impairment study following oral administration of olopatadine was conducted in patients with severe renal impairment. The results indicate that very high plasma concentrations of olopatadine can be expected in this population. Since plasma concentrations following topical ocular administration of olopatadine are 50–200 times lower than those following well-tolerated oral doses, dose adjustment is not expected to be necessary in the elderly or in patients with renal impairment. Dose adjustment is not expected to be necessary in patients with hepatic impairment.

Biotransformation:
Approximately 60–70% of the dose has been detected in urine as the active ingredient. Two metabolites—the mono-desmethyl and N-oxide metabolites—can be detected in urine at low concentrations.

Elimination
According to oral pharmacokinetic studies, the plasma half-life of olopatadine is approximately 8 to 12 hours, and elimination occurs primarily via the kidneys. Olopatadine is excreted in urine primarily unchanged. Metabolism in the liver is a minor route of elimination.

### 5.3 Preclinical safety data
Orally administered olopatadine was not found to be carcinogenic in mice and rats at doses up to 500/mg/kg/day and 200/mg/kg/day, respectively. These doses are approximately 150,000 and 50,000 times higher than the maximum recommended ocular human doses, based on a 40 microliter drop size and a 50 kg human. No mutagenic potential was observed when olopatadine was tested with an in vitro bacterial reverse mutation (Ames) assay, an in vitro mammalian chromosome aberration assay, or an in vivo mouse micronucleus assay. Administration of olopatadine at oral doses of approximately 100,000 times in male and female rats resulted in a slight decrease in the fertility index, and a reduced implantation rate; however no effects on reproductive function were observed at doses approximately 15,000 times the maximum recommended ocular human dose.

Based on conventional studies regarding safety, pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity, the non-clinical data did not indicate any specific risk to humans.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Benzalkonium chloride
Hydroxyethyl cellulose
Sodium chloride
Edetate disodium
Dibasic sodium phosphate, anhydrous
Concentrated hydrochloric acid and sodium hydroxide (for pH adjustment)
Water for injection

### 6.2 Incompatibilities

Not reported.

**6.3 Shelf life**
24 months.
Once the bottle is opened, the medicine should be used within 28 days.

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

**6.5 Nature and contents of container**
The primary packaging material is an opaque white, low-density polyethylene (LDPE) bottle with a twist-off, white polypropylene cap. Our product is presented in a cardboard box containing 1 bottle with 2.5 ml of product and a patient 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. No.:1
34303 Küçükçekmece/İSTANBUL - TÜRKİYE

## 8. MARKETING AUTHORIZATION NUMBER

2019/322

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 01.07.2019
Date of renewal:

## 10. DATE OF REVISION OF THE TEXT