SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the medicinal product

Histolat Syrup

2. Qualitative and quantitative composition

Each 5ml Syrup contains 2.5mg of Levocetirizine Dihydrochloride.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Syrup.
Colourless solution syrupy liquid with a characteristic taste.

4. Clinical particulars

4.1 Therapeutic indications

Histolat® is indicated for treatment of symptoms associated with:

- Seasonal allergic rhinitis (including ocular symptoms);
- Perennial allergic rhinitis
- Chronic urticaria

4.2 Posology and method of administration

Histolat syrup:

The recommended dose for Adults and adolescents 12 years and above is 10 ml of syrup once daily.

The recommended dose for children aged from 6-12 years is 10 ml of syrup once daily.
The recommended dose for children aged from 2-6 years is 2.5 ml of syrup twice daily.

Method of Administration

Oral administration only

4.3 Contraindications

Histolat® is contraindicated in individuals allergic to the active substance, to cetirizine, to hydroxyzine or to any other piperazine derivatives.

Histolat® is contraindicated inpatients with severe impairment of kidney function (severe renal failure with creatinine clearance below 10 ml/min)

4.4 Special warnings and precautions for use

Histolat should be used with caution in Epileptic patients

As levocetrizine is expected to be excreted in breast milk, it should not be administered during breastfeeding.

Children:
Histolat syrup is not recommended for infants and children under 2 years of age.
Histolat tablet is not recommended for infants and children under 6 years of age, since tablets do not allow for dose adaptation.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction study have been performed with levocetrizine (including no studies with CYP3A4 inducers); studies with the racemate compound Cetrizine demonstrated there were no clinically relevant adverse interaction (with pseudoephedrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide,and diazepam). A small decrease in the clearance of cetrizine (16%) was observed in a multiple dose study with theophylline (400mg once a day); while the disposition of theophylline was not altered by concomitant cetrizine administration.

4.6 Pregnancy and Lactation

There are no or limited amount of data from the use of levocetirizine in pregnant women. However, animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development. The use of levocetirizine may be considered during pregnancy, if necessary.
As levocetirizine is expected to be excreted in breast milk, it should not be administered during breastfeeding.

4.7 Effects on ability to drive and use machines

Some patients being treated with levocetirizine may experience somnolence / drowsiness, tiredness and exhaustion. Use caution when driving or operating machinery until you know how this medicine affects you. However, special tests have revealed no impairment of mental alertness, the ability to react or the ability to drive in healthy test persons after taking levocetirizine in the recommended dosage

4.8 Undesirable effects

Dry mouth, headache, tiredness and somnolence/drowsiness.
exhaustion and abdominal pain.

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

Levocetrizine is antihistaminic drug with antiallergic properties .it is a potent and selective antagonist of peripheral H1-receptors with a very poor effect on other receptors and has therefore almost no anticholinergic and antiestrogenic properties.

Levocetrizine is the (R) enantiomer of cetrizine . binding studies revealed that levocetrizine has high affinity for human H1 receptors (ki=3.2nmol/l) levocetrizine has an affinity 2-fold higher than that of cetrizine(ki=6.3nmol/l) Levocetrizine dissociates from H1 –receptors with a half life of 115-+38 min .pharmacodynamic studies in healthy volunteers demonstrate that ,at half the dose Levocetrizine has comparable activity to cetrizine both in the skin and in the nose ,ECGs did not show relevant effects of levocetrizine on QT interval,ECGs have until now only been effectuated on 45 volunteers.

The dosage-determing trials showed an optimal benefit-to risk ratio in the administering of daily doses of 5 mg Levocetrizine .in the treatment of seasonal allergic rhinitis ,formal binding studies showed a statistically significant equivelance between 5 mg Levocetrizine and 10 mg cetrizine doses .as the most important indicators of the pharmacokinetic and pharmacodynamic properties of Levocetrizine,as well as its therapeutic efficiency were investigated using bridging studies ,results from studies on cetrizine relating to further testing on perennial allergic rhinitis and chronic urticaria were also taken into account .to back up these results , Levocetrizine showed a tendency for effectivness in a dosage –determining trial carried out on perennial allergic rhinitis .a therapeutic study carried out on 551 patients with persisting allergic rhinitis (symptoms:4 days a week during at least 4 weeks)and sensibility to acarians and graminae pollens has shown that levocetrizine 5 mg did clinically and statistically induce a much more significant reduction of the symptoms (sneezes, flowing nose, nose and eye itching ,blocked nose) in the six-month study period of the study than placebo .

No tachyphylaxy was observed .during the whole study, Levocetrizine 5mg clinically and statistically improved the patients` life quality

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.

Clinical efficiency 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 5mg 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 pharmacokinetic profile of Levocetrizine is linear and independent of a single or multidose administration, as the interindividual variability is weak. there is no indication suggesting of a significant variability according to sex ,polymorphia or potential tabagism.
The pharmacokinetic profile of Levocetrizine (the [R] enantiomar of cetrizine) is identical to that of cetrizine (racemate)
No chiral inversion is observed during absorption or elimination
Absorption:
Levocetrizine 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 270ng/ml and 308 ng/ml following a single and a repeated

5mg 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. Levocetrizine is 90%bound to plasma protein, the distribution of Levocetrizineis restrictive as the volume of distribution is 0.4 l/kg
Biotransformation:
The extent of metabolism of Levocetrizine 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 CYP3A4 while aromatic oxidation involved multiple and /or unidentified CYP isoforms.
Levocetrizine had no effects on the activities of CYP isoenzymes 1A2,2C9,2C19,2D6,2E1 and 3A4 at concentrations well above peak concentrations achieved following 5 mg oral dose. Due to its low metabolism and abscense of metabolic inhibition potential,the interaction of levocetrizine 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/1.73 m2 the major route of excretion of levocetrizine and metabolism is via urine, accounting for a mean of 85.4% of the dose ,excretion through feces accounts for only 12.9% of the dose ,renal clearance of levocettrizine is about 30 ml /min/1.73m2 once corrected taking into account the protein bound ,this value amounts to 260ml/min/1.73m2 .levocetrizine is excreted both by glomular filtaration and active tubular secretion
Renal impairment:
The apparent body clearance of levocetrizine is correlated to the creatinine clearance in patients with moderate and severe renal impairment (see paragraph posology / method of administration).in anuric end stage renal disease subjects ,the total body clearance is decreased approximately 80% when compared to normal subject .the amount of levocetrizine removed during a standard 4-hour hemodialysis procedure was <10%
Relation between pharmacokinetic and pharmacodynamic:
During the formation of histamine –induced erythyma and pruritic patches,5 mg levocetrizine causes an inhibition comparable to that induced by 10 mg cetrizine .as for cetrizine ,the effect on histamine induced cutaneous reactions is not parallel to the fluctuations of the plasmatic 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.

6. Pharmaceutical particulars
6.1 List of excipients
Sorbitol liquid 70 %
Glycerol
Propylene Glycol
Methyl Paraben
Propyl Paraben

Sodium Acetate
Peach Flavor
Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3years.

6.4 Special precautions for storage
Store below 30 ° C.

6.5 Nature and contents of container
Histolat Syrup is packaged in Amber Pet plastic bottle
Pack sizes of: 60 ml.

6.6 Special precautions for disposal and other handling
No special requirements for disposal

7. APPLICANT/MANUFACTURER

Afrab Chem Limited
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