APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS: S2

1. NAME OF THE MEDICINE

CETIZAL 5 Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains levocetirizine dihydrochloride 5 mg.

Contains sugar: Lactose monohydrate 65,71 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White, film-coated, scored, round, biconvex tablets debossed with '161' on one side and 'H' on other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CETIZAL 5 is indicated for the relief of symptoms associated with the following allergic conditions:

- Seasonal allergic rhinitis.
- Perennial allergic rhinitis.
- Chronic idiopathic urticaria.

4.2 Posology and method of administration

Posology

Adults and adolescents 12 years of age or older

The daily recommended dose is one 5 mg tablet.

Special populations

Elderly population

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

Adults with renal impairment

The dosing intervals must be individualised according to renal function. Use the table below to adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed.

The patient's creatinine clearance can be estimated from the serum creatinine determination using the following formula:

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times Wt\ (kg)}{S_{cr}\ (\mu mol/L)} \times (0,85 \text{ for women})$$

Dosages in patients with renal impairment		
Renal status	**Creatinine clearance (Cl_{cr})**	**Dose**
Normal	> 80 mL/min	5 mg once daily
Mild impairment	50 mL/min to 79 mL/min	5 mg once daily
Moderate impairment	30 mL/min to 49 mL/min	5 mg every second day
Severe impairment	< 30 mL/min	5 mg every third day
End stage renal impairment or receiving dialysis	< 10 mL/min	Contraindicated

Hepatic impairment

No dosage adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see *Renal impairment* above).

Paediatric population

Children aged 6 – 12 years

The daily recommended dose is one 5 mg tablet.

This formulation of CETIZAL 5 is not suitable for children aged 2 – 6 years as no adjusted dosage is possible with CETIZAL 5 which is a film-coated tablet. CETIZAL 5 is therefore not recommended for this age group (see section 4.4).

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/her body weight. There are no specific data for children with renal impairment.

Method of administration

The film-coated tablet must be taken orally, swallowed 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 < 4 days/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 > 4 days/week or during more than 4 weeks), continuous therapy can be proposed to the patient during the period of exposure to allergens. Clinical experience with CETIZAL 5 film-coated tablet is currently available for a 6-month treatment period.

4.3 Contraindications

The use of CETIZAL 5 is contraindicated in:

- Hypersensitivity to levocetirizine or to any of the excipients of CETIZAL 5, or to any piperazine derivative.
- Pregnancy and lactation (see section 4.6).
- End stage renal disease (creatinine clearance < 10 mL/min).
- Infants and toddlers aged less than two years, as safety and efficacy have not been demonstrated (see also section 4.4).

4.4 Special warnings and precautions for use

Alcohol

Precaution is recommended with intake of alcohol (see section 4.5). CETIZAL 5 lacks significant sedative

effects. Patients should, however be warned that a small number of individuals may experience sedation. This effect may be compounded by the simultaneous intake of alcohol or other central nervous system (CNS) depressants (see section 4.5).

Risk of urinary retention

Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as CETIZAL 5 may increase the risk of urinary retention.

Lactose intolerance

CETIZAL 5 contains lactose. Patients with rare hereditary problems of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take CETIZAL 5.

Paediatric population

Children aged less than 6 years

The use of CETIZAL 5 is not recommended in children aged 2 to 6 years since the film-coated tablet does not allow for appropriate dose adaption.

Infants and children under 2 years

Data are not sufficient to support the administration of CETIZAL 5 to infants and toddlers aged less than 2 years. CETIZAL 5 is contraindicated in infants and toddlers aged less than 2 years (see see section 4.3).

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with CETIZAL 5 (including no studies with CYP3A4 inducers). Studies with the racemate compound cetirizine demonstrated that there were no clinically relevant adverse interactions with diazepam, glipizide, ketoconazole, erythromycin, azithromycin, cimetidine and pseudoephedrine.

Alcohol

In sensitive patients, the simultaneous administration of CETIZAL 5 and alcohol or other central nervous system depressants may have effects on the central nervous system. It is advisable to avoid excessive alcohol consumption.

Theophylline

A decrease in clearance of cetirizine (16 %) was reported with theophylline (400 mg once a day), while the disposition of theophylline was not altered by concomitant cetirizine administration.

Ritonavir

It was reported, with 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 decreased (-11 %).

Food

The extent of absorption of CETIZAL 5 is not reduced with food, although the rate of absorption is decreased.

4.6 Fertility, pregnancy and lactation

Pregnancy

CETIZAL 5 is contraindicated in pregnancy as the safety has not been established.

Breastfeeding

Levocetirizine is excreted in breast milk; therefore, CETIZAL 5 is contraindicated in lactating women.

4.7 Effect on ability to drive and operate machines

Patients should be warned that CETIZAL 5 may cause somnolence, fatigue and asthenia, and therefore it may interfere with the patient's daytime activities. This effect may be compounded by the simultaneous intake of alcohol or other nervous system depressants. It is therefore advisable to determine individual response before driving, performing complicated tasks, engaging in potentially hazardous activities or operating machinery.

4.8 Undesirable effects

Clinical trial data:

In therapeutic studies in women and men aged 12 to 71 years, 15,1 % of the patients had at least one adverse reaction. In therapeutic trials, the dropout rate due to adverse events was 1,0 %.

Clinical therapeutic trials with included 935 subjects exposed to the medicine at the recommended dose of 5 mg daily.

Tabulated list of adverse reactions:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Immune system disorders	Not known*	Angioedema.

Nervous system disorders	Frequent	Headache, somnolence.
Gastrointestinal disorders	Frequent	Dry mouth.
	Less frequent	Nausea, gastrointestinal discomfort, abdominal pain.
General disorders and administration site conditions	Frequent	Fatigue.
	Less frequent	Asthenia, malaise.
Skin and subcutaneous tissue disorders	Not known*	In some individuals, hypersensitivity reactions including skin reactions, urticaria and pruritus may develop.

** Cannot be estimated from the available data.*

Paediatric population

In paediatric patients less than 6 years, 159 subjects were exposed to at the dose of 1,25 mg daily for 2 weeks or 1,25 mg twice daily. The following incidence of adverse reactions were reported:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Psychiatric disorders	Frequent	Sleep disorders.
Nervous system disorders	Frequent	Somnolence.
Gastrointestinal disorders	Frequent	Diarrhoea, constipation.
	Frequent	Vomiting.

In children aged 6 to 12 years, double-blind placebo-controlled studies were performed where 243 children were exposed to 5 mg daily for variable periods ranging from less than 1 week to 13 weeks. The following incidence of adverse reactions were reported:

MedDRA system organ class	**Frequency**	**Adverse reactions**
Nervous system disorders	Frequent	Somnolence.
	Less frequent	Headache.

Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported in post-marketing experience, the frequency is unknown (cannot be estimated from the available data):

MedDRA system organ class	**Adverse reactions**
Immune system disorders	Hypersensitivity including anaphylaxis.
Metabolism and nutrition disorders	Increased weight, increased appetite.
Psychiatric disorders	Aggression, agitation, hallucination, depression, insomnia, suicidal ideation.
Nervous system disorders	Convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia.
Eye disorders	Visual disturbances, blurred vision.
Ear and labyrinth disorders	Vertigo.
Cardiac disorders	Palpitations, tachycardia.
Respiratory, thoracic and mediastinal disorders	Dyspnoea.
Gastrointestinal disorders	Nausea, vomiting.
Hepatobiliary disorders	Hepatitis, abnormal liver function test.
Skin and subcutaneous tissue disorders	Angioedema, fixed drug eruption, pruritus, rash, urticaria.
Musculoskeletal, and connective tissue disorders	Myalgia.
Renal and urinary disorders	Dysuria, urinary retention.
General disorders and administration site conditions	Oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Drowsiness is an expected symptom of overdosage in adults. Overdosage in children may produce agitation and restlessness initially, followed by drowsiness.

There is no known specific antidote to CETIZAL 5. Treatment is symptomatic and supportive.

CETIZAL 5 is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 5.7.1 Antihistaminics

Levocetirizine, the (R) enantiomer of cetirizine, is a histamine H1 receptor antagonist.

5.2 Pharmacokinetic properties

Absorption

Levocetirizine is absorbed following oral administration.

Distribution

Levocetirizine is 90 % bound to human plasma proteins. Peak plasma concentrations are achieved 0,9 hour after administration of the oral tablet.

Biotransformation

The extent of metabolism of levocetirizine in humans is less than 14 % of the dose.

Elimination

The plasma half-life in adults is about 8 hours. The main route of excretion is via urine, accounting for approximately 85 % of the dose. Excretion via the faeces accounts for only 13 % of the dose.

Linearity/non-linearity

Plasma levels are linearly related between 2,5 mg and 20 mg.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Colloidal anhydrous silica

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Film-coat

Titanium dioxide

Hypromellose

Macrogol/polyethylene glycol 400

Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Protect from moisture.

Do not remove the blister strips from the cartons until required for use.

6.5 Nature and contents of container

White opaque HDPE container with white opaque polypropylene, plastic cap containing 30 or 180 tablets.

Cold form blister pack comprising of cold formable laminated film with a backing of hard tempered plain silver aluminium foil containing 10 tablets.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

a Sun Pharma Company

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South Africa

8. REGISTRATION NUMBER

46/5.7.1/0329

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06 August 2015

10. DATE OF REVISION OF THE TEXT

04 May 2022