Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Levofree Syrup

2. Qualitative and quantitative composition

Each 5 mL of oral solution contains 2.5 mg of levocetirizine dihydrochloride.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral syrup.

4. Clinical particulars

4.1 Therapeutic indications

LEVOFREE SYRUP (Levocetirizine Syrup 2.5 mg/5 ml) is indicated for the symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 2 years and above.

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years and above: The daily dose is 5 mg (10 mL of oral solution).

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

Renal impairment

The dosing intervals must be 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:

Group	Creatinine clearance (mL/min)	Dosage and frequency
Normal	≥ 80	5 mg once daily
Mild	50 – 79	5 mg once daily
Moderate	30 – 49	5 mg once every 2 days
Severe	< 30	5 mg once every 3 days
End-stage renal disease – patients undergoing dialysis	< 10	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

Paediatric population
Children aged 6 to 12 years: The daily recommended dose is 5 mg (10 ml of solution).
Children aged 2 to 6 years: 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).
Even if some clinical data are available in children aged 6 months to 12 years (see section 4.8, 5.1 and 5.2), these data are not sufficient to support the administration of levocetirizine to infants and toddlers aged less than 2 years (see also section 4.4).

Method of administration
An oral syringe is included in the package. The appropriate volume of oral solution should be measured with the oral syringe and poured into a spoon or 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 experienced for less than four days a week or for less than four weeks a year) should be treated according to the disease and its history; treatment can be stopped once the symptoms have disappeared and restarted when symptoms reappear. In persistent allergic rhinitis (symptoms experienced for more than four days a week or for more than four weeks a year), continuous therapy may 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 with the use of cetirizine (racemate) for up to one year.

4.3 Contraindications
Hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any other piperazine derivative or to any of the other excipients listed in section 6.1.
Severe renal impairment with creatinine clearance less than 10 mL/min.

4.4 Special warnings and precautions for use
Caution is recommended with concurrent intake of alcohol (see section 4.5).
LEVOFREE SYRUP contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).
Caution should be exercised in patients with epilepsy and in patients at risk of convulsion, as levocetirizine may cause seizure aggravation.
Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Caution should be exercised in patients with predisposing factors for urinary retention (e.g. spinal cord lesion, prostatic hyperplasia), as levocetirizine may increase the risk of urinary retention.

Responses to allergy skin tests are inhibited by antihistamines and a wash-out period of 3 days is required before performing them.
Pruritus may occur when levocetirizine is stopped, even if the symptom was not present before treatment initiation. The symptoms may resolve spontaneously. In some cases the symptoms may be intense and may require treatment to be restarted; the symptoms should then resolve.

Paediatric population

Although some clinical data are available in children aged 6 months to 12 years (see sections 4.8, 5.1 and 5.2), these data are not sufficient to support the administration of levocetirizine to infants and toddlers aged less

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 cetirizine demonstrated that there were no clinically relevant adverse interactions with antipyrine, azithromycin, cimetidine, diazepam, erythromycin, glipizide, ketoconazole or pseudoephedrine. A small decrease in the clearance of cetirizine (16%) was observed in a multiple-dose study with theophylline (400 mg once daily), while the disposition of theophylline was not altered by concomitant cetirizine administration.
In a multiple-dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40%, while the disposition of ritonavir was slightly altered (−11%).
The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.
In sensitive patients, the concurrent administration of cetirizine or levocetirizine and alcohol or other central nervous system depressants may cause additional reductions in alertness and impairment of performance.

4.6 Pregnancy and Lactation

Pregnancy

There are no or limited data (fewer 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 1,000 pregnancy outcomes) in pregnant women indicate no malformative or feto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or postnatal development (see section 5.3). The use of levocetirizine may be considered during pregnancy if necessary.

Breast-feeding

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

Fertility

No clinical data are available for levocetirizine.

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.

Nevertheless, some patients may experience somnolence, fatigue and asthenia under therapy with levocetirizine. Patients intending to drive, engage in potentially hazardous activities or operate machinery should therefore take their response to the medicinal product into account.

4.8 Undesirable effects

Clinical studies

Adults and adolescents above 12 years of age

In therapeutic studies in women and men aged 12 to 71 years, 15.1% of patients in the levocetirizine 5 mg group had at least one adverse drug reaction, compared with 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 included 935 subjects exposed to the recommended dose of 5 mg daily. The following incidences of adverse drug reactions were reported at rates of 1% or greater (common: ≥1/100 to <1/10) under levocetirizine 5 mg or placebo:

Preferred term (WHOART)	Placebo (n = 771)	Levocetirizine 5 mg (n = 935)
Headache	25 (3.2%)	24 (2.6%)
Somnolence	11 (1.4%)	49 (5.2%)
Dry mouth	12 (1.6%)	24 (2.6%)
Fatigue	9 (1.2%)	23 (2.5%)

Further uncommon incidences of adverse reactions (uncommon: ≥1/1,000 to <1/100), such as asthenia or abdominal pain, were observed. 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 population

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 doses of 1.25 mg daily for 2 weeks and 1.25 mg twice daily respectively. The following incidences of adverse drug reactions were reported at rates of 1% or greater:

System organ class and preferred term	Placebo (n = 83)	Levocetirizine (n = 159)
Gastrointestinal disorders		
Diarrhoea	0	3 (1.9%)
Vomiting	1 (1.2%)	1 (0.6%)
Constipation	0	2 (1.3%)
Nervous system disorders		
Somnolence	2 (2.4%)	3 (1.9%)
Psychiatric disorders		
Sleep disorder	0	2 (1.3%)

In children aged 6 to 12 years, double-blind placebo-controlled studies were performed in which 243 children were exposed to 5 mg levocetirizine daily for periods ranging from less than 1 week to 13 weeks. The following incidences of adverse drug reactions were reported at rates of 1% or greater:

Preferred term	Placebo (n = 240)	Levocetirizine 5 mg (n = 243)
Headache	5 (2.1%)	2 (0.8%)
Somnolence	1 (0.4%)	7 (2.9%)

As stated in sections 4.2 and 4.4, although clinical data presented in this section are available in children aged 6 months to 12 years, there are insufficient data to support administration of the product to infants and toddlers aged less than 2 years.

Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

Reporting of suspected adverse reactions

Healthcare professionals are asked to report any suspected adverse reactions via the Pharmacy and Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS): https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

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

Management of overdose

There is no known specific antidote to levocetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines for systemic use, piperazine derivatives. ATC code: R06AE09.

Mechanism of action

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), two-fold higher than that of cetirizine (Ki = 6.3 nmol/L). Levocetirizine dissociates from H1 receptors with a half-life of 115 ± 38 minutes. 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.

Pharmacodynamic effects

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-intake in placebo-controlled trials in the model of the allergen challenge chamber

In vitro studies show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic in vivo study (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.

Clinical efficacy and safety

The efficacy and safety of levocetirizine have been demonstrated in several double-blind, placebo-controlled clinical trials in adult patients with 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) with persistent allergic rhinitis and sensitisation to house dust mites and grass pollen demonstrated that levocetirizine 5 mg was clinically and statistically significantly more effective than placebo in relieving the total symptom score of allergic rhinitis throughout the study, without tachyphylaxis, and significantly improved patients' quality of life.

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

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 the QT interval.

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 with 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- and long-term therapeutic studies, including a trial in 29 children aged 2 to 6 years treated with 1.25 mg twice daily for 4 weeks; a trial in 114 children aged 1 to 5 years treated with 1.25 mg twice daily for 2 weeks; a trial in

45 children aged 6 to 11 months treated with 1.25 mg once daily for 2 weeks; and an 18-month 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.

5.2 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 as cetirizine. No chiral inversion occurs during absorption and elimination.

Absorption

Levocetirizine is rapidly and extensively absorbed following oral administration. In adults, peak plasma concentrations are achieved 0.9 hours after dosing and 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, nor concerning passage across the blood-brain barrier. In rats and dogs, the highest tissue levels are found in liver and kidneys and the lowest in the central nervous system compartment. In humans, levocetirizine is 90% bound to plasma proteins; the distribution is restrictive, with a volume of distribution of 0.4 L/kg.

Biotransformation

The extent of metabolism in humans is less than 14% of the dose, and differences resulting from genetic polymorphism or concomitant intake of enzyme inhibitors are therefore expected to be negligible. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP3A4, while aromatic oxidation involves 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, interaction with other substances 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 is via urine, accounting for a mean of 85.4% of the dose; excretion via faeces accounts for only 12.9%. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Special populations

Renal impairment: the apparent body clearance of levocetirizine correlates with creatinine clearance. It is therefore recommended to adjust the dosing intervals based on creatinine clearance in patients with

moderate and severe renal impairment. In anuric end-stage renal disease subjects, total body clearance is decreased by approximately 80% compared with normal subjects. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was less than 10%.
Paediatric population: data from a paediatric pharmacokinetic study with a single oral 5 mg dose in 14 children aged 6 to 11 years with body weight between 20 and 40 kg show that Cmax and AUC values are about two-fold greater than reported in healthy adults in a cross-study comparison. The mean Cmax was 450 ng/mL at a mean time of 1.2 hours; weight-normalised total body clearance was 30% greater and the elimination half-life 24% shorter than in adults. Dedicated pharmacokinetic studies have not been conducted in children younger than 6 years. A retrospective population pharmacokinetic analysis in 323 subjects indicated that administration of 1.25 mg once daily to children aged 6 months to 5 years is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.
Elderly: limited pharmacokinetic data are available. Following once-daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years), total body clearance was approximately 33% lower than in younger adults. The disposition of racemic cetirizine has been shown to depend on renal function rather than age; this finding is also applicable to levocetirizine. The dose should therefore be adjusted in accordance with renal function in elderly patients.
Gender: pharmacokinetic results for 77 patients (40 men, 37 women) were evaluated. The half-life was slightly shorter in women (7.08 ± 1.72 hours) than in men (8.62 ± 1.84 hours); however, the body weight-adjusted oral clearance in women (0.67 ± 0.16 mL/min/kg) appears 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, 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 disease given 10 or 20 mg of the racemate cetirizine as a single dose had a 50% increase in half-life and a 40% decrease in clearance compared with healthy subjects.
Pharmacokinetic/pharmacodynamic relationship: the action on histamine-induced skin reactions is out of phase with plasma concentrations.

5.3 Preclinical safety data

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

6. Pharmaceutical Particulars

6.1 List of Excipients

6.2 Incompatibilities

6.3 Shelf-Life

6.4 Special Precautions for storage

6.5 Nature and Content of container

60ml Syrup packed in PET bottle affixed with coded label which has batch number, manufacturing date and expiry dates packed in unit box with an insert.

6.6 Special precautions for disposal and other handling

7. Marketing Authorization Holder

Manufacturer

Zain Pharma Limited
Plot No. 209/13741, Colchester Park, Godown No. 1, 2, 3
P.O. Box 100167-00101, Nairobi, Kenya.

8. Marketing Authorization Number

H2022/CTD8711/19922

9. Date of first authorization/renewal of the authorization

2022 November 08

10. Date of revision of the text

2022 November 08