JOSWE

LAYAL® Tablets

Levocetirizine dihydrochloride

Pharmaceutical form and strength:

Film coated tablet

Each film coated tablet contains 5 mg levocetirizine dihydrochloride.

PHARMACOTHERAPETIC GROUP

Antiallergic agent, long duration.

Therapeutic indications:

Levocetirizine is indicated for adults and children above 6 years, for the treatment of:

-Seasonal, perennial and persisting allergic rhinitis (hay fever and pollinosis).

-Allergic conjunctivitis.

-Chronic idiopathic urticaria.

PHARMACOLOGICAL PROPERTIES:

PHARMACODYNAMIC:

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

Levocetirizine is the (R) enantiomer of cetirizine. Binding studies revealed that levocetirizine has high affinity for human H1-receptors (ki=3.2nmol/l) levocetirizine has an affinity 2-fold higher than that of cetirizine (ki=6.3nmol/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, ECGs did not show relevant effects of levocetirizine on QT interval, ECGs have until now only been effectuated on 45 volunteers.

The dosage-~~determing 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 statistically significant equivelance between 5 mg levocetirizine and 10 mg cetirizine doses. As the most important indicators of the pharmacokinetic and pharmacodynamic 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 effectivness 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 statistically 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 statistically improved the patients' life quality.

Pharmacokinetic

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 of a significant variability according to sex, polymorphia or potential tabagism. The pharmacokinetic profile of levocetirizine (the [R] enantiomar of cetirizine) is identical to that of cetirizine (racemate). No chiral inversion is observed during absorption or 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 protein, 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 CYP3A4 while aromatic oxidation involved multiple and /or unidentified CYP isoforms.

Levocetirizine had no effects on the activities of CYP isoenzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved following 5 mg oral dose. Due to its low metabolism and ~~absecense~~ 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 metabolism is via urine, accounting for a mean of 85.4% of the dose. Excretion through feces accounts for only 12.9% of the dose. Renal clearance of levocetirizine is about 30 ml/min/1.73m2 once corrected taking into account the protein bound, this value amounts to 260ml/min/1.73m2. Levocetirizine is excreted both by glomular filtaration 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 clearence in patients with moderate and severe renal impairment (see paragraph posology/method of administration). In anuric end stage renal disease subjects, the total body clearance is decreased approximately 80% when compared to normal subject. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was <10%.

Relation between pharmacokinetic and pharmacodynamic:

During the formation of histamine-induced erythyma and pruritic patches, 5 mg levocetirizine causes an inhibition comparable to that induced by 10 mg cetirizine. As for cetrizine, the effect on histamine induced cutaneous reactions is not parallel to the fluctuations of the plasmatic concentration.

Posology and method of administration:

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food.

Adults, adolescents and children ~~aged 6 years and above~~:

The daily recommended dose is 5 mg (1 film coated tablet).

Children aged ~~between 6 and 12 years~~:

Should distribute the dose among 2 administrations (1/2 tablet in the morning and 1/2 tablet in the evening).

Patients with impaired renal function:

The dosing interval must be individualized according to renal function. Refer to the following table and adjust the dose as indicated to use this dosing table, an estimate of the patient creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/m) may be estimated from serum creatinine (mg/dl)

determining using the following formula:

$$\frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

Dosage adjustment for patients with impaired renal function:

Group	Creatinine clearance	Dosage and frequency
Normal	>=80	1 tablet once daily
Mild	50-79	1 tablet once daily
Moderate	30-49	1 tablet once every 2 days
Severe	<30	1 tablet once every 3 days
End-stage renal disease- Patients undergoing dialysis	<10	Contra-indicated

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).

Contra-indications:

History of hypersensitivity to levocetirizine or to any peparizine derivative. Patients with the terminal kidney failure (creatinine clearance ~~10 ml/min~~).

Special warning and special precautions for use:

The use of levocetirizine is not recommended in children aged less than 6 years.

Levocetirizine may increase somnolence, in a way that special care is recommended in patients driving cars, having high risk work or operating machines.

Precaution is also recommended when levocetirizine film coated tablet are taken concomitantly with alcohol since levocetirizine may cause drowsiness.

Patients with impaired kidney function must have their dose adjusted appropriately (see section posology and method of administration).

Interaction with other medicinal products and other forms of interaction:

No interaction study ~~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 interaction (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.

Pregnancy and lactation

No adverse event reactions have been observed in animal reproduction studies. However, as no controlled studies in pregnant woman are available, levocetirizine like other drugs should not be used during pregnancy. In case of accidental intake during pregnancy, no harmful effect on the foetus is anticipated. Treatment should nevertheless be interrupted immediately, as levocetirizine is expected to be excreted in breast milk, it should not be administered when breast feeding.

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-edema, anxious state, convulsion, sinus thrombosis, inflammation, angina pectoris, tachycardia, jugular vein thrombosis, increased rhinitis, difficulty in breathing, exanthema hypotricosis, pruritis, rash, fissures, urticaria, photosensitivity/toxicity, ineffective medication, interaction, dry mucous membrane, gastrointestinal disorders, nausea, increase of liver enzymes, cross reactivity.

Overdose:

a) Symptoms:

Substantial overdose may result in somnolence.

b) 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.

Storage conditions and expiry date:

Store below 30°C.

Keep out of the reach and sight of children.

Don't use after the expiry date stated on the carton box and blister.

Presentation

Boxes containing 10 and 30 film coated tablets.

- ~~A~~ medicament is a product that 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 dispensed the medicament.
- The doctor and the pharmacist are experts in medicine.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicaments out of the reach of children.

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