APPROVED
The Order of Ministry of Health of Ukraine
12.05.2016 №436
Registration certificate
№ UA/8612/02/01

AMENDED
The Order of Ministry of Health of Ukraine
22.02.2019 № 464

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: colourless, transparent, viscous liquid with characteristic odor.

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

Pharmacological properties.
Pharmacodynamics.
Levocetrizin is an active, stable R-enantiomer of cetirizine, which belongs to the group of competitive histamine antagonists. Pharmacological action is caused by blocking of H_1-histamine receptors. The affinity for H_1-histamine receptors in levocetirizine is 2 times higher than that of cetirizine. It affects the histamine-dependent stage of development of an allergic reaction, reduces the migration of eosinophils, vascular permeability, and restricts the release of mediators of inflammation. It prevents development and facilitates the course of allergic reactions, performs anti-exudative, anti-itch, anti-inflammatory action, it almost does not perform anticholinergic and antiserotonin action.
Pharmacokinetics.
The pharmacokinetic parameters of levocetirizine have linear dependence, it does not depend on dose and time, and it has low variability in various patients. The pharmacokinetic profile of 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 absorbed rapidly and intensively after oral administration.
The degree of absorption of the drug does not depend on the dose of the drug and does not change with eating, but the maximum concentration (C_{max}) of the drug decreases and reaches its maximum value later. Bioavailability is 100%.
In 50% of patients, levocetirizine develops after 12 minutes after taking a single dose, and 95% - in 0.5-1 hour. The maximum concentration (C_{max}) in blood serum is achieved after 50 minutes after taking a single intra-therapeutic dose. Equilibrium concentration in the blood is achieved after 2 days of taking the

drug. C_{max} is 270 ng/ml after single use and 308 ng/ml - after repeated administration at a dose of 5 mg, respectively.

Distribution.

There is no information on the distribution of the drug in human tissues, as well as the penetration of levocetirizine through the blood-brain barrier. In 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 the human body, the metabolic rate is less than 14% of the dose of levocetirizine, and therefore the difference as 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 occurs primarily with cytochrome CYP 3A4, while numerous and (or) uncertain CYP isoforms are involved in the aromatic oxidation process. Levocetrizin 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 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 (an average 85.4% of the administered dose is excreted). Only 12.9% of the administered dose of levocetirizine is excreted with faeces.

Specific populations

Renal impairment

The apparent clearance of levocytrizin 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 administrations taking into account creatinine clearance. With anuria 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 withdrawn during a standard 4-hour hemodialysis procedure was <10%.

Clinical characteristics.

Indication.

Symptomatic treatment of allergic rhinitis (including year-round allergic rhinitis) and urticaria.

Contraindication.

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 (clearance of creatinine < 10 ml/min).

Interaction with other drugs and other types of interactions.

Levocetrizin interaction studies (including studies with inducers of CYP3A4) have not been conducted. Studies with cetirizine (racemate compounds) have shown that concomitant use with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole or pseudoephedrine does not cause clinically significant adverse interactions. When co-administered with theophylline (400 mg/day), there was a slight decrease (by 16%) in the total clearance of levocetirizine (distribution of theophylline did not change). In the study of multiple use of ritonavir (600 mg 2 times daily) and cetirizine (10 mg/day), the exposure to cetirizine increased by about 40%, while the ritonavir distribution slightly changed (-11%) to the parallel use of cetirizine.

The meal does not affect the degree of absorption of the drug, but it reduces the rate of its absorption.

Concomitant use of cetirizine or levocytrizine and alcohol or other central nervous system depressants in vulnerable patients may lead to additional reduction in vigilance and ability to do some work.

Administration details.
Use with caution in patients with chronic kidney disease (dosing regimen required) and in elderly patients (glomerular filtration may be reduced). Care should be taken when taking the drug simultaneously with alcohol (see section "Interaction with other drugs and other types of interactions").
When prescribing the drug in patients with certain factors that provoke urinary retention (e.g., spinal cord trauma, prostatic hyperplasia), it should be taken into account that levocetirizine increases the risk of urinary retention.
There are no available data that increase the effect of sedatives when it applied in therapeutic doses. But the use of sedatives during treatment should be avoided.
Since antihistamines can suppress the response to skin allergic tests, it is necessary to have a washout period (from 3 days) prior to their administration.
Itching is possible in the case of discontinuation of levocetirizine, even if these symptoms were not present prior to treatment. Itching may disappear on its own. In some cases, itching may be intense, which may be the reason for the renewal of treatment. After repeated application of levocetirizine itching usually disappear.
Excipients.
The drug contains sucrose, so if You have intolerance to some sugars, consult your doctor before taking this medicine.
The drug contains sodium methyl parahydroxybenzoate and sodium propyl parahydroxybenzoate, which can cause allergic reactions (possibly delayed).

Use during pregnancy or breastfeeding.
Pregnancy
Levocetirizine is contraindicated to use during pregnancy.
Breast-feeding
Cetirizine penetrates into breast milk, so that's why breastfeeding should be stopped if it is necessary.
Fertility
There are no clinical data (including animal studies) about the effect of levocetirizine on fertility.

Effects on ability to drive and operate machinery.
It is necessary to refrain from driving or working with other potentially dangerous mechanisms during drug treatment.

Method of administration and dosage.
The drug should be prescribed to adults and children over 2 years of oral administration, regardless of meal.
Recommended doses:

Patient category	*Age*	*Daily dose*	*Single dose*	*The number of intakes*
Children	From 2 years to 6 years	2,5 mg (5 ml)	1,25 mg (2,5 ml)	2 times per day
	From 6 years to 12 years	5 mg (10 ml)	5 mg (10 ml)	1 time per day
Adolescent	From 12 years to 18 years	5 mg (10 ml)	5 mg (10 ml)	1 time per day
Adults	From 18 years	5 mg (10 ml)	5 mg (10 ml)	1 time per day

The elderly patients with normal renal function do not need a dose adjustment.
Patients with impaired kidney function should calculate the dose taking into account the creatinine clearance in accordance with the table.
To use this dosing table, it is necessary to evaluate the patient's creatinine clearance (CL_C) in ml/min CL_C (ml/min) should be evaluated for the creatinine content in blood serum (mg/dl) using the following formula:

$$CLc = \frac{[140 - \text{age (years)}] \times \text{body weight (kg)} \; (\times 0{,}85 \text{ for women})}{72 \times \text{creatinine of blood serum (mg/dL)}}$$

Correction of the dose of the drug in patients with impaired renal function:

Renal function	*Creatinine Clearance, ml/min*	*Daily dosage*	*The number of intakes*
Normal kidney function	≥ 80	5 mg (10 ml)	1 time per day
Violation of the light degree	50-79	5 mg (10 ml)	1 time per day
Violations of moderate degree	30-49	5 mg (10 ml)	1 time per 2 days
Violation of severe degree	< 30	5 mg (10 ml)	1 time per 3 days
End-stage of kidney disease. Patients who are on dialysis	< 10	Contraindicated	

Children with impaired kidney function should adjust the dose individually, taking into account the renal clearance of the patient and his/her body weight.
There are no specific data about the use of children with impaired kidney function.
Patients with impaired liver function
Patients with exceptionally hepatic insufficiency do not need regimen correction of the dosage. Patients with hepatic and renal insufficiency should adjust the dosage regimen according to the table above.
Duration of use
Patients with periodic allergic rhinitis (duration of symptom expression is less than 4 days a week or less than 4 weeks a year) should be treated according to the course of the disease and anamnesis: 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 onset is more than 4 days a week or more than 4 weeks a year) during contact with allergens the patient can be offered continuous therapy. 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 racemate).

Children.
The use of children under the age of 2 years is not recommended because of the limited data in this age category.
The drug is for use in children over 2 years of age.

Overdose
Symptoms: the symptoms of overdose may include drowsiness in adults and initial exaltation and increased irritability with subsequent sleepiness in children.
Treatment. There is no specific antidote for levocetirizine. In case of symptoms of overdose symptomatic and supportive therapy is recommended. It should be considered the need for gastric lavage after a short time after taking the drug. Hemodialysis is not effective to remove levocetirizine from the body.

Adverse reactions.
Nervous system: drowsiness, headache, increased fatigability, weakness, asthenia, seizures, paresthesia, dizziness, fainting, tremor, dysgeusia.
Psycho: sleep disturbance, agitation, hallucinations, depression, aggression, insomnia, suicidal thoughts.
Heart disorders: increased heartbeat, tachycardia.
Vision organs: visual impairment, blurred vision.
Hearing and balance organs: vertigo.
Liver and bile ducts: hepatitis.
Kidneys and the urinary system: dysuria, urinary retention.
Immune system: hypersensitivity including anaphylaxis and angioneurotic edema.
Respiratory system, thoracic organs and mediastinum: dyspnea.
Digestive tract: diarrhea, vomiting, constipation, dry mouth, nausea, abdominal pain.
Skin and subcutaneous tissues: persistent medication rash, itching, rash, urticaria.
Bone and muscular system: myalgia, arthralgia.
Research results: body weight incresing, deviation of functional liver samples from normal.
Nutritional disorder and metabolism: increased appetite.

General disorders and condition of administration site: edema.

Shelf-life.
3 years.

Storage conditions.
Store at a temperature below 25 ºC in the original package.
Keep out of the reach of children.
After the first opening of the bottle, the drug should be stored for no more than 4 weeks.

Packaging.
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.

Manufacture.
"KUSUM PHARM" LLC.

Address.
40020, Ukraine, Sumy Oblast, Sumy, Skryabina Str., 54

Last revision date.
22.02.2019 № 464