APPROVED
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INSTRUCTION

for medical use

L-CET®

Composition:
active substance: levocetirizine dihydrochloride;
1 coated tablet contains levocetirizine dihydrochloride 5 mg;
excipients: microcystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide anhydrous, Opadry II 85G 51300 green*;
*Opadry II 85G51300 green: polyvinyl alcohol, talc, titanium dioxide (E 171), polyethylene glycol, lecithin, indigo carmine (E 132), quinoline yellow (E 104), Sunset Yellow FCF (E 110).

Pharmaceutical form. Coated tablets.
Main physical and chemical properties: round biconvex tablets with green coating.

Pharmacotherapeutic group.
Antihistamines for systemic use. Piperazine derivatives. ATC Code R06A E09.

Pharmacological properties.
Pharmacodynamics.
Levocetirizine is an active, stable R-enantiomer of cetirizine, which belongs to the group of competitive histamine antagonists. The pharmacological effect is due to the blocking of H1-histamine receptors. The levocetirizine affinity to histamine H_1-receptors is 2 times higher than that of cetirizine. It influences the histamine-dependent stage of the allergic reaction development, reduces migration of eosinophils, vascular permeability, and limits the release of inflammatory mediators. It prevents the development and facilitates the course of allergic reactions, has antiexudative, antipruritic, anti-inflammatory effect, almost has no anticholinergic and antyserotonin actions. It has almost no sedative effect at therapeutic doses.

Pharmacokinetics.
The pharmacokinetics of levocetirizine has a linear correlation, is not dose and time dependent, and exhibits little variability among different subjects. The pharmacokinetic profile with the introduction of a single enantiomer is the same as with the use of cetirizine. In the process of absorption or withdrawal, chiral inversion is not observed.
Absorption.
Levocetirizine is rapidly and intensively absorbed after oral administration. Dose and food intake do not influence the extent of absorption, but the maximum concentration (C_{max}) of the drug decreases and reaches its maximum value later. Bioavailability is 100%.
In 50% of patients the levocetirizine action develops within 12 minutes after a single dose, and in 95% – in 0.5–1 hour. In adults the maximum concentration (C_{max}) in serum is achieved 50 minutes after a single therapeutic dose. Equilibrium concentration in the blood is achieved after 2 days of drug taking. C_{max} is 270 ng/ml after single use and 308 ng/ml after repeated administration at a dose of 5 mg once daily.
Distribution.

There is no information on the distribution of the drug in human tissues, as well as on the penetration of levocetirizine through the blood-brain barrier. In animal studies, the highest concentration is recorded in the liver and kidneys, and the lowest – in the tissues of the central nervous system. Distribution of levocetirizine is limited, since the volume of distribution is 0.4 l/kg. Binding to plasma proteins is 90%.
Biotransformation.
In human body, the metabolic rate is less than 14% of the levocetirizine dose, and therefore the difference in a result of genetic polymorphism or co-administration of enzyme inhibitors is expected to be negligible. The process of metabolism includes aromatic oxidation, N- and O-dealkylation, and coupling with taurine. Dealkylation pathways are primarily mediated by CYP 3A4 cytochrome, whereas in the aromatic oxidation process, the numerical and (or) uncertain CYP isoforms are involved. Levocetirizine did not affect the activity of cytochrome isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4 at concentrations well above the maximum after oral administration of 5 mg. Given the low metabolism and the lack of ability to suppress the metabolism, the interaction of levocetirizine with other substances (and vice versa) is unlikely.
Excretion.
Excretion of the drug occurs mainly in two ways due to glomerular filtration and active tubular secretion. The half-life of levocetirizine in adult plasma ($T_{1/2}$) is 7.9±1.9 hours. The half-life of the drug is shorter in young children. The average apparent total clearance in adults is 0.63 ml/min/kg. Basically, the elimination of levocetirizine and its metabolites from the body occurs in the urine (85.4% of the administered dose is excreted on average). With faeces, only 12.9% of the levocetirizine dose is eliminated.
Specific populations.
Abnormal kidney function.
The apparent clearance of levocetirizine for the body correlates with clearance of creatinine. Therefore, in patients with moderate and severe renal impairment, it is recommended to select intervals between levocetirizine taking into account creatinine clearance. With anuria in patients at the terminal stage of kidney disease, the total clearance of patients compared with the total clearance of the body in people without such disorders decreases by about 80%. The amount of levocetirizine excreted during a standard 4-hour hemodialysis procedure was <10%.

Clinical characteristics.
Indication.
Symptomatic treatment of allergic rhinitis, including whole-year allergic rhinitis, and urticaria in adults and children over 6 years of age.

Contraindications.
Hypersensitivity to levocetirizine, cetirizine, hydroxyzine or to any other piperazine derivatives, as well as to any other excipients of the medicinal product.
Severe chronic renal failure (clearance of creatinine <15 ml/min) (dialysis is required).

Drug interactions and other types of interaction.
Levocetirizine interaction studies (including studies with inducers of CYP3A4) have not been conducted. Cetirizine interaction studies (racemic compound) demonstrated that concurrent drug usage with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole or pseudoephedrine has no clinically significant adverse reactions. When co-administered with theophylline (400 mg/day) in the study of repeated use, there was a slight decrease (by 16%) in the overall clearance of levocetirizine (distribution of theophylline did not change). In the study of multiple use of ritonavir (600 mg 2 times a day) and cetirizine (10 mg/day), the extent of exposure to cetirizine was increased by about 40%, while the disposition of ritonavir was slightly altered (-11%) by concomitant cetirizine administration. There are no data on enhancing the effect of sedatives when used in therapeutic doses. But the use of sedatives while taking levocetirizine should be avoided.
Food intake does not affect the extent of drug absorption, but concomitant food administration reduces its rate of absorption.

Concomitant use of cetirizine or levocetirizine and alcohol or other central nervous system depressants in sensitive patients may lead to an additional reduction in vigilance and ability to perform work.

Special warnings.

Alcohol should be avoided during levocetirizine therapy (see section "Drug interactions and other types of interaction").

When prescribing the drug in the presence of certain factors provoking urinary retention (eg, spinal cord injury, prostate hyperplasia), it should be taken into account that levocetirizine increases the risk of urinary retention.

Care should be taken when prescribing the drug to patients with epilepsy and the risk of seizures, as levocetirizine can intensify seizures.

Antihistaminic drugs suppress the response to the allergic skin test, therefore levocetirizine should be discontinued 3 days before it is performed (elimination period).

Symptoms such as pruritus may occur after discontinuation of levocetirizine, even if such symptoms were not present prior to treatment. These symptoms may disappear on their own. In some cases, the severity of the symptoms may be significant, requiring the repeated application of the drug. After repeated application of treatment, symptoms should disappear.

Children. Levocetirizine in the form of tablets should not be used in children under 6 years of age, as this dosage form does not allow for the dosage to be adjusted accordingly. Levocetirizine in a pharmaceutical form suitable for use in pediatrics is recommended for this category of patients.

Excipients.

The drug contains Sunset Yellow FCF (E 110), which can cause allergic reactions.

This medicinal product contains less than 1 mmol of sodium per 1 tablet, i.e. it is practically sodium-free.

Administration during pregnancy and lactation.

Pregnancy.

Levocetirizine is contraindicated for use during pregnancy.

Lactation.

Cetirizine penetrates into breast milk, so if you need to use a drug breastfeeding should be stopped.

Fertility.

There is no clinical data (including animal studies) on the effect of levocetirizine on fertility.

Influence on ability to drive car or operating machinery.

Comparative clinical trials have found no evidence that levocetirizine at the recommended dose impairs attention, reaction time, or ability to drive vehicles.

However, some patients may experience drowsiness, fatigue, and asthenia during treatment with levocetirizine. Therefore, patients who intend to drive vehicles, engage in potentially hazardous activities or work with mechanisms should consider their reaction to the drug.

Administration and dosage.

The drug should be prescribed for adults and children aged 6 years or more per os in a daily dose of 5 mg once a day, regardless of food intake. The tablet should be swallowed whole with a little amount of water.

Dosage

Adults and children over 12 years old. The daily dose is 5 mg (1 coated tablet) once a day.

Elderly patients. Dose adjustment is recommended for elderly patients with moderate to severe renal impairment (see "Renal impairment" section below).

Renal impairment. Dosage should be individualized based on renal function (eGFR [estimated glomerular filtration rate]) as indicated in the table below.

Table 1. Dose adjustment in patients with impaired renal function.

Renal function	eGFR, ml/min	Dose and dosing frequency
Normal renal function	≥ 90	1 tablet 1 time per day
Mild impairment	60 – <90	1 tablet 1 time per day
Moderate impairment	30 – <60	1 tablet 1 time per 2 days
Severe impairment	15 – <30 (dialysis is not required)	1 tablet 1 time per 3 days
End-stage renal disease	<15 (dialysis is required)	Contraindicated

For pediatric patients with impaired renal function, the dose should be adjusted individually according to the patient's renal clearance and his body weight.
There is no specific data on the use of the drug by children with impaired kidney function.
Liver insufficiency.
Patients with exceptionally hepatic insufficiency do not need correction of the dosage regimen. Patients with hepatic and renal insufficiency should adjust the dosage regimen according to the table above.
Children. Children aged 6 to 12 years: the recommended daily dose is 5 mg (1 coated tablet) once a day. For children aged 2 to 6 years, it is impossible to adjust the doses of levocetirizine in the form of coated tablets. It is recommended to prescribe levocetirizine in a dosage form suitable for use in pediatrics.
Duration of therapy.
Patients with periodic allergic rhinitis (duration of symptoms is less than 4 days per week or less than 4 weeks a year) should be treated according to the disease course and history: treatment can be stopped if the symptoms disappear, and can be restored again in case of recurrence of symptoms. In case of persistent allergic rhinitis (duration of symptoms is more than 4 days a week or more than 4 weeks a year), the patient can be offered continuous therapy during contact with allergens. There is clinical experience with the use of levocetirizine for at least 6 months of treatment. In chronic diseases (chronic allergic rhinitis, chronic urticaria), the duration of treatment is up to 1 year [data available from clinical studies with the use of cetirizine (racemate)].

Children.
The drug in the form of tablets should not be used by children under the age of 6, since this dosage form does not allow for the dosage to be adjusted accordingly. This category of patients should be prescribed levocetirizine in a dosage form suitable for use in pediatrics.

Overdose.
Symptoms.
Overdose symptoms in adults may include drowsiness. At first, children may experience a state of excitement and increased irritability, which are replaced by drowsiness.
Treatment.
There is no specific antidote for levocetirizine. In case of symptoms of overdose symptomatic and supportive therapy is recommended. The need for gastric lavage after a short time since taking the drug should be considered. Hemodialysis is not effective to remove levocetirizine from the body.

Adverse reactions.
Below there are the adverse reactions known from post-marketing experience with the use of the medicinal product. The frequency of these adverse reactions cannot be established from the available data.
Immune system disorders: hypersensitivity, including anaphylaxis.
Nutritional and metabolic disorders: increased appetite.
Nervous system disorders: drowsiness, headache, excessive fatigue, weakness, asthenia, muscle cramps, paresthesia, dizziness, syncope, tremor, dysgeusia.
Mental disorders: sleep disturbances, excitation, hallucinations, depression, aggression, insomnia,

suicidal thoughts, nightmares.
Hearing and balance disorders: vertigo.
Eye disorders: visual impairment, blurring of vision, oculogyration.
Cardiovascular system: palpitation, tachycardia.
Respiratory system disorders: short breath.
Digestive system disorders: diarrhea, vomiting, constipation, dry mouth, nausea, abdominal pain.
Hepatobiliary system disorders: hepatitis.
Kidneys and urinary system disorders: dysuria, urinary retention.
Skin and subcutaneous tissue disorders: angioedema, persistent drug-induced rash, skin itch, rash, urticaria.
Musculoskeletal system and connective tissue disorders: myalgia, arthralgia.
General disorders and injection site conditions: swelling.
Laboratory examinations results: weight gain, liver function tests deviation from the norm.
Description of individual adverse reactions
Pruritus has been reported after discontinuation of levocetirizine.
Reporting of suspected adverse reactions.
The reporting of adverse reactions after the registration of the medicinal product is of great importance. This makes it possible to monitor the benefit/risk ratio when using this medicinal product. Medical and pharmaceutical workers, as well as patients or their legal representatives should be notified of all cases of suspected adverse reactions and lack of efficacy of the medicinal product through the Automated Pharmacovigilance Information System at the link: https://aisf.dec.gov.ua

Shelf life.
3 years.

Storage conditions.
Store at a temperature not more than 25°C.
Keep out of reach of children.

Package.
10 tablets in blister; 1 or 3, or 10 blisters in a cardboard package.

Conditions of supply.
Without prescription.

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Location of manufacturer and its address of business activity.
SP-289 (A), RIICO Industrial area, Chopanki, Bhiwadi, Dist. Alwar (Rajasthan), India.

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