

L-Ceritec

Film Coated Tablet 5mg

1 NAME OF THE MEDICINAL PRODUCT

L-Ceritec Film Coated Tablet 5mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

L-Ceritec Film Coated Tablet 5mg contains 5mg of levocetirizine dihydrochloride.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A white color, elliptical film coated tablet, one side impressed with 'Y'.



4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Levocetirizine is indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and chronic idiopathic urticaria.

4.2 Posology and method of administration

Method of Administration

L-Ceritec Film Coated Tablet 5mg 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 more than four day a week or for more than four weeks a year), continuous therapy can be proposed to the patient throughout 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.

Adults and adolescents 12 years and above: The daily recommended dose is 5mg (1 film coated tablet) once daily.

Children aged 6 to 12 years: The daily recommended dose is 5mg (1 film coated tablet) once daily.

Elderly

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

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.

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

Dosing Adjustments for Patients with Impaired Renal Function:

Group	eGFR (mL/min)	Dosage and frequency
Normal renal function	≥ 90	5 mg once daily
Mildly decreased renal function	60 – < 90	5 mg once daily
Moderately decreased renal function	30 – < 60	5 mg once daily once every 2 days
Severely decreased renal function	15 - < 30 (not requiring dialysis)	5 mg once daily once every 3 days
End-stage renal disease (ESRD)	< 15 (requiring dialysis treatment)	Contraindicated

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 is 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).

4.3 Contraindications

Levocetirizine is contraindicated in:

- Hypersensitivity to levocetirizine, to cetirizine, to hydroxyzine, to any piperazine derivatives or to any of the other excipients listed.
- Patients with end stage renal disease with estimated Glomerular Filtration Rate (eGFR) below 15 ml/min (requiring dialysis treatment).

4.4 Special warnings and precautions for use

Alcohol

Precaution is recommended with concurrent intake of alcohol.

Risk of urinary retention

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.

Risk of seizure aggravation

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

Allergy skin tests

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

Withdrawal syndrome

Pruritus 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.

Excipients

Lactose

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

Sodium

L-Ceritec contains less than 1 mmol sodium (23mg) per film-coated tablet, that is to say essentially 'sodium-free'.

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 antipyrine, pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam).

Theophylline

A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

Ritonavir

In a multiple dose study of ritonavir (600mg twice daily) and cetirizine (10mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

Food

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

Alcohol

In sensitive patients the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

4.6 Fertility, pregnancy and lactation

Fertility

There are no relevant data available.

Pregnancy

The use of levocetirizine may be considered during pregnancy, if necessary. 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 malformative or feto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Lactation

Caution should be exercised when prescribing levocetirizine to lactating women. 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.

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 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.

4.8 Undesirable effects

Clinical Trial Data

Adults and adolescents above 12 years of age

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 dropout 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 dose of 5mg daily.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1000$ to $< 1/100$

Rare $\geq 1/10000$ to $< 1/1000$

Very rare $< 1/10000$

Not known (cannot be estimated from the available data)

Nervous system disorders:

Common: headache, somnolence

Gastrointestinal disorders:

Common: dry mouth

Uncommon: abdominal pain

General disorders and administration site conditions:

Common: fatigue

Uncommon: asthenia

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%).

Post Marketing Data

Immune system disorders:

Not known: hypersensitivity including anaphylaxis

Metabolism and nutrition disorders:

Not known: increased weight, increased appetite

Psychiatric disorders:

Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmares

Nervous system disorders:

Not known: convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia

Eye disorders:

Not known: visual disturbances, blurred vision, oculogyration

Ear and labyrinth disorders:

Not known: vertigo

Cardiac disorders:

Not known: palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders:

Not known: dyspnoea

Gastrointestinal disorders:

Not known: nausea, vomiting, diarrhoea

Hepatobiliary disorders:

Not known: hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders:

Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders:

Not known: myalgia, arthralgia

Renal and urinary disorders:

Not known: dysuria, urinary retention

General disorders and administration site conditions:

Not known: oedema

Skin reactions occurring after discontinuation of levocetirizine

After levocetirizine discontinuation, pruritus has been reported.

4.9 Overdose

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties****General Properties**

Antihistamine for systemic use, piperazine derivative. 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 a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Published data of 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.

Available published data comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, indicates that 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.

Available data of In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. Published data of 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.

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. 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 once daily 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

Metabolism

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 is 0.63ml/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 Populations

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.

Children

Data from a paediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children age 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.

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 20mg 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.

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%.

Other Patient Characteristic

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appears to be comparable to that in men (0.59 ± 0.12 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal Silicon Dioxide

Lactose

Magnesium Stearate

Microcrystalline Cellulose

Opadry White (Titanium Dioxide, Polydextrose, Hypromellose, Triacetin and Macrogol)

Sodium Starch Glycolate

Sodium Stearyl Fumarate

6.2 Incompatibilities

There are no relevant data available.

6.3 Shelf life

3 years from the date of manufacture.

6.4 Special precautions for storage

Store below 30°C. Protect from light.

6.5 Nature and contents of container

L-Ceritec Film Coated Tablet 5mg

Pack Size

Blister 10's x 10, 10's x 50

6.6 Special precautions for disposal

Not applicable.

7 Manufacturer and Product Registration Holder

Y.S.P. INDUSTRIES (M) SDN. BHD. (199001001034)

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