SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Levocetirizine dihydrochloride 2.5 mg/5 mL oral solution
Levozin syrup

2. Qualitative and quantitative composition

Each 5 mL (approximately a teaspoon) contains 2.5 mg of levocetirizine dihydrochloride.

Excipient with known effect
Each 5mL also contains 2g of sucrose, 0.75 mg of propyl benzoate and 6.75 mg of methyl hydroxybenzoate (section 4.4).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral solution.

Clear, colourless to pale yellow-coloured liquid.

4. Clinical particulars

4.1 Therapeutic indications

Levocetirizine dihydrochloride is indicated for 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 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 below).

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)	Contra-indicated

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 above).

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 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 than 2 years (see also section 4.4).

Method of administration
A measuring cup is included in the package. The appropriate volume of oral solution should be measured 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 less than four 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 the case of persistent allergic rhinitis (symptoms experienced for more than four days a week or more than four 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 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 derivatives or any of the other excipients listed in section 6.1. Patients with end-stage renal disease with an estimated Glomerular Filtration Rate (eGFR) below 15 ml/min (requiring dialysis treatment).

4.4 Special warnings and precautions for use
Precaution is recommended with concurrent intake of alcohol (see section 4.5).

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

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.

Response to allergy skin tests is 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 those symptoms were 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 resolve when the treatment is restarted.

Excipients
This medicine contains **sucrose**. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.

This medicine contains **methyl hydroxybenzoate** and **propyl parahydroxybenzoate** which may cause allergic reactions (possibly delayed).

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

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.

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 CNS depressants may cause additional reductions in alertness and impairment of performance.

4.6 Pregnancy, lactation and fertility

Pregnancy
There is 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 indicates no

malformative or foeto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects concerning pregnancy, embryo/fetal development, parturition or postnatal development (see section 5.3).

The use of levocetirizine may be considered during pregnancy, if necessary.

Breastfeeding
Cetirizine, the racemate of levocetirizine, is excreted in humans. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

Fertility
For levocetirizine no clinical data is available.

4.7 Effects on the 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 studies
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 medicinal product at the recommended dose of 5 mg daily.

From this pooling, the following incidence of adverse drug reactions was 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%)
Mouth dry	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) like asthenia or abdominal pain were observed.

The incidence of sedating adverse drug reactions such as somnolence, fatigue, and asthenia were 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 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 at rates of 1% or greater under levocetirizine or placebo:

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 6-12 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 at rates of 1% or greater under levocetirizine or placebo:

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

Post-marketing experience
Adverse reactions from post-marketing experience are per System Organ Class and frequency. The frequency is defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders
Not known: hypersensitivity including anaphylaxis
Metabolism and nutrition disorders
Not known: increased appetite
Psychiatric disorders
Not known: aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare

Nervous system disorders
Not known: convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia
Ear and labyrinth disorders
Not known: vertigo
Eyes disorders
Not known: visual disturbances, blurred vision, oculogyration
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
Renal and urinary disorders
Not known: dysuria, urinary retention
Skin and subcutaneous tissue disorders
Not known: angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
Musculoskeletal, connective tissues, and bone disorders
Not known: myalgia, arthralgia
General disorders and administration site conditions
Not known: oedema
Investigations
Not known: weight increased, abnormal liver function tests

Adverse effects may include upper abdominal discomfort, nausea, metallic taste, heartburn and either constipation or diarrhoea, blackening of the stools, itchy skin eruption, malaise, and bronchospasm.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the e-PV desktop applications (https://drive.google.com/file/d/16hwTz0587ZWtSWadbBAMwQPOD_KSExZP/view) or search for e-PV Mobile applications on Google Play or Apple App Store.

4.9 Overdose

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

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

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacological classification: 5. Antihistamines.

Mechanism of action
Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1 receptors.

Binding studies revealed that levocetirizine has a 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.

Pharmacodynamic effects
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.

Clinical efficacy and safety
The efficacy and safety of levocetirizine have 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 a significant decrease in pruritus severity over the first week and the total treatment period as compared to placebo.

Levocetirizine also resulted in a larger improvement in 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.

Paediatric population
The paediatric safety and efficacy of levocetirizine tablets have 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.

5.2 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 at 0.9 h after dosing. A steady state is achieved after two days. Peak concentrations are typically 270 ng/ml and 308 ng/ml following a single and 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 the liver and kidneys and 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.

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 involves multiple and/or unidentified CYP isoforms. Levocetirizine did not affect 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 population
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 in patients with moderate and severe renal impairment (see section 4.2). 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%.

Paediatric population
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_{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-normalized, total body clearance was 30% greater, and the elimination half-life was 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 on 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 is dependent on renal function rather than on age. This finding would also apply to 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 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 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.

Pharmacokinetic/pharmacodynamic relationship
The action on histamine-induced skin reactions is out of phase with the 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, toxicity to reproduction and development.

6. Pharmaceutical particulars

6.1 List of excipients
Sucrose
Methyl hydroxybenzoate
Propyl hydroxybenzoate
Glycerol
Glacial acetic acid
Sodium acetate anhydrous
Levomenthol
Flavor Tutti Frutti 501103
Hyflow supercel
Purified water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store below 30˚C.

6.5 Nature and contents of the container
An amber PET bottle, with a 'LPL' logo printed on a 25 mm P.P. cap and a 10 ml measuring cup.

Fill volume: 60ml.

6.6 Special precautions for disposal and other handling
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. APPLICANT
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8. MANUFACTURER
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9. REGISTRATION DETAILS

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