Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levocetirizine 5 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 5mg of levocetirizine dihydrochloride.

Contains lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Product imported from the UK:
White to off white, film coated oval shaped tablet; One side of the tablet is debossed with LC5. The other side of the tablet is plain.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Levocetirizine is indicated for the symptomatic treatment of perennial allergic rhinitis, seasonal allergic rhinitis and chronic idiopathic urticaria.

4.2 Posology and method of administration

The film-coated tablet must be taken orally, swallowed whole with liquid and may be taken with or without food.

Adults and adolescents:
The recommended dose is 5 mg once daily

Children aged between 6 and 12 years:
The daily recommended dose is 5 mg once daily
Levocetirizine is not recommended for use in children below the age of 6 due to insufficient data on safety and efficacy.

The elderly:
At present there are no data to suggest that the dose needs to be reduced in elderly subjects provided that their renal function is normal.

Patients with renal impairment:
The dosing intervals must be individualized 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:

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

Dosing Adjustments for Patients with Impaired Renal Function:

Group	Creatinine clearance (ml/min)	Dosage and frequency

Normal	≥80	1 tablet once daily
Mild	50-79	1 tablet once daily
Moderate	30-49	1 tablet once every 2 days
Severe	< 30	1 tablet once every 3 days
End-stage renal disease	< 10-	Contra-indicated

Patients undergoing dialysis

Patients with 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 Patients with renal impairment above).

Duration of use:
The duration of use depends on the type, duration and course of the complaints. For hay fever 3-6 weeks, and in case of short-term pollen exposure as little as one week, is generally sufficient. Clinical experience with 5 mg levocetirizine as a film-coated tablet formulation is currently available for a 6-month treatment period.

4.3 Contraindications

Hypersensitivity to levocetirizine, to other piperazine derivatives or to any of the excipients.

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.

The use of Levocetirizine dihydrochloride is not recommended in children aged less than 6 years since the currently available film-coated tablets do not yet allow dose adaptation.

Precaution is recommended with intake of alcohol (see Interactions).

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

4.5 Interaction with other medicinal products and other forms of interactions

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

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

In sensitive patients the simultaneous administration of cetirizine or levocetirizine and alcohol or other CNS depressants may have effects on the central nervous system, although it has been shown that the racemate cetirizine does not potentiate the effect of alcohol

4.6 Fertility, pregnancy and lactation

Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of cetirizine on pregnancy or on the health of the fetus/newborn child. To date, no other relevant epidemiological data are available. For levocetirizine no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see 5.3). Caution should be exercised when prescribing to pregnant women.

Lactation
Levocetirizine is expected to be excreted into breast milk. Therefore, the use of Levocetirizine during breast feeding is not recommended and should only be considered if the expected benefit to the mother is greater than the risk to the suckling child.

4.7 Effects on ability to drive and use machines

Levocetirizine has no or negligible influence on 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

The following terminologies have been used in order to classify the occurrence of undesirable effects:

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)

	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)
Investigations					Weight increase, abnormal liver function tests	
Cardiac disorders					Palpitations	
Nervous system disorders		Somnolence, headache				
Eye disorders					Visual disturbances	
Respiratory, thoracic, and mediastinal disorders					Dyspnoea	
Gastrointestinal disorders		Dry mouth	Abdominal pain		Nausea	
Skin and subcutaneous tissue disorders					Angioneurotic oedema, pruritus, rash, urticaria	
General disorders and administration site conditions		Fatigue	Asthenia			
Immune system disorders					Hypersensitivity including anaphylaxis	
Hepatobiliary disorders					Hepatitis	

4.9 Overdose

a) Symptoms

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

b) 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 short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivative, ATC code R06A E09
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.

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.

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.

The efficacy and safety of levocetirizine have been demonstrated in several double-blind, placebo controlled, clinical trials performed in patients suffering from seasonal allergic rhinitis or perennial allergic rhinitis. Clinical experience with 5 mg levocetirizine as a film-coated tablet formulation is currently available for a 6-month treatment period.

Pharmacokinetic / pharmacodynamic relationship:
5 mg levocetirizine provide a similar pattern of inhibition of histamine-induced wheal and flare than 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. 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 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 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.

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 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.

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%.

5.3 Preclinical safety data

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

Preclinical results were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate

Film-coat
Hypromellose
Titanium dioxide
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date of this product shall be the date shown on the container and outer package of the product as marketed in the country of origin.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Overlabelled outer carton containing blister strips
Pack size: 30

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

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7 PARALLEL PRODUCT AUTHORISATION HOLDER

Imbat Limited
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8 MARKETING AUTHORISATION NUMBER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd May 2011

10 DATE OF REVISION OF THE TEXT