[GSK logo]

NAME OF THE MEDICINAL PRODUCT
XYZAL

PHARMACEUTICAL FORM AND STRENGTH
Film-coated tablet: White to off-white, oval, film-coated tablet with a Y logo on one side, containing 5 mg of levocetirizine dihydrochloride.

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

POSOLOGY AND METHOD OF ADMINISTRATION
Film-coated tablet: it must be taken orally, swallowed whole with liquid and may be taken with or without food.

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

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

Children aged 6 to 12 years:
The recommended dose is 5 mg once daily(1 film-coated tablet).

Adult patients with 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.

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 every 2 days
Severely decreased renal function	15 - < 30 (not requiring dialysis)	5 mg 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.

Patients with 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 Patients with renal impairment above).*

CONTRAINDICATIONS
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).

Due to the presence of lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take the tablet formulation.

WARNINGS AND PRECAUTIONS
Alcohol
Precaution is recommended with concurrent intake of alcohol *(see 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
(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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
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 or other CNS depressants
In sensitive patients the concurrent administration of cetirizine or levocetirizine and alcohol or other CNS depressants (eg. other antihistamines, anxiolytics and sedatives) 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 feto/neonatal toxicity. 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, the racemate of levocetirizine, has been shown to be excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants.

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

A total of 243 paediatric patients 6 to 12 years of age received 5 mg levocetirizine once daily in two short-term placebo-controlled double-blind trials. The mean age of the patients was 9.8 years, 79 (32%) were 6 to 8 years of age, and 50% were Caucasian. The table below lists adverse reactions that were reported in greater than or equal to 2% of subjects aged 6 to 12 years exposed to 5 mg levocetirizine in placebo-controlled clinical trials and that were more common with levocetirizine than placebo.

Adverse Reactions Reported in ≥2%* of Subjects Aged 6 to 12 Years Exposed to Levocetirizine 5 mg Once Daily in Placebo-Controlled Clinical Trials 4 and 6 Weeks in Duration

Adverse Reactions	Levocetirizine 5 mg (n = 243)	Placebo (n = 240)
Pyrexia	10 (4%)	5 (2%)
Cough	8 (3%)	2 (<1%)
Somnolence	7 (3%)	1 (<1%)
Epistaxis	6 (2%)	1 (<1%)

* Rounded to the closest unit percentage

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.

PHARMACOLOGICAL PROPERTIES

1) Pharmacodynamic properties

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative, ATC code: R06A E09.
Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1-receptors. Binding studies 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 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 5 mg, desloratadine 5 mg, 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.

In vivo and *ex vivo* animal models have shown no significant effect on cholinergic and serotoninergic activity. In clinical studies, however, dry mouth was more common with levocetirizine than with placebo. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1 receptors. Autoradiographic studies with radiolabelled levocetirizine in the rat have shown negligible penetration into the brain. *Ex vivo* experiments in the mouse have shown that systemically administered levocetirizine does not significantly occupy H_1 cerebral receptors.

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 decrease in eosinophil recruitment.

2) 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 iso-enzymes 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 substance, 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. Excretion via 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 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%.

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

Geriatric Patients
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.

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.

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.

3) 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 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 5 mg 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.

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.

EXCIPIENTS
Film-coated tablet: Microcrystalline cellulose, Lactose monohydrate, Colloidal anhydrous silica, Magnesium stearate, Hypromellose, Titanium dioxide, Macrogol 400

STORAGE CONDITIONS AND EXPIRY DATE
Film-coated tablet: 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/label.

NATURE AND CONTENTS OF CONTAINER
Xyzal film-coated tablets are packed in aluminium blisters placed into cardboard boxes containing 10 and 50 film-coated tablets.

Not all presentations may be available locally.

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Manufacturer - film-coated tablet
UCB Farchim S.A.
Bulle – Switzerland

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