Registration Dossier		
PRODUCT NAME: LEVOZIN ® 5 (Levocetrizine dihydrochloride 5 mg Tablet)	CODE: EAP/RD/002/23	EFFECTIVE DATE 01/04/23

Summary of Product Characteristics

1. Name of the finished pharmaceutical product

LEVOZIN®5 (Levocetrizine Dihydrochloride 5 mg tablet)

2. Qualitative and quantitative composition:

Materials	Strength (mg)	Use
Active Ingredient		
Levocetrizine Dihydrochloride	5.0	API
Inactive constituents		
Microcrystalline cellulose (PH 200)	97.5	Diluent/Binder
Lactose anhydrous	47.0	Diluent
Dried Maize starch	22.0	Disintegrant
Sodium Starch Glycolate	4.5	Disintegrant
Colloidal Silicon Dioxide	1.0	Glidant
Purified Talc	5.0	Glidant/ Lubricant
Magnesium Stearate	3.0	Lubricant
WINCOAT WT-AQ-1001	5.55	Film former

3. Pharmaceutical form

A white, biconvex, circular tablet

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4. Clinical particulars

4.1 Therapeutic indications

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LEVOZIN® contains the *R*-enantiomer of cetirizine and isused similarly, for the symptomatic relief of allergic conditions including the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis and the relief of symptoms of chronic idiopathic urticaria.

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.

In adults:

The daily recommended dose for adults and adolescents 12 years and above is 2.5 mg - 5 mg daily (max 5 mg daily) until symptoms have disappeared and can be restarted again when symptoms reappear in intermittent allergic rhinitis. In case of persistent allergic rhinitis continuous therapy (5 mg once daily) can be proposed to the patient during the period of exposure to allergens.

Use in children:

The daily recommended dose in children aged 6 to 12 is max 2.5 mg daily. Levocetirizine is not recommended for use in children below age 6 due to insufficient data on safety and efficacy.

Use in the elderly:

No dose adjustment is needed in elderly patients provided that the renal function is normal.

Patients with hepatic impairment:

No dose adjustment is needed in patients with solely hepatic impairment.

Patients with renal impairment:

Since levocetirizine is mainly excreted via renal route, in cases no alternative treatment can be used, the dosing intervals must be individualized according to renal function.

Group	Creatinine clearance (ml/min)	Dosage and frequency

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R &D MANAGER	QA MANAGER	PLANT T. MANAGER
Signature and Date: 01/04/23	Signature and Date:	Signature and Date: 05/04/2023

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Normal	Greater than or equal to 80	5 mg daily
Mild	50 - 79	2.5 mg once daily
Moderate	30 - 49	2.5 mg every other day
Severe	10 - 29	2.5 mg every 3 or 4 days
End-stage renal disease - patients undergoing dialysis	Less than 10	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, his age and his body weight.

4.2 Contraindications

LEVOZIN® is contraindicated in patients:

- with hypersensitivity to levocetirizine, to hydroxyzine or to any piperazine derivatives;
- with severe renal impairment at less than 10 ml/min creatinine clearance; and
- with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption.

4.3 Special warnings and precautions for use

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At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for a blood alcohol level of 0.5 g/L). Nevertheless, precaution is recommended if alcohol is taken concomitantly. Caution in epileptic patients and patients at risk of convulsion is recommended as levocetirizine may cause seizure aggravation. 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.

4.4 Interaction with other medicinal products and other forms of interaction

- A small decrease in the clearance of Levocetrizine may occur in a multiple dose study with theophylline.
- In sensitive patients, the concurrent administration of levocetirizine and alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.
- The extent of exposure to levocetirizine may be increased while the disposition of ritonavir may be altered further due to concomitant administration of levocetirizine and ritonavir.

4.5 Pregnancy ,lactation and fertility

Pregnancy

No malformative or feto/ neonatal toxicity is expected with the use of levocetirizine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/fetal development, parturition or postnatal development. Therefore, the use of levocetirizine may be considered during pregnancy, if necessary.

Breast-feeding

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.

Fertility

For levocetirizine no clinical data are available.

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4.6 Effects on ability to drive and use machines

Patients intending to drive, engaging in potentially hazardous activities or operating machinery should take their response to the medicinal product into account. In these sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

4.7 Undesirable effects

Blood and lymphatic system disorders:

Very rare: Thrombocytopenia

Immune system disorders:

Rare: Hypersensitivity

Very rare: Anaphylactic shock

Psychiatric disorder:

Common: Somnolence

Uncommon: Agitation

Rare: Aggression, confusion, depression, hallucination, and insomnia

Very rare: Tic

Nervous system disorder:

Common: Dizziness

Uncommon: Paraesthesia

Rare: Convulsion and movement disorder

Very rare: Dysgeusia, syncope, tremor, dystonia, and dyskinesia

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Eye disorder:

Very rare: Accomodation disorder, blurred vision, and oculogyration

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Respiratory, thoracic and mediastinal disorder:

Common: Pharyngitis

Gastrointestinal disorders:

Common: Abdominal pain, dry mouth, and nausea

Uncommon: Diarrhoea

Hepato-biliary disorder:

Rare: Hepatic function abnormality (increased transaminases, alklaline phosphatise, y-GT and bilirubin)

Skin and subcutaneous tissue disorder:

Uncommon: Pruritus and rash

Rare: Urticaria

Very rare: Angioneurotic oedema and fixed drug eruption

General disorders and administration site condition:

Common: Fatigue

Uncommon: Asthenia and malaise

Rare: Oedema and weight increase

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4.8 Overdose

Symptoms of overdose may include drowsiness in adults. In children, agitation and restlessness may initially occur, followed by drowsiness. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug.

5. Pharmacological properties

5.1 Pharmacodynamic properties

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Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivatives,

ATC code: R06A E09.

Mechanism of action

Levocetirizine, the (R) enantiomer of cetirizine, is a potent and selective antagonist of peripheral H_1-receptors.

Binding studies revealed that levocetirizine has high affinity for human H_1-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 H_1-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.

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5.2 Pharmacokinetic properties

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 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.

Plasma protein binding:

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

Elimination:

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 involved multiple and/or unidentified CYP isoforms.

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.

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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

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6.1 List of excipients

Microcrystalline cellulose (PH 200), Lactose anhydrous, Maize starch, Sodium starch glycolate, Colloidal silicon dioxide, Purified talc, and Magnesium Stearate.

6.2 Incompatibilities

Not known.

6.3 Shelf life

Three years from the date of manufacture.

6.4 Special precautions for storage

LEVOZIN® tablets should be stored at room temperature not exceeding 30° C, protect from light and moisture.

6.5 Nature and contents of container

10 tablets are packed with PVC and Aluminum foil blister and 10 or 2 of such blisters in turn are packed in printed box with patient information leaflet.

6.6 Special precautions for disposal

No special requirements.

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P.O.Box 9036
Addis Ababa,
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7. Marketing authorization holder

East African Pharmaceuticals Sh. Co.
Gurde Shola, Bole sub-city, Woreda 07, P.O. Box 9036, Addis Ababa, Ethiopia

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8. Marketing authorization number(s)

07763/08115/NMR/2020

9. Date of first authorization/renewal of the authorization

07/09/2022

10. Date of revision of the text

01/04/2023

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EAP
P.O.Box 9036
Addis Ababa,
Ethiopia

Prepared By	Approved By	Authorized By
R &D MANAGER	QA MANAGER	PLANT T. MANAGER
Signature and Date: 01/04/23	Signature and Date: 01/04/23	Signature and Date: 05/04/2023