CALIVIDA®

Levocetirizine dihydrochloride

0.5 mg/ml oral solution

Composition

Each 1 ml of oral solution contains:

Active ingredient: Levocetirizine dihydrochloride 0.5 mg.

Excipients: Maltitol liquid (E965), glycerol (E422), saccharin sodium, sodium acetate trihydrate, glacial acetic acid, sodium benzoate (E211), wild strawberry aroma, purified water.

Indications

Levocetirizine is indicated for the treatment of:

- Seasonal, perennial and persisting allergic rhinitis (hay fever and pollinosis)
- Allergic conjunctivitis
- Chronic idiopathic urticaria

Dosage and administration

The appropriate volume of **Calivida** oral solution should be measured, and administered directly or poured in a glass of water. If so, it must be taken orally immediately after dilution, and may be taken with or without food.

Adults and children 12 years of age and older:

The daily recommended dose is 5 mg (10 ml of solution) to be administered in the evening.

Children 6 to 11 years:

The recommended dose is 2.5 mg (5 ml of solution) once daily to be administered in the evening.

Children aged between 2 and 6 years:

In this group of age **Calivida** is indicated for the relief of symptoms of perennial allergic rhinitis and the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria.

The daily recommended dose is 1.25 mg (2.5 ml of solution) to be administered in the evening.

Due to the lack of data in this population, the administration of levocetirizine to toddlers aged less than 6 months is not recommended.

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Patients with impaired renal function).

Patients with impaired renal function:

The dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated.

To use the dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in ml/min is needed. The CL_{Cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustments for patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	5 mg once daily
Mild	50 – 79	2.5 mg once daily
Moderate	30 – 49	2.5 mg once every 2 days
Severe	< 30	2.5 mg once every 3 days
End-stage renal disease - Patients undergoing dialysis	< 10	Contra-indicated

In pediatric 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.

Patients with 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 Patients with renal impairment above).

Duration of use

Intermittent allergic rhinitis (symptoms < 4 days/week or during less than 4 weeks) 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 > 4 days/week and during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens. Clinical experience with 5 mg levocetirizine as a film-coated tablet formulation is currently available for a 6-month treatment period. For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

Contraindications

History of hypersensitivity to levocetirizine or any of the other constituents of the formulation or to any piperazine derivatives.

Patients with terminal kidney failure (creatinine clearance < 10 ml/min).

Warnings and precautions

Precaution is recommended with intake of alcohol (see Interactions).

Calivida oral solution contains maltitol: Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Pregnancy and lactation

Pregnancy: For levocetirizine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant or lactating women.

Lactation: As levocetirizine is expected to be excreted in breast milk, it should not be administered when breastfeeding.

Driving and using machines

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

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.

Undesirable effects

From clinical trials, mainly mild to moderate side effects such as dry mouth, headache, fatigue, somnolence and asthenia have been reported commonly (above 1%).

In addition to the adverse reactions reported during clinical studies and listed above, very rare cases of the following adverse drug reactions have been reported in post-marketing experience: anaphylactic reaction, hypersensitivity reaction, angio-oedema, anxious states, convulsions, sinus thrombosis, inflammation, angina pectoris, tachycardia, jugular vein thrombosis, increased rhinitis, difficulty in breathing, exanthema, hypotrichosis, pruritus, rash, fissures, urticaria, photosensitivity/toxicity, interaction, dry mucous membranes, gastrointestinal disorders, nausea, increase of liver enzymes, cross reactivity.

Overdose

Symptoms: Symptoms of overdose may include drowsiness in adults and initially agitation and restlessness, followed by drowsiness in children.

Management of overdoses: There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

Interactions

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

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

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol.

Pharmacodynamics

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivative.

Levocetirizine is an antihistaminic drug with antiallergic properties. It is a potent and selective antagonist of peripheral H1- receptors, with very poor effect on other receptors and has therefore almost no anticholinergic and antiserotonergic properties.

Levocetirizine is the (R) enantiomer of cetirizine. Binding studies revealed that levocetirizine has high affinity for human H1- receptors (Ki= 3.2 nmol/l). Levocetirizine has an affinity 2- fold higher then cetirizine (Ki= 6.3 nmol/l). Levocetirizine dissociates from H1- receptors with a half life of 115± 38 min. 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.

The dose-determining trials showed an optimal benefit- to- risk ratio in the administering of daily doses of 5 mg levocetirizine. In the treatment of seasonal allergic rhinitis, formal bridging studies showed a statically significant equivalence between 5 mg levocetirizine and 10 mg cetirizine doses. As the most important indicators of pharmacodynamic and pharmacokinetic properties of levocetirizine, as well as its therapeutic efficiency, were investigated using bridging studies, results from studies on cetirizine relating to further testing on perennial allergic rhinitis and chronic urticaria were also taken into account. To back up these results, levocetirizine showed a tendency for effectiveness in a dosage-determining trial carried out on perennial allergic rhinitis. A therapeutic study carried out on 551 patients with persisting allergic rhinitis (symptoms: 4 days a week during at least 4 weeks) and sensibility to acarians and graminae pollens has shown that levocetirizine 5 mg did clinically and statically induce a much more significant reduction of the symptoms (sneezes, flowing nose, nose and eye itching, blocked nose) in the six-month period of the study than placebo. No tachyphylaxy was observed. During the whole study, levocetirizine 5 mg clinically and statically improved patients' life quality.

Pharmacokinetics

The pharmacokinetic profile of levocetirizine is linear and independent of a single or multidose administration, as the interindividual variability is weak. There is no indication suggesting a significative variability according to sex, polymorphism or potential tabagism.

The pharmacokinetic profile of levocetirizine (the (R) enantiomer of cetirizine) is identical to that of cetirizine (racemate). No chiral inversion occurs during the process of absorption and elimination.

Absorption: Levocetirizine is rapidly and extensively absorbed following oral administration. 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. 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 mean apparent total body clearance 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 feces accounts for only 12.9% of the dose. Renal clearance of levocetirizine is about 30 ml/min/1.73m^2. Once corrected taking into account the protein bound, this value amounts to 260 ml/min/1.73m^2. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

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 (see paragraph posology and administration). 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%.

Relation between pharmacokinetics and pharmacodynamics: During the formation of histamine-induced erythema and pruritic patches, 5 mg levocetirizine causes an inhibition comparable to that induced by 10 mg cetirizine. As for cetirizine, the effect on histamine induced cutaneous reactions is not parallel to the fluctuations of plasmatic concentrations.

Presentation

Calivida 0.5 mg/ml oral solution is a clear and colorless solution, wild strawberry-like smell and flavored presented in a 200 ml bottle.

Expiry date and storage conditions

See the expiry date printed on the outer carton.
Beware not to use **Calivida** after this date.
Store below 30°C.
Keep all medicines out of reach of children.

Manufactured by: **Medana Pharma SA**
Sieradz, Poland
For: **ARWAN Pharmaceutical Industries Lebanon s.a.l.**
Jadra, Lebanon

THIS IS A MEDICAMENT

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of the reach of children.

Council of Arab Health Ministers, Union of Arab Pharmacists

CALIVIDA®