

XYZAL

Levocetirizine dihydrochloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

Film-coated tablet containing 5 mg of levocetirizine dihydrochloride

Excipients

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

Microcrystalline cellulose, Lactose monohydrate, Colloidal anhydrous silica, Magnesium stearate, Hypromellose, Titanium dioxide, Macrogol 400

PHARMACEUTICAL FORM

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

White to off-white, oval, film-coated tablet with a Y logo on one side.

CLINICAL INFORMATION

Indications

Levocetirizine is indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and chronic idiopathic urticaria.

Dosage and Administration

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

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 < 4 days/week or for less than 4 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 > 4 days/week or for more than 4 weeks a year), continuous therapy can be proposed to the patient during 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 use of cetirizine (racemate) for up to one year.

Route of Administration

For oral use.

Adults and adolescents 12 years and above

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

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

Children

Children aged 6 to 12 years

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

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*).

Renal impairment

The dosing intervals must be individualised according to renal function (eGFR – estimated Glomerular Filtration Rate). Refer to the following table and adjust the dose as indicated.

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

Dosing Adjustments for Patients with Impaired Renal Function:

Group	eGFR (ml/min)	Dosage and frequency
Normal renal function	≥ 90	5 mg once daily
Mildly decreased renal function	60 – < 90	5 mg once daily
Moderately decreased renal function	30 – < 60	5 mg once daily once every 2 days
Severely decreased renal function	15 – < 30 (not requiring dialysis)	5 mg once daily once every 3 days
End-stage renal disease (ESRD)	< 15 (requiring dialysis treatment)	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.

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 *Renal impairment*).

Contraindications

Levocetirizine is contraindicated in:

- hypersensitivity to levocetirizine, to cetirizine, to hydroxyzine, to any piperazine derivatives or to any of the excipients,
- Patients with end stage renal disease with estimated Glomerular Filtration Rate (eGFR) below 15 ml/min (requiring dialysis treatment).

Warnings and Precautions

Alcohol

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

Risk of urinary retention

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.

Risk of seizure aggravation

Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.

Allergy skin tests

Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

Withdrawal syndrome

Pruritus may occur when levocetirizine is stopped even if those symptoms were not present before treatment initiation (see *Section Adverse Reactions*). 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.

Excipients

Lactose

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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, pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam).

Theophylline

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.

Ritonavir

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.

Food

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

Alcohol

In 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.

Pregnancy and Lactation

Fertility

There are no relevant data available.

Pregnancy

The use of levocetirizine may be considered during pregnancy, if necessary. There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of levocetirizine in pregnant women. However, for cetirizine, the racemate of levocetirizine, a large amount of data (more than 1000 pregnancy outcomes) on pregnant women indicate no malformative or fetoneonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Lactation

Caution should be exercised when prescribing to lactating women. Cetirizine, the racemate of levocetirizine has been shown excreted in human. Therefore, the excretion of levocetirizine in

human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants.

Ability to perform tasks that require judgement, motor or cognitive skills

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

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.

Adverse Reactions

Clinical Trial Data

Adults and adolescents above 12 years of age

In therapeutic studies in women and men aged 12 to 71 years, 15.1% of the patients in the levocetirizine 5 mg group had at least one adverse drug reaction compared to 11.3% in the placebo group. 91.6% of these adverse drug reactions were mild to moderate. In therapeutic trials, the dropout rate due to adverse events was 1.0% (9/935) with levocetirizine 5 mg and 1.8% (14/771) with placebo. Clinical therapeutic trials with levocetirizine included 935 subjects exposed to the drug at the dose of 5 mg daily.

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1000$ to $< 1/100$

Rare $\geq 1/10000$ to $< 1/1000$

Very rare $< 1/10000$

Not known (cannot be estimated from the available data).

Nervous system disorders

Common: headache, somnolence

Gastrointestinal disorders

Common: dry mouth

Uncommon: abdominal pain

General disorders and administration site conditions

Common: fatigue

Uncommon: asthenia

The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia was altogether more common (8.1%) under levocetirizine 5 mg than under placebo (3.1%).

Post Marketing Data

Immune system disorders

Not known: hypersensitivity including anaphylaxis

Metabolism and nutrition disorders

Not known: increased weight, increased appetite

Psychiatric disorders

Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmares

Nervous system disorders

Not known: convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia

Eye disorders

Not known: visual disturbances, blurred vision, oculogyration

Ear and labyrinth disorders

Not known: vertigo

Cardiac disorders

Not known: palpitations, tachycardia

Respiratory, thoracic, and mediastinal disorders

Not known: dyspnoea

Gastrointestinal disorders

Not known: nausea, vomiting, diarrhoea

Hepatobiliary disorders

Not known: hepatitis, abnormal liver function test

Skin and subcutaneous tissue disorders

Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria

Musculoskeletal and connective tissue disorders

Not known: myalgia, arthralgia

Renal and urinary disorders

Not known: dysuria, urinary retention

General disorders and administration site conditions

Not known: oedema

Skin reactions occurring after discontinuation of levocetirizine

After levocetirizine discontinuation, pruritus has been reported (see Section Warnings and Precautions).

Overdosage

Symptoms and Signs

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

Treatment

There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by haemodialysis.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

Clinical Pharmacology

Pharmacodynamics

Pharmacotherapeutic group

Antihistamine for systemic use, piperazine derivative.

ATC Code

R06A E09

Mechanism of Action/Pharmacodynamic Effects

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

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

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

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 pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:

In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p < 0.001$) compared with placebo and desloratadine.

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.

Pharmacokinetics

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. In adults, 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 once daily 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. 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.

Metabolism

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 half-life is shorter in small children. The mean apparent total body clearance in adults 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 faeces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special patient populations

Children

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

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 urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

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. The amount of levocetirizine removed during a standard 4-hour hemodialysis procedure was < 10%.

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.

Other patient characteristics

Gender

Pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated for 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.

Race

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

Clinical Studies

The efficacy and safety of levocetirizine has been demonstrated in several double-blind, placebo controlled, clinical trials performed in adult patients suffering from seasonal allergic rhinitis, perennial allergic rhinitis, or persistent allergic rhinitis. Levocetirizine has been shown to significantly improve symptoms of allergic rhinitis, including nasal obstruction in some studies.

A 6-month clinical study in 551 adult patients (including 276 levocetirizine-treated patients) suffering from persistent allergic rhinitis (symptoms present 4 days a week for at least 4 consecutive weeks) and sensitized to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more potent than placebo on the relief from the total symptom score of allergic rhinitis throughout the whole duration of the study, without any tachyphylaxis. During the whole duration of the study, levocetirizine significantly improved the quality of life of the patients.

In a placebo-controlled clinical trial including 166 patients suffering from chronic idiopathic urticaria, 85 patients were treated with placebo and 81 patients with levocetirizine 5mg once daily over six weeks. Treatment with levocetirizine resulted in significant decrease in pruritus severity over the first week and over the total treatment period as compared to placebo. Levocetirizine also resulted in a larger improvement of health-related quality of life as assessed by the Dermatology Life Quality Index as compared to placebo.

Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, levocetirizine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria.

ECGs did not show relevant effects of levocetirizine on QT interval.

Pharmacokinetic / pharmacodynamic relationship:

The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

Paediatric population

The paediatric safety and efficacy of levocetirizine tablets has been studied in two placebo controlled clinical trials including patients aged 6 to 12 years and suffering from seasonal and perennial allergic rhinitis, respectively. In both trials, levocetirizine significantly improved symptoms and increased health-related quality of life.

In children below the age of 6 years, clinical safety has been established from several short- or long-term therapeutic studies:

- one clinical trial in which 29 children 2 to 6 years of age with allergic rhinitis were treated with levocetirizine 1.25 mg twice daily for 4 weeks
- one clinical trial in which 114 children 1 to 5 years of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg twice daily for 2 weeks
- one clinical trial in which 45 children 6 to 11 months of age with allergic rhinitis or chronic idiopathic urticaria were treated with levocetirizine 1.25 mg once daily for 2 weeks
- one long-term (18 months) clinical trial in 255 levocetirizine - treated atopic subjects aged 12 to 24 months at inclusion.

The safety profile was similar to that seen in the short-term studies conducted in children 1 to 5 years of age.

NON-CLINICAL INFORMATION

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction.

PHARMACEUTICAL INFORMATION

Storage

Store below 30°C. Keep out of the reach and sight of children. Do not use after the expiry date stated on the carton box and blister.

Shelf Life

The shelf life is stated on the packaging.

Nature and Contents of Container

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

Cold form foil/foil blister pack or cold form foil/child resistant lidding foil blister packs placed into cardboard boxes containing 50 film-coated tablets.

Incompatibilities

There are no relevant data available.

Use and Handling

There are no special requirements for use or handling of this product.

Manufacturer

Xyzal Film-Coated Tablets:

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Version number: 06

Reference: NCDS08

Date of local revision: 1 December 2022