PRODUCT INFORMATION

1 NAME OF THE MEDICINE

Livostine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredients: levocabastine (as hydrochloride) 0.05%w/v.
Excipients with known effect: benzalkonium chloride and disodium edetate (both 0.15 mg/mL) as preservatives.

3 PHARMACEUTICAL FORM

Eye drops: a sterile white ophthalmic microsuspension (pH 6-8)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Allergic conjunctivitis (classic and vernal).
Livostine eye drops is indicated for the rapid and long-lasting relief of eye complaints such as itching, redness, and watering eyes associated with allergies, for example to grass, pollen, moulds and dust.

4.2 DOSE AND METHOD OF ADMINISTRATION

As LIVOSTIN® eye drops is available as a microsuspension, the bottle should be shaken before each application.

Eye Drops:

As with all ophthalmic preparations containing benzalkonium chloride, patients are advised not to wear soft (hydrophilic) contact lenses while under treatment with LIVOSTIN® eye drops.

Adults and children 6 years of age and over: the usual dose is one drop of LIVOSTIN® eye drops per eye, twice daily. If necessary, the dose may be increased to one drop 3 to 4 times daily. The bottle should be well shaken before use. The duration of treatment should be limited to 8 weeks.

Systemic absorption of levocabastine is very low. However, the systemic absorption of drugs from ophthalmic solutions can be minimised by pressure on the tear duct immediately after application.

LIVOSTIN® eye drops should be used within one month of first opening of the bottle. Patients should be instructed to take appropriate measures to avoid contamination of the container.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Mental Alertness

In clinical trials there was no significant difference in the incidence of slowed patient reactions with LIVOSTIN® compared to placebo and active comparator drugs. LIVOSTIN®, therefore, would not be expected to interfere with the ability to drive a motor vehicle or operate machinery. Should drowsiness occur, caution is advised.

Renal impairment

After a single oral dose of 0.5mg levocabastine in solution, the terminal half-life of levocabastine in moderate to severe renal impairment (Creatinine Clearance 10 – 50mL/min) increased from 36 hours to 95 hours. Overall exposure to levobabastine based on AUC was increased by 56%.

Given the extremely low plasma concentrations after ocular application, a dose adjustment is unlikely to be required in patients with renal impairment receiving levocabastine eye drops. As hepatic metabolism of levocabastine is negligible, dose adjustments in patients with impaired hepatic function should not be necessary.

Paediatric use

No data available on use in children less than six years of age.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions have been seen with LIVOSTIN® eye drops.

4.6 FERTILITY, PREGNANCY AND LACTATION

Use in pregnancy – Pregnancy Category B3

In pregnant rats, levocabastine readily crossed the placental barrier and was distributed extensively in foetal tissues. Reproductive studies in mice and rats showed that levocabastine was embryolethal at oral doses greater than 40 mg/kg/day in both species, and teratogenic at oral doses greater than 40 mg/kg/day in mice and 20 mg/kg/day in rats. The main foetal malformations observed were open eyes in mice, and polydactyly, hydrocephalus, anophthalmia/microphthalmia, hydronephrosis and arthrogryposis in rats. There are limited postmarketing data on the use of LIVOSTIN® eye drops in pregnant women. The risk for humans is unknown. Therefore, LIVOSTIN® eye drops should not be used during pregnancy.

Use in lactation

Based on determinations of levocabastine concentrations in saliva and breast milk in a nursing woman, who received a single oral dose of 0.5mg levocabastine, it is expected that approximately 0.3% of the total ophthalmically administered dose of levocabastine may be transferred to a nursing infant. However, due to the limited nature of the clinical and experimental data, it is recommended that LIVOSTIN® eye drops be avoided in breast-feeding mothers.

Effects on fertility

No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Data

The safety of LIVOSTIN® eye drops was evaluated in 508 subjects who participated in 4, placebo-controlled clinical trials and one open-label clinical trial. All adverse drug reactions (ADRs) reported by subjects in LIVOSTIN® eye drops clinical trials are presented in Table 1.

Table 1: Adverse Drug Reactions Reported by LIVOSTIN® Eye Drops Treated Subjects in 5 Clinical Trials

MedDRA System Organ Class MedDRA PT	LIVOSTIN (n=508) %	**Placebo** (n=178) %
Eye Disorders Eye Irritation	11.6	4.5

Postmarketing Data

Additional adverse drug reactions first identified during postmarketing experience with LIVOSTIN® eye drops are included in Table 2. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Therefore, the frequencies are provided according to the following convention:

Very Common :	≥ 1/10
Common:	≥ 1/100 and < 1/10
Uncommon:	≥ 1/1000 and < 1/100
Rare:	≥ 1/10000 and < 1/1000
Very rare:	≥ 1/10000, including isolated reports

In the table below ADR's are presented by frequency category based on incidence in clinical trials or epidemiology studies when known.

Table 2: Adverse Drug Reactions Identified During Postmarketing Experience with LIVOSTIN® Eye Drops by Frequency Category Estimated from Spontaneous Reporting Rates	
Cardiac Disorders Very Rare	Palpitations
Eye Disorders Very Rare	Eye pain, Conjunctivitis, Eyelid oedema, Eye swelling, Blepharitis, Ocular hyperaemia, Vision blurred
General Disorders and Administrative Site Conditions Very Rare	Application site reaction including eye burning sensation, eye redness, eye pain, eye swelling, eye itching, watery eyes and vision blurred.
Immune System Disorders Very Rare	Anaphylaxis, Angioneurotic oedema, Hypersensitivity
Skin and Subcutaneous Tissue Disorders Very Rare	Contact dermatitis, Urticaria
Nervous System Disorders Very Rare	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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 OVERDOSE

There has been no experience with overdose of LIVOSTIN® eye drops to date. After accidental intake of the contents of the bottle, sedation may occur. In case of overdose, the patient should be advised to drink plenty of water in order to accelerate the renal elimination of levocabastine.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

LIVOSTIN® eye drops contain levocabastine, a potent, fast-acting and highly selective histamine H1-antagonist with a sustained duration of action. After topical application to the eyes, it almost immediately and for several hours relieves the typical symptoms of allergic conjunctivitis (itching, redness, chemosis, eyelid swelling, tearing).

Clinical trials

Clinical studies have shown that LIVOSTIN® eye drops is effective for the indications listed above. The duration of treatment with the eye drops alone was generally 2 - 4 weeks but lasted up to 3 months in two studies and 4 months in one study.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After ocular application, the absorption of levocabastine is incomplete with a systemic bioavailability ranging from 30 to 60% for the eye drops. However, as the amount of levocabastine applied ocularly is small, the levocabastine plasma concentrations achieved are very low. Steady-state concentrations of levocabastine are attained within 7 to 10 days following multiple dosage and are predictable from single-dose pharmacokinetics

Distribution

After single intravenous dosing, levocabastine is rapidly distributed over the tissues, and the terminal half-life is 33 h. The total steady-state volume of distribution is 82 L (1.14 L/kg) with a total plasma clearance of 30 mL/min.

The plasma protein binding of levocabastine is 55% with albumin being the main binding protein.

Excretion

Levocabastine undergoes minimal hepatic metabolism, i.e. ester glucuronidation, and is predominantly cleared by the kidneys. 70% of the parent drug is recovered unchanged in the urine, and 10% of the dose is excreted in the urine as the acylglucuronide of levocabastine. The remaining 20% is excreted unchanged in the faeces.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

In female mice, dietary administration of levocabastine for 20 months stimulated the development of pituitary adenomas and mammary adenocarcinomas. The no-effect dose level for the pituitary tumours was 3 mg/kg/day, but a no-effect dose level has not been established for the mammary tumours. In female rats, there was an equivocal increase in the incidence of mammary tumours at the highest dose level of 34 mg/kg/day administered in the diet for 24 months. There was no evidence of carcinogenic activity in male rats or mice. The mechanism of the carcinogenic effects of levocabastine in female mice (and possibly rats) may involve antagonism of dopamine D2-receptors in the pituitary gland and subsequent elevation of serum prolactin levels.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Propylene glycol, disodium phosphate, sodium dihydrogen phosphate monohydrate, hypromellose 2910 3000 mPa.s, polysorbate 80, benzalkonium chloride solution, disodium edetate, water for injection.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5: Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

The expiry date of the product is indicated on the packaging materials.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

4 mL in 5 mL bottle.

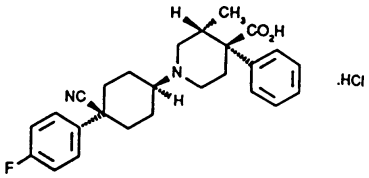
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Levocabastine hydrochloride is a white powder, insoluble in water except at higher pH and only fairly soluble in other solvents such as acetone.

Chemical structure



Chemical Name: Levocabastine, (-)-[3S-[1(cis), 3 alpha, 4 beta]]-1-[4-cyano-4-(4-fluorophenyl) cyclohexyl]-3-methyl-4-phenyl-4-piperidine-carboxylic acid monohydrochloride is a highly selective histamine H1-antagonist for topical use.

Chemical formula: C26H29FN2O2.HCl

MW: 456.99

CAS number CAS-79547-78-7

7 MANUFACTURER

JNTL Consumer Health (Belgium) BV, Antwerpen, Belgium.

8 REGISTRATION HOLDER

Kenvue Hellas Commercial Single Member S.A., Yakum, 6097200, Israel.

9 REGISTRATION NUMBER

141-53-27673-02

Revised in 09.2025.