doses up to 2500 times (on a mg/kg basis) the recommended maximum ocular clinical dose, did not reveal any embryotoxic or teratogenic effects. In rodents, levocabastine at systemic doses beyond 5000 times (on a mg/kg basis) the recommended maximum ocular dose, teratogenicity and/or increased embryonal resorption were observed.

There are limited postmarketing data on the use of levocabastine eye drops in pregnant women. The risk for humans is unknown. Therefore, Livostin eye drops should not be used during pregnancy, unless the potential benefit to the women 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 0.3% 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 caution be exercised when administering Livostin eye drops to nursing women.

Effects on Ability to Drive and Use Machines

Livostin eye drops do not produce sedation nor do they impair psychomotor performance; therefore they can be used by patients driving cars or operating machinery.

Undesirable Effects

Clinical trial data

The safety of Livostin eye drops was evaluated in 508 subjects who participated in four 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.
Treatment
In case of accidental ingestion, the patient should be advised to drink a lot of non-alcoholic liquids in order to accelerate the renal elimination of levocabastine.

PHARMOACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Livostin eye drops contain levocabastine, a very 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).

Pharmacokinetic Properties
Absorption
After instillation in the eyes, levocabastine is slowly and incompletely absorbed. After ophthalmic application of 15 μg/drop dose, about 6 μg of levocabastine is absorbed. After ophthalmic administration levocabastine reaches peak plasma levels after about 6 hours.

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

Metabolism
The primary metabolite of levocabastine, an acyl glucuronide, 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 39–70 hours. The plasma pharmacokinetics of ophthalmic 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%.

| Table 1: Adverse Drug Reactions Reported by Livostin Eye Drops Treated Subjects in Five Clinical Trials |
|-----------------------------------------------|-----------------------------------------------|
| MedDRA System Organ Class | MedDRA PT | Livostin (n=508) | Placebo (n=178) |
| Eye Disorders | Eye irritation | 11.6 | 4.5 |

Postmarketing data
Adverse drug reactions (ADRs) 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 Table 2, ADRs are presented by frequency category based on spontaneous reporting rates.

| Table 2: Adverse Drug Reactions Identified During Postmarketing Experience with Livostin Eye Drops by Frequency Category Estimated from Spontaneous Reporting Rates |
|-----------------------------------------------|-----------------------------------------------|
| Eye Disorders | Very rare | Eye pain, Conjunctivitis, Eyelid oedema, Eye swelling, Blepharitis, Ocular hyperaemia, Vision blurred |
| General Disorders and Administration 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 | Angioneurotic oedema, Hypersensitivity |
| Skin and Subcutaneous Tissue Disorders | Very rare | Contact dermatitis, Urticaria |
| Nervous System Disorders | Very rare | Headache |

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.
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%.

Preclinical Safety Data
Nonclinical data revealed no specific drug related ocular hazards for humans based on conventional studies with acute dosing (oral, intravenous, inhalation, and dermal administration) and repeated dosing (oral, intravenous, dermal and 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 for injections.

Incompatibilities
None known.

Shelf Life
Observe expiry date on the outer pack. Livostin eye drops should be used within one month of the first opening of the bottle.

Special Precautions for Storage
Store at 25°C or below. Keep out of reach of children.

Nature and Contents of Container
5 ml plastic bottles containing 4 ml of white microsuspension.

Instructions for Use and Handling
As Livostin eye drops are available as a microsuspension, the bottle should be shaken before each application.

MANUFACTURED BY
See outer carton

DATE OF REVISION OF THE TEXT
May 2009