

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CREBROS® 5 mg film tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

It contains 5 mg levocetirizine dihydrochloride.

Excipients:

Lactose monohydrate 66.77mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets

White, oval, convex film-coated tablet with a “LS” logo on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CREBROS® is indicated in the symptomatic treatment of allergic rhinitis (including intermittent/persistent or seasonal/perennial) and chronic idiopathic urticaria in patients above 6 years old.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

Children aged 6 to 12 years:

The daily recommended dose is 5 mg (1 film-coated tablet).

Adults and adolescents 12 years and above:

The daily recommended dose is 5 mg (1 film-coated tablet).

In the treatment of chronic hives (chronic urticaria), your doctor may increase the dose of CREBROS® up to 20 mg (4 film-coated tablets) per day.

Elderly:

Adjustment of the dose is recommended in elderly patients with moderate to severe renal impairment (see Section “Renal impairment”).

Intermittent allergic rhinitis (symptoms <4days/week or during less than 4 weeks) 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 >4days/week and during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens. Clinical studies with 5 mg levocetirizine film-coated tablet is currently available for a 6-month treatment period.

For chronic urticaria and chronic allergic rhinitis, up to one year's clinical experience is available for the racemate (cetirizine).

Method of administration:

The film-coated tablet must be taken orally, swallowed whole with liquid. It may be taken with or without food. It is recommended to take the daily dose in one single intake.

Additional information on special population:**Renal/hepatic 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 (CL_{cr}) in ml/min is needed.
- The CL_{cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times (0,85 \text{ for women})$$

Dosing Adjustments for Patients with Impaired Renal Function:

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥80	5 mg once daily
Mild	50 – 79	5 mg once daily
Moderate	30 – 49	5 mg once every two days
Severe	< 30	5 mg once every three days
End-stage renal disease - Patients undergoing dialysis	< 10	Contra-indicated

- In pediatric 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.
- 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 Section “renal impairment”*).

Pediatric population:

There is no adjusted dosage for children aged 2 to 6 years with the film-coated tablet formulation. It is recommended to use a pediatric formulation of levocetirizine.

Geriatric population:

See section “4.2. Posology and method of administration, Renal/Hepatic impairment”

4.3 Contraindications

CREBROS® is contraindicated in hypersensitivity to levocetirizine, to other piperazine derivatives, or to any of the excipients.

It is contraindicated in patients with severe renal impairment (with less than 10 ml/min creatinine clearance).

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

4.4. Special warnings and precautions for use

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. Therefore it is recommended to use a pediatric formulation of levocetirizine.

Precaution is recommended with intake of alcohol (*see Section 4.*).

Levocetirizine is possibly increase the risk of urinary retention, therefore precaution is recommended for patient who has predisposing factor of urinary retention (e.g. spinal cord lesions, prostatic hyperplasia).

Caution should be exercised in patients with epilepsy and in patients at risk of convulsions, as levocetirizine may cause increased seizure severity.

The response to skin allergy tests is inhibited by antihistamines and antihistamine use should be discontinued 3 days before these tests are performed.

Itching may occur when levocetirizine is discontinued, even if it was not present at the start of treatment. Symptoms may resolve spontaneously. In some cases, symptoms may be severe and may require treatment to be restarted. Symptoms when treatment is restarted must be fixed.

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

4.5 Interactions 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 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.

In a multidose study of ritonavir (600 mg b.i.d.), exposure to cetirizine was increased as 40% and the distribution of ritonavir was slightly decreased when combined with cetirizine (10 mg once a day). (-11%)

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 Pregnancy and lactation

General information:

Pregnancy category: B

Women of childbearing potential/ birth control (Contraception):

Women of child-bearing potential may be treated with CREBROS[®].

The concomitant use of levocetirizine with oral contraceptives is not expected to reduce the efficacy of contraception.

Pregnancy:

For levocetirizine there are limited or no clinical data (less than 300 pregnancy data) for use in pregnancy. However, a large amount of data in pregnant women (more than 1000 pregnancy data) for cetirizine, the racemate of levocetirizine, has shown that it does not cause any malformations or fetal/newborn toxicity. Animal studies do not show any direct or indirect harmful effects related to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3).

Lactation:

Cetirizine is excreted in human milk. Therefore, it is possible that levocetirizine is also excreted in human milk. Adverse reactions associated with levocetirizine may be observed in breastfed infants.

It is not recommended for breastfeeding women.

Reproduction/Fertility

There are no data for levocetirizine.

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

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 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 %)
Dry mouth	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%).

Pediatric population:

In a two week, two placebo-controlled studies a total of 159 pediatric patients 6 to 11 months of age and less than 1 to 6 years old, received respectively 1.25 mg levocetirizine once daily and 1.25 mg levocetirizine two times. Patients receiving levocetirizine and placebo were reported following side effects in the determined frequency and in the frequency of 1% and more:

Preferred Term and System Organ Class	Placebo (n =83)	Levocetirizine 5 mg (n = 159)
Gastrointestinal disorders		
Diarrhea	0	3 (1.9 %)
Nausea	1 (1.2%)	1 (0.6 %)
Constipation	0	2 (1.3 %)
Nervous system disorders		
Somnolence	2 (2.4%)	3 (1.9%)
Psychiatric disorders		
Sleep disorders	0	2 (1.3%)

A double blinded, placebo-controlled study was conducted in patients aged between 6 to 15 years old received 5 mg levocetirizine for less than 1 week to 13 weeks. Patients receiving levocetirizine and placebo were reported following side effects in the determined frequency and in the frequency of 1% and more:

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 taken from any source are listed in the table below according to system organ class. Classification very common ($\geq 1/10$); common ($\geq 1/100$, <1/10); uncommon ($\geq 1/1,000$, <1/100); rare ($\geq 1/10,000$, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from available data).

Immune system disorders

Very rare: Hypersensitivity including anaphylactic shock

Not known: Hypersensitivity including anaphylaxis

Metabolism and nutrition disorders

Not known: Increased appetite

Psychiatric disorders

Very rare: Aggression, agitation, hallucination, depression, insomnia, suicide thoughts

Nervous system disorders:

Common: Headache, somnolence

Not known: Convulsion, dizziness, paresthesia, somnolence, shaking, dysgusia

Eye Disorders

Very rare: Visual disturbances, blurred vision, oculogyration

Ear and labyrinth disorders

Not known: Vertigo

Cardiac disorders:

Very rare : Palpitations, tachycardia

Respiratory, thoracic and mediastinal disorders

Very rare: Dyspnea

Gastrointestinal disorders

Common: Dry mouth

Uncommon: Abdominal pain

Not known: Vomiting, nausea

Hepatobiliary disorders

Not known: Hepatitis

Renal and urinary disorders

Not known: Dysuria, urine 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

General disorders and administration site conditions

Common: Weakness

Uncommon: Asthenia

Not known: Oedema

Investigations:

Not known: Weight increased, abnormal liver function tests

Reporting side affects

Post-authorization reporting of suspected adverse drug reactions is of great importance. Reporting allows the benefit/risk balance of the medicinal product to be continuously monitored. Healthcare professionals are encouraged to report any suspected adverse reactions in Turkey. Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose

Symptoms:

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

Treatment:

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: 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 ($K_i = 3.2$ nmol/l). Levocetirizine has an affinity 2-fold higher than that of cetirizine ($K_i = 6.3$ 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.

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.

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 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.

The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

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

5.2 Pharmacokinetic properties

General 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 feces accounts for only 12.9% of the dose. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

Linearity/non-linearity:

Levocetirizine shows linear pharmacokinetics.

Characteristics in patients

Hepatic/Renalinsufficiency:

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%.

Pediatric population:

In a crossover design pediatric pharmacokinetic study, oral administration of a single dose of 5 mg levocetirizine to 14 children aged 6-11 years, body weight 20-40 kg, resulted in C_{max} and AUC (area under the curve) values approximately twice those reported in healthy adults.

The mean C_{max} of 450 ng/ml was reached in an average of 1.2 hours, total body clearance was 30% higher and elimination half-life was 24% shorter in the pediatric population at normalized weight compared to adults. No specific pharmacokinetic studies have been conducted in pediatric patients younger than 6 years. A retrospective pharmacokinetic analysis was performed in 323 individuals (181 children aged 1-5 years, 18 children aged 6-11 years, 124 adults aged 18-55 years) receiving single or multiple doses of levocetirizine between 1.25 mg and 30 mg. Based on the data from this analysis, administration of 1.25 mg levocetirizine once daily to children aged 6 months to 5 years is expected to result in plasma concentrations similar to adults receiving 5 mg levocetirizine once daily.

Geriatric population:

Pharmacokinetic data for elderly subjects are limited. When 9 elderly patients (65-74 years) were administered 30 mg levocetirizine once daily for 6 days, total body clearance was approximately 30% lower than in younger adults. The pharmacokinetics of racemic cetirizine have been shown to depend on renal function rather than age. Since both levocetirizine and cetirizine are predominantly excreted in the urine, this finding also applies to levocetirizine. Therefore, the dose of levocetirizine in elderly patients should be adjusted according to renal function.

Gender:

Pharmacokinetic results from 77 patients (40 males, 37 females) were evaluated for a possible 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, body weight-adjusted oral clearance in women (0.67 ± 0.16 ml/min/kg) appeared similar to that in men (0.59 ± 0.12 ml/min/kg). The same doses and dose ranges apply to men and women with normal renal function.

Race:

The effect of race on levocetirizine has not been studied. Since levocetirizine is primarily excreted by the kidney and there are no significant racial differences in creatinine clearance, the pharmacokinetic character of levocetirizine is not expected to differ between races. No racial differences were observed with racemic cetirizine.

Hepatic impairment:

The pharmacokinetics of levocetirizine have not been tested in patients with hepatic impairment. Single doses of 10 or 20 mg racemic cetirizine given to patients with chronic liver disease (hepatocellular, cholestatic and biliary cirrhosis) resulted in a 50% increase in half-life and 40% decrease in clearance compared to healthy subjects.

Pharmacokinetic/pharmacodynamic relationship:

The effect on histamine-induced skin reactions has not been studied in the same phase as 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
- Lactose monohydrate (bovine origin)
- Povidone K 25
- Colloidal anhydrous silica
- Croscarmellose sodium
- Magnesium stearate
- Hypromellose
- Talc
- Titanium dioxide (E 171)
- Macrogol (PEG 6000)

6.2. Incompatibilities

Incompatibility with other drugs is not known.

6.3. Shelf life

36 months

6.4. Special precautions for storage

Store below 25°C in its original packaging.

6.5 Nature and contents of container

Aluminium/ Aluminium (Alu / Alu) (30/30) blister strip of 20 and 40 film coated tablets.

6.6 Special precautions for disposal

Unused products or waste materials should be disposed of in accordance with the “Medicinal Waste Control Regulation” and “Packaging Waste Control Regulation”.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

217/21

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 13.11.2008

Date of renewal of authorization:

13.11.2008

10. DATE OF REVISION OF THE SPC

13.11.2008