Livostin Spray Nasal, Nasal Spray, Nebulizador Nasal

NAME OF THE MEDICINAL PRODUCT

Livostin™ (levocabastine) Nasal Spray

QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocabastine hydrochloride equivalent to 0.5 mg levocabastine/ml
For excipients, see List of Excipients.

PHARMACEUTICAL FORM

Nasal spray, suspension

CLINICAL PARTICULARS

Therapeutic Indications

Symptoms of allergic rhinitis

Posology and Method of Administration

As Livostin nasal spray is available as a microsuspension, the bottle should be shaken before each application.
Adults and children: the usual dose is 2 puffs of Livostin nasal spray per nostril, twice daily. The dose may be increased to 2 puffs 3 to 4 times daily. Treatment should be continued as long as required for symptom relief.
Patients should be instructed to clear the nasal passages prior to administering the spray and to inhale through the nose during spraying. Before using the pump delivery system for the first time, the pump reservoir should be filled up by priming until a fine spray is delivered.

Contreindications

Hypersensitivity to any of the ingredients.

Special Warnings and Special Precautions for Use

Limited data are available on the use of oral levocabastine, in patients with renal impairment. Caution should be exercised when administering Livostin nasal spray to patients with renal impairment (see section *Pharmacokinetic Properties — Elimination*).

Interactions with Other Medicinal Products and Other Forms of Interaction

Pharmacodynamic Interactions

Interactions with alcohol or any other drugs were never reported in clinical trials. In specifically designed studies, there was no evidence of potentiation of the effects of either alcohol or diazepam by Livostin nasal spray used in normal dosages.

Pharmacokinetic Interactions

The decongestant oxymetazoline may transiently reduce the absorption of nasal levocabastine.
Co-administration of the CYP3A4 inhibitors ketoconazole or erythromycin had no impact on the pharmacokinetics of intranasal levocabastine.
Intranasal levocabastine did not change the pharmacokinetics of loratadine.

Pregnancy and Lactation

Use during pregnancy

In mice, rats and rabbits, levocabastine at systemic doses up to 1250 times (on a mg/kg basis) the recommended maximum nasal clinical dose, did not reveal any embryotoxic or teratogenic effects. In rodents, levocabastine, at systemic doses beyond 2500 times (on a mg/kg basis) the recommended maximum nasal dose, teratogenicity and/or increased embryonal resorp-tion were observed.
There are limited postmarketing data on the use of levocabastine nasal spray in pregnant women. The risk for humans is unknown. Therefore, Livostin nasal spray should not be used during preg-nancy, unless the potential benefit to the woman justifies the potential risk to the fetus.

Use during lactation

Based on determinations of levocabastine concentrations in saliva and breast milk in a nursing woman who received a single oral dose of 0.5 mg levocabastine, it is expected that approximately 0.6% of the total intranasally 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 caution be exercised when administering Livostin nasal spray to nursing women.

Effects on Ability to Drive and Use Machines

Livostin nasal spray will generally not cause clinically relevant sedation nor does it impair psychomotor performance as compared with placebo. Livostin, therefore, would not be expected to interfere with the ability to drive a car or operate machinery. Should drowsiness occur, caution is advised.

Undesirable Effects

Clinical Trial Data

The safety of levocabastine nasal spray was evaluated in 2328 subjects who participated in 12 double-blind, placebo-controlled clinical trials. Adverse drug reactions (ADRs) reported in ≥1% of subjects in these trials are presented in Table 1.

Table 1:
Adverse Drug Reactions Reported by ≥1% Livostin Nasal Spray Treated Subjects in 12 Double-Blind, Placebo-Controlled Clinical Trials

MedDRA System Organ Class MedDRA PT	Livostin Nasal Spray (n=2328) %	Placebo (n=1537) %
Gastrointestinal Disorders		
Nausea	1.3	1.2
General Disorders and Administrative Site Conditions		
Fatigue	2.1	0.9
Pain	1.2	0.9
Infections and Infestations		
Sinusitis	1.8	0.9
Nervous System Disorders		
Headache	10.1	11.9
Somnolence	2.1	0.8
Dizziness	1.3	0.9
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal pain	2.9	2.3
Epistaxis	1.6	1.0
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Additional ADRs reported for <1% of Livostin Nasal Spray treated subjects in the application of 12 clinical trials are presented in Table 2.

Table 2:
Adverse Drug Reactions Reported by <1% Livostin Nasal Spray Treated Subjects in 12 Double-Blind, Placebo-Controlled Clinical Trials

MedDRA System Organ Class MedDRA PT
General Disorders and Administrative Site Conditions
Application site irritation
Application site pain
Application site dryness
Application site burn
Application site discomfort
Respiratory, Thoracic, and Mediastinal Disorders
Nasal discomfort
Nasal congestion

Postmarketing Data
Additional adverse drug reactions first identified during postmarketing experience with Livostin nasal spray are included in Table 3. 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 Table 3, ADRs are presented by frequency category based on spontaneous reporting rates.

Table 3:
Adverse Drug Reactions Identified During Postmarketing Experience with Livostin Nasal Spray by Frequency Category Estimated from Spontaneous Reporting Rates

Cardiac Disorders	
Very Rare	Tachycardia
Eye Disorders	
Very Rare	Eyelid Oedema
General Disorders and Administrative Site Conditions	
Very Rare	Malaise
Immune System Disorders	
Very Rare	Hypersensitivity
Respiratory, Thoracic, and Mediastinal Disorders	
Very Rare	Bronchospasm, Dyspnoea, Nasal oedema

Overdose
Symptoms
There have been no reports of overdosing with Livostin. Some sedation after accidental intake of the contents of the bottle cannot be excluded.
Treatment
In case of accidental ingestion, the patient should be advised to drink a lot of non-alcoholic fluids in order to accelerate the renal elimination of levocabastine.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Livostin nasal spray contains levocabastine, a very potent, fast-acting and highly selective histamine H_1-antagonist with a sustained duration of action. After topical application to the nose, it almost immediately and for several hours relieves the typical symptoms of allergic rhinitis (sneezing, itchy nose, rhinorrhoea).

Pharmacokinetic Properties
Absorption
After intranasal application of a 50 µg/puff dose, about 30-45 µg of levocabastine is absorbed. Levocabastine reaches peak plasma levels about 3 hours after nasal administration.

Distribution
Protein binding of levocabastine in plasma is approximately 55%.

Metabolism
The primary metabolite of levocabastine, an acylglucuronide, is produced by glucuronidation, the major metabolic pathway.

Elimination
Levocabastine is predominantly excreted in the urine as unchanged drug (about 70% of the absorbed dose). The terminal half-life of levocabastine is approximately 35-40 hours. The plasma pharmacokinetics of nasal levocabastine are linear and predictable.

Special Populations
Elderly
In the elderly, after multiple nasal administrations of 0.4 mg levocabastine, the terminal half-life of levocabastine was increased by 15%, and the peak plasma level was increased by 26%.

Renal Impairment
After a single oral dose of 0.5 mg levocabastine in solution, the terminal half-life of levocabastine in moderate to severe renal impairment (Creatinine Clearance 10-50 ml/min) increased from 36 hours to 95 hours. Overall exposure to levocabastine based on AUC was increased by 56% (see section *Special warnings and special precautions for use*).

Preclinical Safety Data
Nonclinical data revealed no specific drug related topical hazards for humans based on conventional studies with acute dosing (oral, intravenous, inhalation, and dermal administration), and repeat dosing (oral, intravenous, dermal, or ocular administration), including ocular irritation, dermal sensitization, cardiovascular safety pharmacology, oral reproduction, gene toxicity, and oral carcinogenicity studies. Effects were observed only at exposures considered sufficiently in excess of the maximum human dose level to indicate little, if any, relevance to clinical use.

PHARMACEUTICAL PARTICULARS
List of Excipients
Propylene glycol, polysorbate, disodium phosphate, monosodium phosphate, disodium edetate, hypromellose, benzalkonium chloride and water.

Incompatibilities
None known.

Shelf Life
Observe expiry date on the outer pack.

Special Precautions for Storage
Store between 15 and 30°C. Keep out of reach of children.

Nature and Contents of Container
Plastic bottles with a nominal volume of 10 or 15 ml of a white microsuspension.

Instructions for Use and Handling
The bottle should be shaken before each application.

MANUFACTURED BY
See outer carton

DATE OF REVISION OF THE TEXT
May 2009