APPROVED
Order of Ministry of Health of Ukraine
12.05.2016 №436
Registration certificate
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INSTRUCTION
for medical use

L-CET®

Composition:
active substance: levocetirizine dihydrochloride;
5 ml of syrup contains levocetirizine dihydrochloride 2.5 mg;
excipients: glycerin, propylene glycol, sodium methyl parahydroxybenzoate (E 219), sodium propyl parahydroxybenzoate (E 217), sucrose, glacial acetic acid, sodium acetate trihydrate, peppermint flavor, banana flavor, purified water.

Pharmaceutical form. Syrup.
Basic physico-chemical properties: colorless, clear, viscous liquid with a characteristic odor.

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 peripheral H_1-histamine receptor antagonists. Pharmacological action is caused by blocking of H_1-histamine receptors. Binding studies revealed that levocetirizine has high affinity for human H_1-receptors (K_i = 3.2 nmol/l). The affinity of levocetirizine is 2 times higher than that of cetirizine (K_i = 6.3 nmol/l). Levocetirizine dissociates from H_1-receptors with a half-life of 115±38 min. After single administration receptor binding of levocetirizine was 90 % after 4 hours and 57 % after 24 hours. Pharmacodynamic studies in healthy volunteers have shown that half the dose of levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.
Pharmacokinetics.
The pharmacokinetics of levocetirizine is linear, dose- and time-independent, and has low inter-subject variability. The pharmacokinetic profile when given as the single enantiomer is the same as with the use of cetirizine. No chiral inversion occurs during the process of absorption and elimination.
Absorption. Levocetirizine is rapidly and extensively absorbed following oral administration. The peak plasma concentration is achieved 0.9 hours after dosing. Steady state is achieved after 2 days. The peak concentration (C_{max}) is usually 270 ng/ml and 308 ng/ml respectively following single and multiple use of the medicinal product at a dose of 5 mg 1 time per day. The extent of absorption is dose-independent. The extent of absorption is not altered by food, but the peak concentration (C_{max}) of the drug is reduced and delayed.
Distribution. No data concerning the tissue distribution are available in humans, neither concerning the passage of levocetirizine through the blood-brain barrier. In animal studies, the highest concentration is found in the liver and kidneys, and the lowest one – in tissues of the central nervous system. Distribution of levocetirizine is limited as the volume of distribution is 0.4 l/kg. Binding to plasma proteins is 90 %.
Metabolism. The metabolic rate in humans is less than 14 % of the dose and therefore differences resulting from genetic polymorphism or concomitant use of liver enzyme inhibitors are expected to be negligible. The process of metabolism includes aromatic oxidation, N- and O-dealkylation and taurine

conjugation. Dealkylation occurs primarily with cytochrome CYP 3A4, while numerous and/or unidentified CYP isoforms are involved in the aromatic oxidation process. Levocetirizine does not affect the activity of cytochrome isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1, 3A4 at concentrations well above peak concentrations after oral administration of a 5 mg dose. Due to its low metabolism and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances (and vice-versa), is unlikely.

Elimination. Excretion of the drug occurs in two ways: by glomerular filtration and active tubular secretion. The elimination half-life of the drug in adults ($T_{1/2}$) is 7.9 ± 1.9 hours. The elimination half-life of the drug is shorter in young children. The mean apparent total clearance in adults is 0.63 ml/min/kg. Levocetirizine and its metabolites are mainly excreted in the urine (a mean of 85.4 % of the administered dose is excreted). Only 12.9% of the administered dose of the drug is excreted with feces.

Special populations

Renal impairment.

The apparent total clearance of levocetirizine is correlated with creatinine clearance. Therefore, it is recommended to adjust dosing intervals of levocetirizine based on creatinine clearance in patients with moderate and severe renal impairment. With anuria in patients with end-stage renal disease, the total clearance is decreased by approximately 80 % compared to the total clearance in subjects without such disorders. The amount of levocetirizine eliminated during a standard 4-hour hemodialysis procedure was < 10 %.

Children.

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

Elderly patients.

Data concerning the pharmacokinetics in elderly patients are limited. Following repeated oral administration of 30 mg levocetirizine once daily for 6 days, the total clearance was approximately 33 % lower in 9 elderly subjects (aged 65–74 years) than in younger adult patients. Distribution of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding may also be applicable for levocetirizine, as levocetirizine and cetirizine are predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender

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

Race

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

Hepatic impairment

The pharmacokinetics of levocetirizine in patients with hepatic impairment has not been studied. A 50% increase in elimination half-life along with a 40% decrease in clearance have been observed in patients

with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis), who received 10 or 20 mg of the racemic compound cetirizine as a single dose, compared to healthy subjects.

Clinical characteristics.

Indications.

Symptomatic treatment of allergic rhinitis (including perennial allergic rhinitis) and urticaria in adults and children over 2 years of age.

Contraindications.

Hypersensitivity to levocetirizine, cetirizine, hydroxyzine, to any other derivatives of piperazine or to any of the other excipients of the drug.
Severe chronic renal failure (creatinine clearance < 15 ml/min) (requiring dialysis).

Interaction with other medicinal products and other forms of interaction.

No interaction studies with levocetirizine have been conducted (in particular interaction studies with CYP3A4 inducers); studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions (with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole and pseudoephedrine). A small decrease in the cetirizine clearance (16 %) was observed in a multiple dose study with concomitant use of theophylline (400 mg 1 time per day); distribution of theophylline did not change with concomitant use of cetirizine.
In a multiple dose study of ritonavir (600 mg 2 times daily) and cetirizine (10 mg per day), the exposure to cetirizine increased by 40 %, and the exposure to ritonavir changed slightly (-11 %).
Food intake does not affect the extent of absorption of levocetirizine, though the absorption rate is decreased.
Concomitant use of cetirizine or levocetirizine and alcohol or other central nervous system depressants in sensitive patients may cause additional reduction in alertness and performance.

Administration details.

Alcohol intake should be avoided during treatment with levocetirizine (see section «Interaction with other medicinal products and other forms of interaction»).
When prescribing the medicinal product to patients with predisposing factors of urinary retention (e.g., spinal cord trauma, prostatic hyperplasia), it should be taken into account that levocetirizine increases the risk of urinary retention.
Caution should be exercised when prescribing the medicinal product to patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure exacerbation.
Response to allergy skin tests is inhibited by antihistamines, therefore the use of the medicinal product should be discontinued 3 days before performing them (a wash-out period).
Pruritus may occur when levocetirizine is discontinued, even if these symptoms were not present before treatment initiation. These symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment with the medicinal product to be reinitiated. The symptoms should resolve when the treatment is reinitiated.

Pediatric population

Available clinical data concerning the use of levocetirizine in children aged 6 months to 12 years are not sufficient to justify its use in infants and children under 2 years of age.

Excipients.

The drug contains sucrose, so if you have intolerance to some sugars, consult your physician before taking this medicine.
The drug contains sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

Use during pregnancy or breastfeeding.

Pregnancy.

There are no or limited data (less than 300 pregnancy outcomes) on 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 indicates no malformative or feto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryonic/fetal development, parturition or postnatal development.
The use of levocetirizine may be considered during pregnancy, if necessary.
Breastfeeding.
Cetirizine, the racemate of levocetirizine, has been shown to be excreted from the human body. Therefore, the excretion of levocetirizine in breast milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to women who are breastfeeding.
Fertility
There are no clinical data about the effect of levocetirizine on fertility.

Effect on reaction rate when driving motor transport or using other mechanisms.
Comparative clinical trials have revealed no evidence that levocetirizine at the recommended dose impairs mental alertness, reactivity or the ability to drive.
However, some patients may experience somnolence, fatigue and asthenia during treatment with levocetirizine. Therefore, patients intending to drive, engage in potentially hazardous activities or use mechanisms should consider their response to the medicinal product.

Dosage and administration.
The drug should be prescribed to adults and children over 2 years of age to be taken orally with or without food.
Dosage
Adults and children over 12 years of age.
The daily dose is 5 mg (10 ml of syrup) 1 time per day.
Elderly patients.
Dose adjustment is recommended in elderly patients with moderate to severe renal impairment (see section "Renal impairment").
Renal impairment.
The dosing intervals should be individualised according to renal function (eGFR – estimated glomerular filtration rate). Refer to the table and adjust the dose as indicated.

Table. Dosing adjustment for patients with impaired renal function.

Group	eGFR (ml/min)	Dosage and frequency
Normal renal function	≥ 90	5 mg (10 ml of syrup) 1 time per day
Mildly impaired renal function	60 – <90	5 mg (10 ml of syrup) 1 time per day
Moderately impaired renal function	30 – <60	5mg (10 ml of syrup) 1 time every 3 days
Severely decreased renal function	15 – <30 (not requiring dialysis)	5mg (10 ml of syrup) 1 time every 3 days
End-stage renal disease	<15 (requiring dialysis treatment)	Contraindicated

In children with renal impairment, the dose should be adjusted individually taking into account the renal clearance of the patient and his body weight.
There are no specific data concerning the use of the drug in children with renal impairment.
Hepatic impairment.
No dose adjustment is required in patients with solely hepatic impairment. In patients with hepatic and renal impairment, dose adjustment is recommended according to the abovementioned table.
Children

Children aged 6 to 12 years: the daily recommended dose is 5 mg (10 ml of syrup) 1 time per day.
Children aged 2 to 6 years: the daily recommended dose is 2.5 mg divided into 2 doses of 1.25 mg (2.5 ml of syrup 2 times per day).
Duration of use.
Patients with intermittent allergic rhinitis (symptoms experienced for less than 4 days a week or for less than 4 weeks a year) should be treated according to the progression of the disease and history: treatment may be discontinued, if symptoms resolve, and be reinitiated again when symptoms recur. In case of persistent allergic rhinitis (symptoms experienced for more than 4 days a week or for more than 4 weeks a year), continuous therapy can be proposed to the patient throughout the period of exposure to allergens. There is clinical experience of the use of levocetirizine for treatment periods of at least 6 months. In chronic diseases (chronic allergic rhinitis, chronic urticaria), the treatment period is up to 1 year (data available from clinical studies of the use of cetirizine (racemate)).

Children.
The use in children under 2 years of age is not recommended due to limited data in this age category. The drug should be used in children over 2 years of age.

Overdose.
Symptoms.
Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness.
Management of overdoses.
There is no specific antidote to levocetirizine. Should overdose symptoms occur, symptomatic and supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug. Levocetirizine is not effectively removed by hemodialysis.

Adverse reactions.
Clinical studies
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 reaction compared to 11.3% in the placebo group. 91.6 % of these adverse 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 medicinal product at the recommended dose of 5 mg daily. From this pooling, the following incidence of adverse reactions was reported at rates of 1% or greater (common: ≥1/100 to <1/10) under levocetirizine 5 mg or placebo:

Adverse reaction	Placebo (n =771)	Levocetirizine 5 mg (n = 935)
headache	25 (3.2%)	24 (2.6%)
somnolence	11 (1.4%)	49 (5.2%)
dry mouth	12 (1.6%)	24 (2.6%)
increased fatigability	9 (1.2%)	23 (2.5%)

Asthenia and abdominal pain have also been reported uncommonly (≥ 1/1000, <1/100).
The frequency of sedating adverse reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).
Children
In two placebo-controlled studies in pediatric patients aged 6 to 11 months and aged 1 to 6 years, 159 subjects were exposed to levocetirizine at a dose of 1.25 mg daily for 2 weeks and 1.25 mg twice daily respectively. The following frequency of adverse reactions was reported at rates of 1% or greater under levocetirizine or placebo.

Organ systems and adverse reactions	Placebo (n=83)	Levocetirizine (n=159)
gastrointestinal disorders		
diarrhea	0	3(1.9%)
vomiting	1(1.2%)	1(0.6%)
constipation	0	2(1.3%)
nervous system disorders		
somnolence	2(2.4%)	3(1.9%)
psychiatric disorders		
sleep disorders	0	2(1.3%)

In children aged 6 to 12 years double blind placebo-controlled studies were performed where 243 children were exposed to 5 mg levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following frequency of adverse reactions was reported at rates of 1% or greater under levocetirizine or placebo.

Adverse reactions	Placebo (n=240)	Levocetirizine 5mg (n=243)
headache	5(2.1%)	2(0.8%)
somnolence	1(0.4%)	7(2.9%)

Post-marketing experience
The frequency is classified as: 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), frequency not known (the frequency cannot be estimated from the available data).
Immune system disorders: frequency not known: hypersensitivity, including anaphylaxis.
Nutrition and metabolism disorders: frequency not known: increased appetite.
Nervous system disorders: frequency not known: somnolence, headache, increased fatigability, weakness, asthenia, convulsions, paresthesia, dizziness, syncope, tremor, dysgeusia.
Psychiatric disorders: frequency not known: sleep disturbance, agitation, hallucination, depression, aggression, insomnia, suicidal ideation, nightmares.
Ear and labyrinth disorders: frequency not known: vertigo.
Eye disorders: frequency not known: visual disturbances, blurred vision, oculogyration.
Cardiac disorders: frequency not known: palpitation, tachycardia.
Respiratory, thoracic and mediastinal disorders: frequency not known: dyspnea.
Gastrointestinal disorders: frequency not known: diarrhea, vomiting, constipation, dry mouth, nausea, abdominal pain.
Hepatobiliary disorders: frequency not known: hepatitis.
Renal and urinary system disorders: frequency not known: dysuria, urinary retention.
Skin and subcutaneous tissue disorders: frequency not known: angioedema, fixed drug eruption, pruritus, rash, urticaria.
Musculoskeletal system, connective tissue and bone disorders: frequency not known: myalgia, arthralgia.
General disorders and administration site conditions: frequency not known: edema.
Investigation results: frequency not known: bodyweight increased, abnormal liver function tests.
Description of selected adverse reactions
Pruritus has been reported after levocetirizine discontinuation.
Reporting of suspected adverse reactions.
Reporting adverse reactions after the registration of the medicinal product is of great importance. It allows to monitor the correlation of the benefits and risks related to the use of the medicinal product. Healthcare and pharmaceutical professionals, as well as patients or their legal representatives are asked to report any suspected adverse reactions and lack of efficacy of the medicinal product through the Automated pharmacovigilance information system available at: https://aisf.dec.gov.ua

Shelf-life.
3 years.

Storage conditions.
Store at a temperature not more than 25 °C in the original package.
Keep out of reach of children.
After first opening the bottle, the drug should be stored for no more than 4 weeks.

Package.
60 ml or 100 ml are in polyethylene or glass bottles. Each bottle is in a carton package with a measuring spoon.

Conditions of supply.
Without prescription.

Manufacturer.
LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Skryabina Str. 54.

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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