Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rinozal 5 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5 mg levocetirizine dihydrochloride (equivalent to 4.2 mg of levocetirizine).

Excipient with known effect
Each film-coated tablet contains 64.0 mg lactose monohydrate.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval, biconvex film-coated tablets, debossed with ‘L9CZ’ on one side and ‘5’ on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levocetirizine is indicated for:
- the relief of symptoms of chronic idiopathic urticaria.

4.2 Posology and method of administration

Posology
Adults and adolescents 12 years and above
The daily recommended dose is 5 mg (one film-coated tablet) once daily.

Elderly
For the time being, there is no data to suggest that the dose needs to be reduced in elderly patients provided that the renal function is normal.

Renal impairment
There are no data to document the efficacy/safety ratio in patients with renal impairment. Since levocetirizine is mainly excreted via renal route (see section 5.2), in cases no alternative treatment can be used, 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:

$$CL_{cr} = \frac{[140 - age(years)] \, x \, weight(kg)}{72 \, x \, serum \, creatinine(mg/dl)} \, (x \, 0.85 \, for \, women)$$

Dosing adjustments for adult patients with impaired renal function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥ 80	One tablet daily

Mild	50 - 79	One tablet daily
Moderate	30 - 49	One tablet every two days
Severe	< 30	One tablet every three 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, his age and his body weight.

Hepatic impairment
No dose adjustment is needed in patients with solely hepatic impairment.

Hepatic impairment and renal impairment
Dose adjustment is recommended (see “Renal impairment” above).

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

Levocetirizine is not recommended for use in children below age 6 due to insufficient data on safety and efficacy.
Method of administration
The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance, to hydroxyzine or to any piperazine derivatives or to any of the excipients listed in section 6.1.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings and precautions for use

Do not exceed the stated dose.

At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly.

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 convulsion 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.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of levocetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

The extent of absorption of levocetirizine is not reduced with food, although the rate of absorption is decreased.

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 1,000 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, embryonal/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. Therefore, the excretion of levocetirizine in human milk is likely. Adverse reactions associated with levocetirizine may be observed in breast-fed 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

Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 5 mg.
Patients intending to drive, engaging in potentially hazardous activities or operating machinery should not exceed the recommended dose and should take their response to the medicinal product into account. In these sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

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, following incidence 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 %)
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 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 %)

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)

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

Nervous system disorders
Not known: convulsion, paraesthesia, dizziness, syncope, tremor, dysgeusia

Ear and labyrinth disorders
Not known: vertigo

Eye 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 and connective tissues disorders
Not known: myalgia, arthralgia

General disorders and administration site conditions
Not known: oedema

Investigations
Not known: 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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms
Symptoms observed after an overdose of levocetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.
Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor and urinary retention.

Management of overdoses
There is no known specific antidote to levocetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence.
Levocetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives, ATC code: R06A E09

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 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.
Levocetirizine inhibits the histamine-mediated early phase of the allergic reaction and also reduces the migration of certain inflammatory cells and the release of certain mediators associated with the late allergic response.

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 or perennial allergic rhinitis.

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 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.

Pharmacokinetic / pharmacodynamic relationship
5 mg levocetirizine provides a similar pattern of inhibition of histamine-induced wheal and flare as 10 mg cetirizine. As for cetirizine, the action on histamine-induced skin reactions was out of phase with the plasma concentrations.

ECGs did not show relevant effects of levocetirizine on QT interval.

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. 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 mean apparent total body clearance is 0.63 ml/min/kg. The major route of excretion of levocetirizine and metabolites is via urine, accounting for a mean of 85.4 % of the dose. Excretion via faeces accounts for only 12.9 % of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Renal impairment
The apparent body clearance of levocetirizine is correlated to the creatinine clearance. It is therefore recommended to adjust the dosing intervals of levocetirizine, based on creatinine clearance in patients with moderate and severe renal impairment. In anuric end stage renal disease subjects, the total body clearance is decreased by approximately 80 % when compared to normal subjects.

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Lactose monohydrate
Cellulose microcrystalline
Magnesium stearate (E572)

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/PVDC:Al blisters or oPA/Al/PVC:Al blisters

Pack sizes:
Blisters containing 10, 14, 20, 28, 40, 50, 60, 80 or 100 tablets
Unit dose blisters containing: 30x1 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd.
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/179/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th October 2009

Date of last renewal: 21st June 2012

10 DATE OF REVISION OF THE TEXT

August 2018