

Paper 35 to 50 gsm



LEVOCETIRIZINE Hydrochloride

HICET-L

5 mg Film Coated Tablet

ANTIHISTAMINE (PIPERAZINE DERIVATIVE)

PRODUCT NAME:
Hicet-L

NAME AND STRENGTH:
Levocetirizine hydrochloride 5 mg tablets

PHARMACOLOGIC CATEGORY:
Antihistamine (piperazine derivatives)

PRODUCT DESCRIPTION:
Light pink coloured, caplet shaped, film-coated tablets with a breakline on one surface and Plain on the other surface.
Breakline is to facilitate breaking for ease of swallowing and not for dividing into equal doses.

FORMULATION/COMPOSITION:
Each film-coated tablet contains
Levocetirizine hydrochloride 5 mg

PHARMACODYNAMICS/PHARMACOKINETICS:
Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivatives, ATC code: R06A E09.

Mechanism of action

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 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.

Pharmacodynamic effects

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

In a study comparing the effects of levocetirizine 5 mg, desloratadine 5 mg, 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 5 mg 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.

Pharmacokinetics

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. In adults, 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.

In humans, 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 half-life is shorter in small children. The mean apparent total body clearance in adults 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 faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special population

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 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%.

Size: 240 (L) x 350 (H) mm

Folding size: 30 x 90 mm

Carton size: 46 x 51 x 106 mm

↓ Front Side

Paediatric population

Data from a paediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children aged 6 to 11 years with body weight ranging between 20 and 40 kg show that C_{max} and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean C_{max} was 450 ng/ml, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender

Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive and use machines. 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.

Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

Hepatic impairment

The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50% increase in half life along with a 40% decrease in clearance compared to healthy subjects.

Pharmacokinetic / pharmacodynamic relationship

The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

INDICATION(s):

Levocetirizine 5 mg film-coated tablets are indicated in the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above.

DOSAGE AND MODE/ROUTE OF ADMINISTRATION:

Posology

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 Renal impairment below).

Renal impairment

The dosing intervals must be individualised according to renal function (eGFR – estimated Glomerular Filtration Rate). Refer to the following table and adjust the dose as indicated.

Dosing adjustments for patients with impaired renal function:

Group	eGFR (ml/min)	Dosage and frequency
Normal renal function	≥ 90	1 tablet once daily
Mildly decreased renal function	60 – < 90	1 tablet once daily
Moderately decreased renal function	30 – < 60	1 tablet once every 2 days
Severely decreased renal function	15 – < 30 (not requiring dialysis)	1 tablet once every 3 days
End stage renal disease (ESRD)	< 15 (requiring dialysis treatment)	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.

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 Renal impairment above).

Paediatric population

Children aged 6 to 12 years:

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

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.

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.

Duration of use:

Intermittent allergic rhinitis (symptoms experienced for less than four days a week or for less than four weeks a year) 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. In case of persistent allergic rhinitis (symptoms experienced for more than four days a week or for more than four weeks a year), continuous therapy can be proposed to the patient during the period of exposure to allergens.

There is clinical experience with the use of levocetirizine for treatment periods of at least 6 months. In chronic urticaria and chronic allergic rhinitis, there is clinical experience of use of cetirizine (racemate) for up to one year.

CONTRAINDICATION(s), PRECAUTION(s), WARNING(s):

Hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any other piperazine derivatives or to any of the other excipients.

Patients with end stage renal disease with estimated Glomerular Filtration Rate (eGFR) below 15 ml/min (requiring dialysis treatment).

Size: 240 (L) x 350 (H) mm

Folding size: 30 x 90 mm

Carton size: 46 x 51 x 106 mm

↓ Back Side

Paper 35 to 50 gsm

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Folding size: 30 x 90 mm

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PRECAUTIONS & WARNINGS:

Precaution is recommended with concurrent intake of alcohol.

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.

Response to allergy skin tests is inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

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

Puritis may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Paediatric population

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of levocetirizine.

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 and use machines.

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.

PREGNANCY AND LACTATION:

Pregnancy

There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicate no malformation or feto/ neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development.

Breast-feeding

Cetirizine, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

Fertility

For levocetirizine no clinical data are available.

INTERACTION(S):

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 antipyrene, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole and pseudoephedrine). 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 coconitant cetirizine administration.

MICRO LABS LIMITED, BANGALORE, INDIA						
1	Product Name	Hicet-L		Colours Used		
2	Strength	5 mg		 BLACK <u>Colours not for Printing</u>  Keylines		
3	Component	Leaflet				
4	Category	Export - Philippines				
5	Dimension	240 (L) x 350 (H) mm				
6	Artwork Code	EXG-ML05I-0324				
7	Pharma Code	N/A				
8	Reason for Change	New Artwork				
		Prepared by (DTP)	Checked by (PD)	Approved by		
Sign		Kanthalaju L.		Head CQA	Head Production/ Packing (Site)	
Date		09-02-2023		Head QC (Site)	Head QA (Site)	