8020620-9093

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

UVNIL

(Levocetirizine Dihydrochloride Tablets I.P. 5 mg)

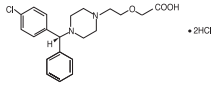
COMPOSITION

Each film coated tablet contains :

Levocetirizine Dihydrochloride I.P.	5 mg
Excipients	q.s.
Colour : Titanium Dioxide I.P.	

DESCRIPITON

Levocetirizine dihydrochloride is (*R*)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride. It is white or almost white powder. Its molecular formula is $C_{21}H_{25}N_2O_3Cl.2HCl$ and its molecular weight is 461.8.



PHARMACOLOGY

Pharmacodynamics

Levocetirizine, the (R)-enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1-receptors. Binding studies have revealed that levocetirizine has high affinity for human H_1-receptors (Ki = 3.2 nmol/L).

Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/L). Levocetirizine dissociates from H_1-receptors with a half-life of 115±38 minutes.

After single administration, levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber.

In *vitro* studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study in vivo (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: Inhibition of VCAM-1 release, modulation of vascular permeability, and a decrease in eosinophil recruitment.

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.

Pharmacokinetic/pharmacodynamic relationship 5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations. ECGs did not show relevant effects of levocetirizine on QT interval.

Pharmacokinetics

The pharmacokinetics of levocetirizine is linear with dose, and time-independent with low inter-subject variability. The pharmacokinetic profile is the same when given as the single enantiomer or when given as cetirizine. 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 hours after dosing. Steady state is achieved after 2 days. Peak concentrations are typically 270ng/mL and 308ng/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, concerning the passage of levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in the liver and kidneys, and the lowest in the central nervous system (CNS) compartment. 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 its metabolites is via the urine, accounting for a mean of 85.4% of the dose. Excretion via the faeces accounts for only 12.9% of the dose. 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 the creatinine clearance in patients with moderate and severe renal impairment. 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 haemodialysis procedure was <10%.

INDICATIONS

UVNIL is indicated in the symptomatic treatment of perennial and seasonal allergic rhinitis and chronic idiopathic urticaria.

DOSAGE AND ADMINISTRATION

UVNIL must be taken orally, swallowed whole with liquid and may be taken with or without food. It is recommended to take the daily dose in one single intake.

UVNIL

Adults and adolescents 12 years and above:
The daily recommended dose is 5 mg (1 tablet).
Children aged 6 to 12 years:
The daily recommended dose is 5 mg (1 tablet).

CONTRAINDICATIONS

Hypersensitivity to levocetirizine, cetirizine, or its parent compound hydroxyzine. Patients with severe renal impairment (<10 ml/min creatinine clearance) should not be administered UVNIL Patients with rare hereditary problems of galactose intolerance, fructose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

WARNINGS AND PRECAUTIONS

Avoid engaging in hazardous occupations requiring complete mental alertness such as driving or operating machinery when taking levocetirizine. Avoid concurrent use of alcohol or other central nervous system depressants with levocetirizine.

Drug Interactions

In vitro data indicate that levocetirizine is unlikely to produce pharmacokinetic interactions through inhibition or induction of liver drug-metabolizing enzymes. No in vivo drug-drug interaction studies have been performed with levocetirizine. Drug interaction studies have been performed with racemic cetirizine.

Pharmacokinetic interaction studies performed with racemic cetirizine demonstrated that cetirizine did not interact with antipyrine, pseudoephedrine, erythromycin, azithromycin, ketoconazole and cimetidine. There was a small decrease (~16%) in the clearance of cetirizine caused by a 400 mg dose of theophylline. It is possible that higher theophylline doses could have a greater effect.

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

Ritonavir increased the plasma AUC of cetirizine by about 42% accompanied by an increase in half-life (53%) and a decrease in clearance (29%) of cetirizine. The disposition of ritonavir was not altered by concomitant cetirizine administration. 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.

Renal Impairment

Since the body clearance of levocetirizine is correlated to the creatinine clearance, it is, therefore, recommended that the dosing intervals of levocetirizine be adjusted, based on the creatinine clearance in patients with moderate and severe renal impairment. The dosing intervals must be individualized according to renal function.

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	5 mg once daily
Moderate	30-49	5 mg once every 2 days
Severe	< 30	5 mg once every 3 days
End-stage renal disease, Patients undergoing dialysis	<10	Contraindicated

In paediatric 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.

Pregnancy

There are no adequate and well-controlled studies of levocetirizine in pregnant women. Because animal reproduction studies are not always predictive of human response, UVNIL should be used during pregnancy only if clearly needed.

Lactation

Cetirizine has been reported to be excreted in human breast milk. Because levocetirizine is also expected to be excreted in human milk, use of UVNIL in nursing mothers is not recommended.

Effects on ability to drive and use 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.

Pediatric Use

The safety and effectiveness of UVNIL in pediatric patients under 6 years of age have not been established. For children aged 2 to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirine.

Geriatric Use

Clinical studies of levocetirizine for each approved indication did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

UNDESIRABLE EFFECTS

Use of levocetirizine has been associated with somnolence, fatigue, nasopharyngitis, dry mouth, and pharyngitis in subjects 12 years of age and older and pyrexia, somnolence, cough, and epistaxis in children 6 to 12 years of age. Further uncommon incidences of adverse reactions like asthenia or abdominal pain were observed.

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.

Immune system disorders: hypersensitivity including anaphylaxis
Psychiatric disorders: aggression, agitation
Nervous system disorders: convulsion
Eyes disorders: visual disturbances
Cardiac disorders: palpitations
Respiratory, thoracic, and mediastinal disorders: dyspnoea
Gastrointestinal disorders: nausea
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
Musculoskeletal, connective tissues, and bone disorders: myalgia
Investigations: weight increased, abnormal liver function tests

OVERDOSAGE

Symptoms of overdose may include drowsiness in adults, and in children, initially agitation and restlessness, followed by drowsiness. There is no known specific antidote to levocetirizine. Should overdose occur, consider standard measures to remove any unabsorbed drug. Gastric lavage should be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

STORAGE

Store in a dry & dark place at a temperature not exceeding 25°C.
Keep all medicines out of reach of children.

PRESENTATION

UVNIL is available as blister strip of 10 tablets

torrent

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured in India by :
Akums Drugs & Pharmaceuticals Ltd.
19, 20, 21, Sector-6 A, I.I.E.,
SIDCUL, Ranipur, Haridwar - 249 403