SUMMARY OF PRODUCT CHARACTERISTICS

1. **Name of the medicinal product**

Trade Name: **Allergostop**

Generic Name: Levocetirizine Tablets 5 mg

2. **Qualitative and Quantitative Composition**

Each uncoated tablet contains:

Levocetirizine Dihydrochloride	5mg
Excipients	q.s.

For a full list of excipients, see Section 6.1

3. **Pharmaceutical form**

Oral Solid preparation (Uncoated Tablet)

Description: White to off white coloured, uncoated oval shaped tablets.

4. **Clinical particulars**

4.1 Therapeutic indications

Levocetirizine Tablets are intended for the treatment of:

-Symptoms of allergic rhinitis (including throughout the year (persistent) and seasonal (intermittent) allergic rhinitis) and allergic conjunctivitis, such as itching, sneezing, nasal congestion, rhinorrhea, lacrimation, conjunctival hyperemia;

-Pollinose (haying time fever);

-Urticaria

-Other allergic dermatoses and accompanied by itching and rashes.

4.2 Posology and method of administration

Adults and adolescents 12 years and above:

The daily recommended dose is 5 mg (1 tablet)

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment.

Renal impairment (Adults):

There is recommended an individual selection of interval between the doses of drug in accordance with the level of Creatinine clearance (CC). The CC (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CC = \frac{[140 - \text{age (years)}] \times \text{body weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} - (\times 0.85 \text{ for women})$$

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 - Patients undergoing dialysis	< 10	Contraindicated

Renal impairment (Paediatrics):
In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance and body weight of the patient.

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.

Paediatric population
Children aged 6 to 12 years:
The daily recommended dose is 5 mg (1 tablet)
For children aged 2 to 6 years no adjusted dosage is possible with the tablet formulation. It is recommended to use a paediatric formulation of levocetirizine.

Method of administration
Oral administration; 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 (symptoms 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 more than four day a week or for more than four weeks a year), continuous therapy can be proposed to the patient throughout 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

Levocetitizine Tablets are contra-indicated in:

- An increased sensitivity towards an active substance, cetirizine, hydroxyzine, any derivative piperazine or towards any other auxiliary substance of the drug
- Terminal stage of the renal impairment (creatinine clearance is < 10mL / min).
- Children aged up to 6 years.
- Deficiency of lactose, intolerance of lactose, glucose galactose malabsorption

4.4 Special warnings and precautions for use

- Intake of alcohol

  Precaution is recommended with concurrent intake of alcohol.
- Patients with predisposing factors of urinary retention

  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.
- Liver impairment

  This medicine should be used with caution in patients with liver diseases.
- In chronic renal impairment (there is a need of adjustment of the dosing regimen). In elderly patients (with the age-related reduction in glomerular filtration)
- Driving or operating machinery

  Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
- Caution should be taken in patients with epilepsy and patients at risk of convulsion as levocetirizine may cause seizure aggravation.
- Patients with rare hereditary problems of galactose intolerance, the Lapp 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.

- **Pregnancy & Breastfeeding**

  However, there is no evidence of teratogenicity; patients suggested to avoid the use of Levocetirizine during pregnancy. The use of Levocetirizine may be considered during pregnancy, if necessary.

  Most antihistamines are present in breast milk in varying amounts; although not known to be harmful. 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.

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 andpseudoephedrine).

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 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, embryonal/foetal development, parturition or postnatal development.

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

Lactation

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 breastfed infants. Therefore, caution should be exercised when prescribing levocetirizine to lactating women.

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

Data on safety obtained during the studies of cetirizine

The following undesirable reactions observed:

Rarely (≥1/10000, <1/1000),

There were reported the light and temporary undesirable phenomena such as tiredness, disorders of concentration, drowsiness, headache, dizziness, excitement, dry mouth and gastro-intestinal disturbances (constipation). In some cases, there were observed the reactions of hypersensitivity and angioneurotic edema.

And also it was reported on separate cases of convulsions, photosensitization reaction, damaged liver, anaphylactic shock, disorders of the blood circulation, deafness, poor health, itching, vasculitis, visual disturbances and nightmares dreaming.

Clinical data studies

Clinical studies showed that by 14.7% of patients who have used Levocetirizine in a dose of 5mg, there were observed the undesirable reactions in comparison with 11.3% in patients of placebo group. 95% of these undesirable reactions were mild or moderately pronounced.

In clinical trials, frequency of therapy discontinuation due to which the development of possible side effects comprised 0.7% (4/538) in patients, randomized for obtaining Levocetirizine in a dose of 5mg & 0.8% (3/382) for patients, randomized in a placebo group.

The following undesirable reactions were detected in patients (n = 538) participated in the clinical trial and using Levocetirizine in the recommended doses (5mg once a day):

With frequency 1 – 10%

Undesirable reactions	*Levocetirizine 5mg (n=538)*	*Placebo (n=382)*
Drowsiness	5.6%	1.3%
Dry mouth	2.6%	1.3%
Headache	2.4%	2.9%
Fatigability	1.1%	1.3%

Although frequency of cases of drowsiness in a group of Levocetirizine was greater than such in a group of placebo, in most cases, this undesirable phenomenon was mild or moderate degree of severity.

Not often (0.1-1%): Abdominal pain.

Post-marketing studies

In a period of post-marketing use of the drug, the following possible side effects observed:

For immune system:

Reactions of hypersensitivity, including anaphylactic

For metabolism and nutrition:
An increase in appetite
Disorders of psyche:
Anxiety, aggression, agitation, hallucinations, depression, insomnia, suicidal ideas, nightmares

Nervous system:
Convulsions, thrombosis of the sinuses of the dura mater, paresthesia, dizziness, vertigo, fainting, tremor, dysgeusia

Disorders of vision:
Inflammatory manifestations, visual impairment, blurred visual perception, involuntary movements of the eyeballs (nystagmus).

Heart:
Stenocardia, tachycardia, heart palpitations

Vessels:
Jugular vein thrombosis
Respiratory system, chest organs and mediastinum:
Increased symptoms of rhinitis, shortness of breath

Skin and subcutaneous tissues:
Angioedema, zsantema, hypotrichosis, pruritus, rash, hives, urticaria, photosensitivity / toxicity, persistent drug erythema

Common disturbances:
Ineffectiveness of product and its interaction, dryness of mucous membranes

Gastro-intestinal tract:
Nausea, vomiting

Liver and biliary tracts:
Hepatitis

Skeletal – muscular, bone system and connecting tissue:
Pain in muscle, arthralgia

Kidney and urine excretory tracts:
Dysuria, urine retention

Common disturbances and disorders at the injection site:
Edema

Laboratory and instrumental data:
An increase in body weight, the change in the functional test of liver, adverse reactivity

Description of individual undesirable reactions
In a small number of patients, there was observed itching after the discontinuation of the use of Levocetirizine

Further Information
Non-sedating antihistamines such as levocetirizine cause less sedation and psychomotor impairment than the older antihistamines, but can still occur; sedation is generally minimal.

4.9 Overdose

Symptoms
Symptoms of overdose may include drowsiness in adults. In children, at the beginning agitation and restlessness may initially occur, followed by drowsiness.
Treatment
There is no known specific antidote to levocetirizine.
symptomatic or supportive treatment is recommended.
Gastric lavage or charcoal intake should 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; H_1-histamine receptors blocker
ATC code: R06AE09

Pharmacodynamic effects
Mechanism of action
Levocetirizine, the active enantiomer of cetirizine, It is powerful and selective antagonist of histamine, blocking H_1-histamine receptors. Levocetirizine has an effect on histamine-dependency stage of allergic reactions, and also it decreases the migration of eosinophilia, and reduces vascular permeability, limits the release of inflammatory mediators.
Levocetirizine prevents the development and relieves the process of the allergic reactions, has anti-exudative, anti-pruritic action, practically does not render anti-cholinergic and anti-serotonin action. In therapeutic doses, practically there is no sedative effect.

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.

In human, levocetirizine is 90% bound to plasma proteins. The distribution of levocetirizine is restrictive, as the volume of distribution is 0.4 l/kg. Bioavailability reaches 100%.

Metabolism

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 feces 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 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 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 450ng/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 30mg. 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 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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline Cellulose PH 101
Maize starch
Povidone K-30
Purified water
Crospovidone (XL-10)
Colloidal Anhydrous Silica
Magnesium Stearate

6.2 Incompatibilities

None

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at temperature up to 30°C in a dry place, Protected from light.
Keep out of reach of children.

6.5 Nature and contents of container

10 tablets are packed in an Alu-PVDC blister; further 1 blister along with package leaflet is packed in a unit carton.

6.6 Instructions for use and handling and disposal

No special requirements.

7. Marketing authorization holder:

Manufacturer:

C-7 to C-13 and C-59 to C-64,
Sigaddi Growth Center, SIDCUL,
Sigaddi, Kotdwar – 246149,
Dist. Pauri Garhwal, Uttarakhand, India

8. Number(s) in the national register of finished pharmaceutical products:

11076/NMR/2023

9. Date of first authorisation/renewal of the authorisation:

Dec 30, 2023

10. Date of revision of the text: Not applicable