Levocetirizine dihydrochloride

Xyzal®
Oral Preparations

PRODUCT DESCRIPTION
Each film-coated tablet of Levocetirizine dihydrochloride (Xyzal®) contains 5 mg of levocetirizine. Each mL of Levocetirizine dihydrochloride (Xyzal®) oral drops contains 5 mg of levocetirizine. Each mL of Levocetirizine dihydrochloride (Xyzal®) oral solution contains 500mcg of levocetirizine.

PHARMACOLOGIC PROPERTIES

Pharmacodynamics
Pharmacotherapeutic group
Antihistamine for systemic use, piperazine derivative.

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

(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 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.

Pharmacokinetic / pharmacodynamic relationship:
The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

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

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 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. 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 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 aged 6 to 11 years with body weight ranging between 20 and 40 kg show that $C_{\text{max}}$ and AUC values are about 2-fold greater than that reported in healthy adult subjects in a cross-study comparison. The mean $C_{\text{max}}$ 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. Dedicated pharmacokinetic studies have not been conducted in paediatric 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 30 mg. 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 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
There are no relevant data available.

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.
INDICATIONS
For the symptomatic treatment of:
- allergic rhinitis (including persistent allergic rhinitis)
- urticaria, from 6 months of age

DOSAGE AND ADMINISTRATION
Levocetirizine dihydrochloride (Xyzal®) 5 mg film-coated tablets
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.

Levocetirizine dihydrochloride (Xyzal®) 5 mg/ml oral drops, solution
The drops should be poured in a spoon or diluted in water, and taken orally. If dilution is used, it should be considered, especially for administration to children, that the volume of water to which the drops are added, needs to be adapted according to the quantity of water the patient is able to swallow. The diluted solution should be taken immediately. When counting the drops, the bottle should be held vertically (top down). In case of lack of flow of drops, if the right amount of drops has not been delivered, turn the bottle over in upright position, then hold it top down again and continue counting the drops.

The drops may be taken with or without food.

Levocetirizine dihydrochloride (Xyzal®) 5 mg/10ml oral solution
A dosing oral syringe is included in the package. The appropriate volume of oral solution should be measured with the oral syringe, and poured in a spoon or in a glass of water. The oral solution must be taken orally immediately after dilution, and may be taken with or without food.

Duration of use
Intermittent allergic rhinitis (symptoms < 4 days/week or during less than 4 weeks) 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 and during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens.

Clinical experience with 5 mg levocetirizine as a film-coated tablet formulation is currently available for a 6-month treatment period. For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate.

Route of Administration
For oral use.

Adults
Levocetirizine dihydrochloride (Xyzal®) 5 mg film-coated tablets
The daily recommended dose is 5 mg (1 film-coated tablet).

Levocetirizine dihydrochloride (Xyzal®) 5 mg/ml oral drops, solution
The daily recommended dose is 5 mg (20 drops).

Levocetirizine dihydrochloride (Xyzal®) 5 mg/10ml oral solution
The daily recommended dose is 5 mg (10 ml of solution).

Children
For children aged 6 months to 6 years no adjusted dosage is possible with the film-coated tablet formulation. It is recommended to use a paediatric formulation of levocetirizine (see Section Warnings and Precautions).

Infants and children aged less than 6 months
Due to limited data in this population, the administration of levocetirizine to neonates and infants aged less than 6 months is not recommended.

Infants and children aged 6 months to 12 months
Levocetirizine dihydrochloride (Xyzal®) 5 mg/ml oral drops, solution
The daily recommended dose is 1.25 mg once daily (5 drops once daily).

Levocetirizine dihydrochloride, 0.5 mg/ml oral solution
The daily recommended dose is 1.25 mg once daily (2.5 ml of solution once daily).

Children aged 1 to 6 years
Levocetirizine dihydrochloride (Xyzal®) 5 mg/ml oral drops, solution
The daily recommended dose is 2.5 mg to be administered in 2 intakes of 1.25 mg (5 drops twice daily).

Levocetirizine dihydrochloride (Xyzal®) 5 mg/10ml oral solution
The daily recommended dose is 2.5 mg to be administered in 2 intakes of 1.25 mg (2.5 ml of solution twice daily).

Children aged 6 and older
Children older than 6 years may be given the adult dose of 5 mg once daily.

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. 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:

\[
CL_{cr} = \frac{140 - \text{age(years)} \times \text{weight(kg)}}{72 \times \text{serum creatinine(mg/dl)}} (\times 0.85 \text{ for women})
\]
Dosing Adjustments for Patients with Impaired Renal Function:

<table>
<thead>
<tr>
<th>Group</th>
<th>Creatinine clearance (ml/min)</th>
<th>Dosage and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>≥ 80</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>Mild</td>
<td>50 - 79</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>Moderate</td>
<td>30 - 49</td>
<td>5 mg once every 2 days</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt; 30</td>
<td>5 mg once every 3 days</td>
</tr>
<tr>
<td>End-stage renal disease – Patients undergoing dialysis</td>
<td>&lt; 10</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

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. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see renal impairment).

CONTRAINDICATIONS

Tablets

Levocetirizine is contraindicated in:
- Hypersensitivity to levocetirizine, to any piperazine derivatives or any of the excipients
- Severe renal impairment at less than 10 ml/min creatinine clearance.

Oral drops, oral solution

Levocetirizine is contraindicated in:
- Hypersensitivity to levocetirizine, to any piperazine derivatives, to methyl parahydroxybenzoate, to propyl parahydroxybenzoate, or to any other excipients
- Severe renal impairment at less than 10 ml/min creatinine clearance

WARNINGS AND PRECAUTIONS

Alcohol

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

Infants and children under 2 years

Due to the lack of data in this population, the administration of levocetirizine to infants and children aged less than 2 years is not recommended.

Tablets

Children aged less than 6 years

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 paediatric formulation of levocetirizine.

Lactose

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.

Oral drops

Methyl parahydroxybenzoate, propyl parahydroxybenzoate

The presence of methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed) (see Section Contraindications).

Oral solution

Maltitol

This medicinal product contains maltitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Methyl parahydroxybenzoate, propyl parahydroxybenzoate

The presence of methyl parahydroxybenzoate and propyl parahydroxybenzoate may cause allergic reactions (possibly delayed) (see Section Contraindications).

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 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 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.

PREGNANCY AND LACTATION

Fertility
There are no relevant data available.

Pregnancy
Caution should be exercised when prescribing to pregnant women.
For levocetirizine no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Lactation
Caution should be exercised when prescribing to lactating women. Cetirizine is excreted in human milk.

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.
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 EFFECTS

Clinical Trial Data
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 recommended dose of 5 mg daily.
Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥1/10
Common ≥1/100 to <1/10
Uncommon ≥1/1000 to <1/100
Rare ≥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%).

Paediatric Patients
In two placebo-controlled studies in paediatric patients aged 6-11 months and aged 1 year to less than 6 years, 159 subjects were exposed to levocetirizine at the dose of 1.25 mg daily for 2 weeks and 1.25 mg twice daily respectively. The following incidence of adverse drug reactions was reported under levocetirizine.

Psychiatric disorders
Common: sleep disorders
Nervous system disorders
Common: somnolence
Gastrointestinal disorders
Common: diarrhoea, constipation
Uncommon: vomiting

In children aged 6-12 years double blind placebo controlled studies were performed where 243 children were exposed to 5 mg levocetirizine daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse drug reactions was reported.

Nervous system disorders
Common: somnolence
Uncommon: headache

Post Marketing Data
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
Not known: hypersensitivity including anaphylaxis
Metabolism and nutrition disorders
Not known: increased weight
Psychiatric disorders
Not known: aggression, agitation, hallucination, depression
Nervous system disorders
Not known: convulsions, paraesthesia, dizziness
Eye disorders
Not known: visual disturbances, blurred vision
Cardiac disorders
Not known: palpitations, tachycardia
Respiratory, thoracic and mediastinal disorders
Not known: dyspnoea
Gastrointestinal disorders
Not known: nausea, vomiting
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
Renal and urinary disorders
Not known: dysuria

OVERDOSAGE AND TREATMENT

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

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.

STORAGE CONDITIONS
Levocetirizine dihydrochloride (Xyzal®) 5mg tablet: Store below 25°C.
Levocetirizine dihydrochloride (Xyzal®) 5mg/mL oral drops: Store at temperatures not exceeding 30°C.
Levocetirizine dihydrochloride (Xyzal®) 500mcg/mL oral solution: Store at temperatures not exceeding 30°C.

AVAILABILITY
*Levocetirizine dihydrochloride (Xyzal®) 5mg tablet: 10 tablets per blister (box of 30’s)
**Levocetirizine dihydrochloride (Xyzal®) 5mg/mL oral drops: glass bottle of 10 mL
**Levocetirizine dihydrochloride (Xyzal®) 500mcg/mL oral solution: glass bottle of 30mL, 75mL

CAUTION
Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.
Keep all medicines out of reach of children.

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