1. Name of the medicinal product

ALERFREE SYRUP (Levocetirizine Syrup 2.50 mg/5ml)

2. Qualitative and Quantitative Composition

Label Claim:

Each 5 ml Contains:

Levocetirizine Dihydrochloride 2.50 mg

Flavoured Syrup Base ..... Q.S.

Colour: Sunset Yellow

3. Pharmaceutical form

Liquid Syrup

Description: It is Orange colored, Sweet and flavoured syrup.

4. Clinical Particulars

4.1 Therapeutic indications

It is indicated for symptomatic treatment of allergic rhinitis (including persistent allergic rhinitis) and urticaria in adults and children aged 2 years and above.

4.2 Posology and method of administration

Method of administration: For oral administration only. The appropriate volume of oral solution should be measured with measuring cup. Poured oral solution in a measuring cup up to mark or in a glass of water. It must be taken orally immediately after dilution, and may be taken with or without food or as directed by physician.

Duration of use:

Intermittent or in case of persistent 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 or continuous therapy can be proposed to the patient during the period of exposure to allergens. The use of levocetirizine for treatment periods of at least 6 months. In chronic urticaria

and chronic allergic rhinitis: use of cetirizine (racemate) for up to one year. It can be stopped once the symptoms have disappeared and can be restarted again when symptoms reappear.

Adults and adolescents 12 years and above: The recommended dose is (5 mg) 10 ml.

Elderly: Recommended dose need to adjustment for in elderly patients with moderate to severe renal impairment.

Renal impairment: The dosing intervals must be individualized according to renal function. Dose adjust as indicated, 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:

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

Normal, (creatinine clearance [CLcr] = ≥ 80 mL/min), a dose 5 mg once daily. Mild, (creatinine clearance [CLcr] = 50-79 mL/min), a dose 5 mg once daily. Modereate, (creatinine clearance [CLcr] = 30-49 mL/min), a dose 5 mg once every 2 days. Severe, (creatinine clearance [CLcr] =< 30 mL/min), a dose 5 mg once every 3 days. End-stage renal disease-Patients undergoing dialysis, (creatinine clearance [CLcr] = <10 mL/min), a dose: contra-indicated.

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 and his body weight. There are no specific data for children with renal impairment.

Hepatic Impairment: No dosage adjustment is necessary for patients with hepatic impairment.

Paediatric population: Children aged 2 to 6 years: The daily recommended dose is 2.5 mg to be administered in 2 intakes of 1.25 mg (2.5 ml of solution twice daily). Children aged 6 to 12 years: The daily recommended dose is 5 mg (10 ml of solution). Even if some clinical data are available in children aged 6 months to 12 years, these data are not sufficient to support the administration of levocetirizine to infants and toddlers aged less than 2 years.

4.3 Contraindications

Patients with known hypersensitivity to the active substance, to cetirizine, to hydroxyzine, to any other piperazine derivatives or to any of the other excipients, severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings and precautions for use

Somnolence, fatigue and asthenia are associated with levocetirizine treatment. Patients should exercise caution when performing hazardous activities requiring mental alertness and physical coordination (e.g., driving, operating machinery). Concurrent use of levocetirizine with alcohol or other central nervous system (CNS) depressants should be avoided.

Caution for use: It contain excipients with known effects, Sucrose: May be harmful to the teeth, Glycerol: May cause headache, stomach upset and diarrhea, methyl parahydroxybenzoate, propyl parahydroxybenzoate: May cause allergic reactions (possibly delayed).

4.5 Interaction with other medicinal products and other forms of interaction

CNS Depressants (e.g., Alcohol): Avoid concomitant use due to possible additive effect (i.e., additional reduction in alertness, additional impairment of CNS performance). Ritonavir: Ritonavir disposition is not altered but this may cause increased plasma AUC (42%), increased half-life (53%) and decreased clearance (29%) of cetirizine. Theophylline: Theophylline disposition is not altered but this may cause decreased clearance (16%) of cetirizine.

Ketoconazole: Concomitant administration with cetirizine caused prolongation of QTC interval (increase of 17.4 msec). This was not considered clinically important. Ketoconazole: Concomitant administration with cetirizine caused prolongation of QTC interval (increase of 17.4 msec). This was not considered clinically important. Antipyrine, Azithromycin, cimetidine, erythromycin, ketoconazole, and pseudoephedrine: no clinically important changes in ECG parameters and no pharmacokinetic interactions were observed with cetirizine.

4.6 Fertility, pregnancy and lactation

Pregnancy: Pregnancy Category B. No adequate and well-controlled studies in pregnant women are available for levocetirizine. Levocetirizine should only be used during pregnancy when clearly needed.

Lactation: The use of levocetirizine is not recommended in breastfeeding women as it is possibly distributed into milk (cetirizine is distributed into milk).

4.7 Effects on ability to drive and use machines

Patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, and motor coordination such as operating machinery or driving a motor vehicle after ingestion of Levocetirizine Dihydrochloride Syrup.

4.8 Undesirable effects

Common (above 1%), children 6 to 11 months old: Diarrhea, constipation, children 1 to 5 years old: Pyrexia, diarrhea, vomiting, otitis media, children 6 to 12 years old: Pyrexia, cough, somnolence, epistaxis (nosebleed), adults and Children>12 years old: Somnolence, nasopharyngitis, fatigue, dry mouth, pharyngitis, uncommon (0.1 to 1%) to Very Rare (< 0.01%) General: Asthenia, malaise, edema, hypersensitivity, and anaphylactic shock. Neurologic: Agitation, paresthesia, aggression, confusion, depression, hallucination, insomnia, convulsions, movement disorders, tic, dystonia, dyskinesia, dysgeusia, syncope, tremor. Dermatologic: Pruritus, rash, urticaria, angioneurotic edema, and fixed drug eruption. Gastrointestinal: Abdominal pain and diarrhea. Hepatobiliary: Increased transaminases, alkaline phosphatase, gamma-glutamyl transpeptidase (GGT), and bilirubin. Ophthalmic: Accomodation disorder, blurred vision and oculogyration. Genitourinary: Dysuria and enuresis. Others: Tachycardia, thrombocytopenia and increased weight.

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 the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

In event of levocetirizine dihydrochloride overdosage following symptoms may occur. Symptoms: In adults may include drowsiness. In children, symptoms are initially agitation and restlessness,

followed by drowsiness. Management of overdoses: If you have taken more than

the recommended dosage, consult a physician. There is no known specific antidote to levocetirizine. Gastric lavage may be considered following short-term ingestion. Levocetirizine is not effectively removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine

ATC Code: R06A E09

Levocetirizine, the active enantiomer of cetirizine, is an antihistamine; its principal effects are mediated via selective inhibition of H1 receptors. Levocetirizine is a selective H2 antagonist that is the active enantiomer of cetirizine, a second generation antihistamine. In vitro studies have shown that levocetirizine has twice the H1 receptor affinity of cetirizine. Levocetirizine (at half of cetirizine dosage) appears to be as potent as cetirizine in inhibiting histamine-induced sneezing, nasal airway resistance and skin wheal and flare. Compared with other antihistamines (e.g., desloratadine, loratadine, fexofenadine), it exhibits greater and more consistent inhibition of histamineinduced wheal and flare. The action on histamine-induced skin reactions is out of phase with the plasma concentrations.

5.2 Pharmacokinetic properties

It has 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: It 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: It is 90% bound to plasma proteins. The distribution is restrictive, as the volume of distribution is 0.4 l/kg.

Metabolism: The extent of metabolism of levocetirizine in humans is less than 14% of the dose. Metabolic pathways include aromatic oxidation, N- and O-dealkylation and taurine conjugation. Dealkylation pathways are primarily mediated by CYP 3A4, while aromatic oxidation involves multiple and/or unidentified CYP isoforms. It has no effect on the activities of CYP iso-enzymes 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 at concentrations well above peak concentrations achieved follow 5 mg oral dose. Due to its low and absence of metabolic inhibition potential, the interaction of levocetirizine with other substances, or viceversa, 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. Special population:

Renal impairment: The dosing intervals must be individualized according to renal function. Dose adjust as indicated, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. Paediatric population: based on Paediatric pharmacokinetic study a single dose of 5 mg oral solution in age 6 to 11 years: body weight between 20 and 40 kg: Cmax: 450 ng/ml, mean time of 1.2 hours and AUC values are about 2 fold greater than in healthy subjects. Weight- normalized, total body clearance was 30% greater, and the elimination half-life 24% shorter in this paediatric population than in adults. Paediatric patients younger than 6 years of age: Patients who received single or multiple doses of levocetirizine ranging from 1.25 mg to 30 mg. 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.

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 and development.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Benzoate BP

Sodium Saccharine BP

Citric Acid (Mono) BP

Colour Sunset Yellow Supra IH

Sodium Methyl Paraben BP

Sodium Propyl Paraben BP

Sugar BP

Menthol BP

Sorbitol 70 % BP

Ess Orange Liq IH

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store in a cool & dry place. Protect from light.

6.5 Nature and contents of container

60 ml

7. Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:

NATIONAL PHARMACY LTD,

Colchester Park,

P.O Box 17843 - 00500

Nairobi, Kenya.

Manufacturer:

BRUSSELS LABORATORIES PVT. LTD.

33. Changodar Ind. Estate. Sarkhej-Bavla Road,

Changodar, Ahmedabad-382210, Gujarat, India..

8. Marketing Authorization Number:

H2018/CTD4203/585ER

9. Date of first Authorization /renewal of the authorization:

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10. Date of revision of text:

September 2024

11. DOSIMETRY (IF APPLICABLE)

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12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

N/A