Summary Product Characteristics for Pharmaceutical Product

1. NAME OF THE MEDICINAL PRODUCT

Xyzal (Levocetirizine dihydrochloride), 5 mg, film-coated tablet

Xyzal (Levocetirizine dihydrochloride), 0.5 mg/ml, oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride.

Levocetirizine dihydrochloride, 0.5 mg/ml, oral solution

Each 1 ml of oral solution contains 0.5 mg levocetirizine dihydrochloride.

3. PHARMACEUTICAL FORM

Levocetirizine dihydrochloride, 5 mg, film-coated tablet

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

Levocetirizine dihydrochloride, 0.5 mg/ml, oral solution

Clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

For the symptomatic treatment of:

- allergic rhinitis (including persistent allergic rhinitis),
- urticaria.

4.2. Posology and method of 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.

Levocetirizine dihydrochloride, 0.5 mg/ml, oral solution

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 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).

Levocetirizine dihydrochloride, 0.5 mg/ml, oral solution
The daily recommended dose is 5 mg (10 ml of solution).

Children

Children aged less than 2 years
The administration of levocetirizine to infants and toddlers aged less than 2 years is not recommended *(see Section Warnings and Precautions)*.

Children aged 2 to 6 years

Levocetirizine dihydrochloride, 5 mg, 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 paediatric formulation of levocetirizine *(see Section Warnings and Precautions)*.

Levocetirizine dihydrochloride, 0.5 mg/ ml, 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 to 12 years
Levocetirizine dihydrochloride, 5 mg, film-coated tablet
The daily recommended dose is 5 mg (1 film-coated tablet).

Levocetirizine dihydrochloride, 0.5 mg/ ml, oral solution
The daily recommended dose is 5 mg (10 ml of solution).

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.

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 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)*.

4.3. 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).

4.4. Special warnings and precautions for use

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.

Infants and children under 2 years
Even if some clinical data are available in children aged 6 months to 12 years (*see Section Adverse Reactions*), these data are not sufficient to support the administration of levocetirizine to infants and toddlers aged less than 2 years. Therefore, the administration of levocetirizine to infants and toddlers 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.

4.5. 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

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.

4.6. Fertility, 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 excreted in human. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants.

4.7. 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.

4.8. Undesirable effects

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 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

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

Please note that even if clinical data presented in this section are available in children aged 6 months to 12 years, we do not have sufficient data to support the administration of the product to infants and toddlers aged less than 2 years.

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

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

4.9. Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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 H_1-receptors.

Binding studies revealed that levocetirizine has high affinity for human H_1- 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 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. 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.

5.2. 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. 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. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 323 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.

5.3. 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 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 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.

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.

5.4. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Xyzal Tablets: Lactose monohydrate, Microcrystalline Cellulose, Colloidal anhydrous silica, Magnesium stearate, Titanium dioxide, Macrogol 400, Hypromellose
Xyzal OS: Sodium acetate, Acetic acid, glacial, Maltitol, Liquid, Glycerol, 85 %, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Saccharin sodium, Tutti frutti flavour 501103A7

6.2. Incompatibilities

There are no relevant data available.

6.3. Shelf life

As registered locally.

6.4. Special precautions for storage

The expiry date is indicated on the packaging.

6.5. Nature and contents of the container

As registered locally.

6.6. Special precautions for disposal

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

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorization Holder

GlaxoSmithKline Trading Services Ltd 12 Riverwalk, Citywest Business Campus, Dublin 24, Ireland.

Zyxal Tablets:

Manufactured by:

UCB Farchim SA

Z.I de Planchy

1630 Bulle Swizerland.

Packed by:

Aesica Pharmaceuticals S.r.l.

Via Praglia, 15

10044 Pianezza (TO)

Italy.

Xyzal OS:

Manufactured by:

Aesica Pharmaceuticals S.r.l.

Via Praglia, 15

10044 Pianezza (TO)

Italy.

8. MARKETING AUTHORIZATION NUMBER

Xyzal Tablets H2003/15018/185

Xyzal Oral Solution H2005/402

9. RENEWAL OF THE REGISTRATION

March 30th 2026

10. DATE OF REVISION OF THE TEXT

March 30th 2026