

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

L-Histasin 5mg, film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocetirizine dihydrochloride

Each film-coated tablet contains 5mg levocetirizine dihydrochloride (equivalent to 4.2 mg of levocetirizine).

Excipient: each film-coated tablet contains 64.0 mg lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

The film-coated tablets are white to off-white, oval, biconvex tablets, debossed with 'L9CZ' on one side and '5' on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Seasonal and perennial rhinitis and chronic idiopathic urticaria.

4.2 Posology and method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

Adults and adolescents 12 years and above

The daily recommended dose is 5 mg (1 film-coated tablet).

Elderly

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with renal impairment below).

Children aged 6 to 12 years

The daily recommended dose is 5 mg (1 film-coated tablet).

Children aged 2 to 6 years

For children aged 2 to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirizine.

The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended due to the lack of data in this population (see also section 4.4).

Patients with renal impairment

The dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed. The CL_{cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$\frac{[140 - \text{age}(\text{years})] \times \text{weight}(\text{kg})}{72 \times \text{serum creatinine}(\text{mg/dl})} (\times 0.85 \text{ for women})$$

Dosing Adjustments for Patients with Impaired Renal Function:

| Group | Creatinine clearance (ml/min) | Dosage and frequency |
|--|-------------------------------|----------------------------|
| Normal | ≥ 80 | 1 tablet once daily |
| Mild | 50 – 79 | 1 tablet once daily |
| Moderate | 30 – 49 | 1 tablet once every 2 days |
| Severe | < 30 | 1 tablet once every 3 days |
| End-stage renal disease - Patients undergoing dialysis | < 10 | Contra-indicated |

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance of the patient and his body weight. There are no specific data for children with renal impairment.

Patients with hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with renal impairment above).

Duration of use

Intermittent allergic rhinitis (symptoms <4 days/week or during less than 4 weeks) has to be treated according to the disease and its history; it can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear. For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

4.3 Contraindications

Hypersensitivity to levocetirizine, to other piperazine derivatives, or to any of the excipients.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

The use of levocetirizine tablets is not recommended in children less than 6 years of age since the currently available film-coated tablets do not allow dose adaptation yet.

The administration of levocetirizine to infants and toddlers less than 2 years of age is not recommended.

Precaution is recommended with intake of alcohol (see Interactions).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with levocetirizine (including no studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam). A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

4.6 Pregnancy and lactation

For levocetirizine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant or lactating women.

4.7 Effects on ability to drive and use machines

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive. Nevertheless, some patients could experience somnolence, fatigue and asthenia under therapy with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the medicinal product into account.

4.8 Undesirable effects

In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6 % of these adverse drug reactions were mild to moderate.

In therapeutic trials, the drop out rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo.

Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the drug at the recommended dose of 5 mg daily. From this pooling, following incidence of adverse drug reactions were reported at rates of 1 % or greater (common:>1/100, <1/10) under levocetirizine 5 mg or placebo:

| Preferred Term (WHOART) | Placebo (n =771) | Levocetirizine 5 mg (n = 935) |
|------------------------------------|-----------------------------|--|
| Headache | 25 (3.2 %) | 24 (2.6 %) |
| Somnolence | 11 (1.4 %) | 49 (5.2 %) |
| Mouth dry | 12 (1.6%) | 24 (2.6%) |
| Fatigue | 9 (1.2 %) | 23 (2.5 %) |

Further uncommon incidences of adverse reactions (uncommon>1/1000, <1/100) like asthenia or abdominal pain were observed.

The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following adverse drug reactions have been reported in post-marketing experience.

- Investigations: weight increased, abnormal liver function tests
- Cardiac disorders: palpitations
- Nervous system disorders: convulsions
- Eye disorders: visual disturbances
- Respiratory, thoracic, and mediastinal disorders: dyspnoea
- Gastrointestinal disorders: nausea
- Skin and subcutaneous tissue disorders: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
- Musculoskeletal, connective tissue, and bone disorders: myalgia
- Immune system disorders: hypersensitivity including anaphylaxis
- Hepatobiliary disorders: hepatitis
- Psychiatric disorders: aggression, agitation

4.9 Overdose

a) Symptoms

Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children.

b) Management of overdoses

There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, piperazine derivatives;
ATC Code: R06A E09

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H₁-receptors.

Binding studies revealed that levocetirizine has high affinity for human H₁-receptors (K_i = 3.2 nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine (K_i = 6.3 nmol/l). Levocetirizine dissociates from H₁-receptors with a half-life of 115 ± 38 min. After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:

In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p < 0.001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis or perennial allergic rhinitis.

The paediatric safety and efficacy of levocetirizine tablets has been studied in two placebo controlled clinical trials including patients aged 6 to 12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.

Pharmacokinetic / pharmacodynamic relationship

5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations.

ECGs did not show relevant effects of levocetirizine on QT interval.

5.2 Pharmacokinetic properties

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. No chiral inversion occurs during the process of absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. Peak plasma concentrations are achieved 0.9 h after dosing. Steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and a repeated 5 mg o.d. dose, respectively. The extent of absorption is dose-independent and is not altered by food, but the peak concentration is reduced and delayed.

Distribution:

No tissue distribution data are available in humans, neither concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the CNS compartment.

Levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14% of the dose and therefore differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O- dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4 while aromatic oxidation involved multiple and/or unidentified CYP isoforms. Levocetirizine had no effect on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following a 5 mg oral dose.

Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or vice-versa, is unlikely.

Elimination

The plasma half-life in adults is 7.9 ± 1.9 hours. The mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4% of the dose. Excretion via feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Renal impairment

The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Cellulose microcrystalline
Magnesium stearate (E572)

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

2 years.

6.4 Special precautions for storage

Store in the original package to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC:Al blisters or oPA/Al/PVC:Al blisters

Pack sizes:

Blisters containing 1, 2, 4, 5, 7, 10, 14, 15, 20, 21, 28, 30, 40, 50, 56, 60, 70, 90, 100, 112 or 120 tablets

Unit dose blisters containing: 30x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavíkurvegi 76-78,
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

MA628/04901

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15th December 2009