Levotrex®

Levocetirizine Dihydrochloride

FORMS AND PRESENTATION

Levotrex®: Tablets: Box of 30.

COMPOSITION

Levotrex®: Each film coated tablet contains Levocetirizine Dihydrochloride 5mg.

Excipients: lactose, microcrystalline cellulose, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, polysorbate.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Therapeutic class: Antihistamines for systemic use.

ATC code: R06AE09.

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H1-receptors.

Levocetirizine has high affinity for human H1-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 H1-receptors with a half-life of 115 ± 38 min. After single administration, Levocetirizine shows receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells.

Levocetirizine inhibits the histamine-mediated early phase of the allergic reaction and also reduces the migration of certain inflammatory cells and the release of certain mediators associated with the late allergic response.

Pharmacokinetic Properties

The pharmacokinetics of Levocetirizine are 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 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, neither concerning the passage of Levocetirizine through the blood-brain-barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys, the lowest in the 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 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. 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. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80% when compared to normal subjects.

INDICATIONS

Levotrex® is indicated for:

- The relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis;
- The relief of symptoms of chronic idiopathic urticaria.

CONTRAINDICATIONS

- Hypersensitivity to Levocetirizine, to any of the excipients, to hydroxyzine or to any piperazine derivatives.
- Patients with severe renal impairment at less than 10 ml/min creatinine clearance.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take Levocetirizine film coated tablets.

PRECAUTIONS

- Do not exceed the stated dose.
- The use of Levocetirizine Dihydrochloride is not recommended in children aged less than 6 years since the currently available film-coated tablets do not yet allow dose adaptation.
- At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly.
- Caution in epileptic patients and patients at risk of convulsions is recommended.

Ability to drive and use machines

Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 5 mg.

Patients intending to drive, engaging in potentially hazardous activities or operating machinery should not exceed the recommended dose and should take their response to the medicinal product into account. In these sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

PREGNANCY AND LACTATION

Very rare 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.

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Caution should be exercised when prescribing to pregnant or breast feeding women because Levocetirizine passes into breast milk.

DRUG INTERACTIONS

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of Levocetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

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

ADVERSE EFFECTS

The frequency of undesirable effects has been defined as: very common (≥ 1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥ 1/10,000 to ≤1/1,000); very rare (≤1/10,000); not known (cannot be estimated from the available data).

- Blood and lymphatic system disorders: Thrombocytopenia (very rare).
- Immune system disorders: Hypersensitivity (rare); anaphylactic shock (very rare).
- Psychiatric disorders: Somnolence (common); agitation (uncommon); aggression, confusion, depression, hallucination, insomnia (rare); tic (very rare).
- Nervous system disorders: Dizziness, headache (common); paraesthesia (uncommon); convulsions, movement disorders (rare); dysgeusia, syncope, tremor, dystonia, dyskinesia (very rare).
- Eye disorders: Accomodation disorder, blurred vision, oculogyration (very rare).
- Cardiac disorders: Tachycardia (rare).
- Respiratory, thoracic and mediastinal disorders: Pharyngitis, rhinitis in children (common).
- Gastrointestinal disorders: Abdominal pain, dry mouth, nausea (common); diarrhea (uncommon).
- Hepatobiliary disorders: Abnormal hepatic function (increased transaminases, alklaline phosphatise, γ-GT and bilirubin) (rare).
- Skin and subcutaneous tissue disorders: Pruritus, rash (uncommon); urticaria (rare); angioneurotic edema, fixed drug eruption (very rare).
- Renal and urinary disorders: Dysuria, enuresis (very rare).
- General disorders and administration site conditions: Fatigue (common); asthenia, malaise (uncommon); edema (rare).
- Investigations: Weight increase (rare).

DOSAGE AND ADMINISTRATION

Levotrex® must be taken orally, swallowed whole with liquid and may be taken with or without food.

Adults and adolescents 12 years and above

The daily recommended dose is 5 mg (one film-coated tablet) once daily.

Children aged 6 to 12 years

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

Levotrex® is not recommended for use in children below age 6 due to insufficient data on safety and efficacy.

Elderly

For the time being, there is no data to suggest that the dose needs to be reduced in elderly patients provided that the renal function is normal.

Patients with moderate to severe renal impairment: there are no data to document the efficacy/safety ratio in patients with renal impairement. Since Levocetirizine is mainly excreted via renal route, in cases no alternative treatment can be used, the dosing intervals 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's creatinine clearance (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustments for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	One tablet daily
Mild	50 - 79	One tablet daily
Moderate	30 - 49	One tablet every two days
Severe	< 30	One tablet every three 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, his age and his body weight.

Patients with hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment.

Patients with hepatic impairment and renal impairment

Dose adjustment is recommended (see Patients with moderate to severe renal impairment above).

OVERDOSAGE

Symptoms observed after an overdose of Levocetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.

Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor and urinary retention.

There is no known specific antidote to Levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence.

Levocetirizine is not effectively removed by dialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

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Manufactured By
Hetero Labs Limited, India
Packed By
Benta S.A.L.

This is a medicament
- A 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 medicine, its 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
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists