Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levocetirizine Krka 5mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride.

Excipient(s) with known effect: 88.63 mg lactose/tablet.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

The tablets are white, round, biconvex film-coated tablets with bevelled edges.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 6 years and above.

4.2 Posology and method of administration

Posology
Adults and adolescents 12 years of age and above:
The recommended daily dose is 5 mg (1 film-coated tablet).

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

Renal impairment

Dosage adjustments in patients with impaired renal function:

Group	*eGFR (ml/min)*	*Dosage and frequency*
Normal renal function	≥90	1 tablet once daily
Mild renal impairment	60 - < 90	1 tablet once daily
Moderate renal impairment	30- < 60	1 tablet once every 2 days
Severe renal impairment	15- <30 (not requiring dialysis)	1 tablet once every 3 days
End-stage renal disease	< 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 above).

Paediatric population
Children aged 6 to 12 years:
The recommended daily dose is 5 mg (1 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.

Method of administration
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.

Duration of use
Intermittent allergic rhinitis (experienced for less than four days a week or for 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 case of persistent allergic rhinitis (symptoms experienced for more than four days a week or for 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 use of cetirizine (racemate) for up to one year.

4.3 Contraindications

Hypersensitivity to levocetirizine, to cetirizine, to hydroxyzine, to any piperazine derivatives or to any of the excipients listed in section 6.1.
Patients with end-stage renal disease with an eGFR (estimated Glomerular Filtration Rate) 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 predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine may increase the risk of urinary retention.

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

Response 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 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.

Paediatric population
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.

This product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Fertility, pregnancy and lactation

Pregnancy
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 foeto/ 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. 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 are available.

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 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 drop out 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. From this pooling, following incidence of adverse drug reactions were reported at rates of 1 % or greater (common: ≥ 1/100, < 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 ≥1/1000, <1/100) like 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 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 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, 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 experience:
Adverse reactions from post-marketing experience are per System Organ Class and per 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).

	Not known
Immune system disorders	hypersensitivity including anaphylaxis
Metabolism and nutrition disorders	increased appetite
Psychiatric disorders	aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare
Nervous system disorders	convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia
Eye disorders	visual disturbances, blurred vision, oculogyration
Ear and labyrinth disorders	vertigo
Cardiac disorders	palpitations, tachycardia
Respiratory, thoracic and mediastinal disorders	dyspnoea
Gastrointestinal disorders	nausea, vomiting, diarrhoea
Hepatobiliary disorders	hepatitis
Skin and subcutaneous tissue disorders	angioneurotic oedema, fixed drug eruption, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders	myalgia, arthralgia
Renal and urinary disorders	dysuria, urinary retention
General disorders and administration site conditions	oedema
Investigations	weight increased, abnormal liver function tests

Description of selected adverse reactions
After levocetirizine discontinuation, pruritus has been reported.

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

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 overdoses
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 of the drug. 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). Levocetirizine has an affinity 2-fold higher than that of cetirizine (Ki = 6.3 nmol/l). Levocetirizine dissociates from H1-receptors with a half-life of 115 ± 38 min.
After single administration, levocetirizine shows a receptor occupancy of 90% at 4 hours and 57% at 24 hours.

Pharmacodynamic studies in healthy volunteers demonstrate that, at half the dose, levocetirizine has comparable activity to cetirizine, both in the skin and in the nose.

Pharmacodynamic effects
The pharmacodynamic activity of levocetirizine has been studied in randomised, controlled trials:
In a study comparing the effects of levocetirizine 5mg, desloratadine 5mg, and placebo on histamine-induced wheal and flare, levocetirizine treatment resulted in significantly decreased wheal and flare formation which was highest in the first 12 hours and lasted for 24 hours, ($p<0.001$) compared with placebo and desloratadine.

The onset of action of levocetirizine 5 mg in controlling pollen-induced symptoms has been observed at 1 hour post drug intake in placebo controlled trials in the model of the allergen challenge chamber.

In vitro studies (Boyden chambers and cell layers techniques) show that levocetirizine inhibits eotaxin-induced eosinophil transendothelial migration through both dermal and lung cells. A pharmacodynamic experimental study *in vivo* (skin chamber technique) showed three main inhibitory effects of levocetirizine 5 mg in the first 6 hours of pollen-induced reaction, compared with placebo in 14 adult patients: inhibition of VCAM-1 release, modulation of vascular permeability and a decrease in eosinophil recruitment.

Clinical efficacy and safety
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 5mg 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.

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.

5.2 Pharmacokinetic properties

The pharmacokinetics of levocetirizine are linear, dose- and time-independent, with low 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 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 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, 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-normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Dedicated pharmacokinetic studies have not been conducted in paediatric patients younger than 6 years of age. A retrospective population pharmacokinetic analysis was conducted in 324 subjects (181 children 1 to 5 years of age, 18 children 6 to 11 years of age, and 124 adults 18 to 55 years of age) who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. Data generated from this analysis indicated that administration of 1.25 mg once daily to children 6 months to 5 years of age is expected to result in plasma concentrations similar to those of adults receiving 5 mg once daily.

Elderly
Limited pharmacokinetic data are available in elderly subjects. Following once daily repeat oral administration of 30 mg levocetirizine for 6 days in 9 elderly subjects (65–74 years of age), the total body clearance was approximately 33% lower compared to that in younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than on age. This finding would also be applicable for levocetirizine, as levocetirizine and cetirizine are both predominantly excreted in urine. Therefore, the levocetirizine dose should be adjusted in accordance with renal function in elderly patients.

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.

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

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

The tablet core:
Lactose monohydrate
Cellulose, microcrystalline
Silica, colloidal anhydrous
Magnesium stearate

The tablet coating:
Lactose monohydrate
Hypromellose 6cP
Titanium dioxide (E171)
Macrogol 3000
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC-PVDC/Alu) with 7 or 10 tablets, in a box.
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 60, 90, 98 and 100 film-coated tablets.

Blister (OPA-Alu-PVC/Alu) with 7 or 10 tablets, in a box.
Pack sizes: 7, 10, 14, 20, 28, 30, 50, 60, 90, 98 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto
Šmarješka cesta 6
8501 Novo mesto
Slovenia

8 MARKETING AUTHORISATION NUMBER

PA1347/043/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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