Levotrex®

Levocetirizine Dihydrochloride

FORMS AND PRESENTATION

Levotrex®: Film coated tablets. Box of 30.

COMPOSITION

Levotrex®: Each film coated tablet contains Levocetirizine Dihydrochloride 5mg. Excipients: Microcrystalline cellulose, lactose monohydrate, colloidal silicon dioxide, magnesium stearate, hydroxypropyl methylcellulose, talc, titanium dioxide, macrogol.

PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative,

ATC code: R06A E09.

Mechanism of action:

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

Binding studies revealed that levocetirizine have a 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, it shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacokinetic properties

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 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 the liver and kidneys, the lowest in the CNS compartment.

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 CYP3A4 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 half-life is shorter in small children. 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. Levocetirizine is excreted both by glomerular filtration and active tubular secretion. Excretion via feces accounts for only 12.9% of the dose.

Special population

Renal impairment:

The apparent body clearance of levocetirizine is correlated to 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. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

Pediatric population:

Data from a pediatric pharmacokinetic study with oral administration of a single dose of 5 mg levocetirizine in 14 children aged 6 to 11 years with body weight ranging between 20 and 40 kg show that Cmax and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean Cmax was 450 ng/ml, occurring at a mean time of 1.2 hours, weight-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this pediatric population than in adults.

Dedicated pharmacokinetic studies have not been conducted in pediatric patients younger than 6 years of age.

A retrospective population pharmacokinetic analysis was conducted in 324 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30mg.

Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly:

Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in the urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

Gender:

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for the potential effect of gender. The half-life was slightly shorter in women (7.08 ± 1.72 hr) than in men (8.62 ± 1.84 hr); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appears to be comparable to that in men (0.59 ± 0.12 ml/min/kg). The same daily doses and dosing intervals are applicable for men and women with normal renal function.

Hepatic impairment:

The pharmacokinetics of levocetirizine in hepatically impaired subjects have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50% increase in half-life along with a 40% decrease in clearance compared to healthy subjects.

INDICATIONS

Levotrex® is indicated in:

- The symptomatic treatment of allergic rhinitis, including persistent allergic rhinitis.
- Patients with end stage renal disease with estimated Glomerular Filtration Rate (eGFR) below 15ml/min (requiring dialysis treatment).

CONTRAINDICATIONS

- Hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any other piperazine derivatives, or to any of the excipients.
- Severe renal impairment at less than 10 ml/min creatinine clearance.

PRECAUTIONS

- Precaution is recommended with concurrent intake of alcohol.
- Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.
- Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.
- Response to allergy skin tests is inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.
- Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.
- Pruritus may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.
- The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a pediatric formulation of levocetirizine.

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 this into account.

PREGNANCY AND LACTATION

Pregnancy

There is a limited amount of data on the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data on pregnant women indicates no malformative or foeto/ neonatal toxicity.

The use of Levocetirizine may be considered during pregnancy, if necessary.

Breast-feeding

Cetirizine, the racemate of levocetirizine, has been shown to be excreted in humans. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

DRUG 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 antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole, and pseudoephedrine). A small decrease in the clearance of cetirizine (16%) was observed with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration.

In a multiple-dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

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

For sensitive patients, the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

ADVERSE EFFECTS

Frequency categories are defined according to the following convention: 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), and not known (cannot be estimated from the available data).

Immune system disorders: hypersensitivity including anaphylaxis (not known).
Metabolism and nutrition disorders: increased appetite (not known).
Psychiatric disorders: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare (not known).
Nervous system disorders: convulsion, paraesthesia, dizziness, syncope, tremor, dysgueusia (not known).
Ear and labyrinth disorders: Vertigo (not known).
Eyes disorders: visual disturbances, blurred vision, oculogyration (not known).
Cardiac disorders: palpitations, tachycardia (not known).
Respiratory, thoracic, and mediastinal disorders: dyspnoea (not known).
Gastrointestinal disorders: nausea, vomiting, diarrhoea (not known).
Hepatobiliary disorders: hepatitis (not known).
Renal and urinary disorders: dysuria, urinary retention (not known).
Skin and subcutaneous tissue disorders: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria (not known).
Musculoskeletal, connective tissues, and bone disorders: myalgia, arthralgia (not known).
General disorders and administration site conditions: oedema (not known).

DOSAGE AND ADMINISTRATION

Posology

Adults and adolescents 12 years and above:

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

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Renal impairment below).

Renal impairment:

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:

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

Dosing adjustments for patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	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

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.

Hepatic impairment:

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

Pediatric population

For children aged 6 to 12 years, the daily recommended dose is 5 mg (1 film-coated tablet).

For children aged 2 to 6 years, no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a pediatric formulation of levocetirizine.

Method of administration

The film-coated tablet 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.

Duration of use:

Intermittent allergic rhinitis (symptoms experienced for less than four days a week or for less than four weeks a year) 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 experienced more than four days a week or for more than four weeks a year), continuous therapy can be proposed to the patient throughout the period of exposure to allergens.

There is clinical experience with the use of levocetirizine for treatment periods of at least 6 months. In chronic urticaria and chronic allergic rhinitis, there is clinical experience of the use of cetirizine (racemate) for up to one year.

OVERDOSAGE

Symptoms

In adults, symptoms of overdose may include drowsiness. In children, agitation and restlessness may initially occur, followed by drowsiness.

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 shortly after ingestion of the drug. Levocetirizine is not effectively removed by hemodialysis.

STORAGE CONDITIONS

Store below 30°C.

Keep in original pack in intact conditions.

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Marketing Authorization Holder and Manufacturer
Benta S.A.L. – Lebanon

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