

## PROFESSIONAL INFORMATION

### FOR CETAWAY SOLUTION

#### SCHEDULING STATUS

**S2**

#### 1. NAME OF THE MEDICINE

**CETAWAY™ SOLUTION** 0,5 mg/ml oral solution

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml solution contains 0,5 mg levocetirizine dihydrochloride.

Contains preservative sodium benzoate 0,4 % *m/v*.

Contains maltitol liquid 400 mg/ml.

Contains sweeteners glycerol 230 mg/ml and saccharin sodium 2 mg/ml.

For the full list of excipients, see section 6.1.

#### 3. PHARMACEUTICAL FORM

Oral solution

Clear and colourless oral solution, essentially free from particles, with a wild strawberry-like smell and flavour.

#### 4. CLINICAL PARTICULARS

##### 4.1 Therapeutic indications

CETAWAY SOLUTION 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 and older

The daily recommended dose is 5 mg (10 ml) once daily.

### Special populations

#### *Elderly*

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

#### *Adults with renal impairment*

The dosing interval must be individualised 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<sub>cr</sub>) in ml/min is needed. The CL<sub>cr</sub> (ml/min) may be estimated from serum creatinine (μmol/l) using the following formula:

$$CL_{cr} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})} \quad (\times 0,85 \text{ for women})$$

### 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 2 days |
| Severe                                                       | < 30                          | 5 mg once every 3 days |
| End-stage renal disease -<br>Patients undergoing<br>dialysis | < 10                          | Contraindicated        |

#### ***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.

#### ***Patients with hepatic 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 Patients with renal impairment above).

#### ***Paediatric population***

##### ***Children aged less than 2 years***

The administration of CETAWAY SOLUTION to infants and toddlers aged less than 2 years is not recommended (see section 4.4).

##### ***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) once daily.

### **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 CETAWAY SOLUTION is currently available for a 6-month treatment period.

### **Method of administration**

For oral administration.

### **4.3 Contraindications**

CETAWAY SOLUTION is contraindicated:

- in hypersensitivity to levocetirizine, to any piperazine derivative or to any of the excipients of CETAWAY SOLUTION (see section 4.4)
- in infants and toddlers aged less than 2 years, as safety and efficacy have not been demonstrated
- during breastfeeding of infants and while pregnant (see section 4.6) and lactation
- in patients with end-stage renal disease, at less than 10 ml/min creatinine clearance.

### **4.4 Special warnings and precautions for use**

#### *Alcohol*

Precaution is recommended with intake of alcohol. CETAWAY SOLUTION 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 depressants (see section 4.5).

#### *Risk of urinary retention*

Caution should be exercised in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as levocetirizine, contained in CETAWAY SOLUTION, may increase the risk of urinary retention.

#### *Risk of convulsion*

Caution should be taken in patients with epilepsy and patients at risk of convulsion as CETAWAY SOLUTION may cause seizure aggravation.

#### *Skin reactions*

Pruritus may occur when levocetirizine, as in CETAWAY SOLUTION, is stopped even if those symptoms were not present before treatment initiation. The symptoms may resolve spontaneously. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

#### *Allergy skin tests*

Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

#### **Information on excipients**

CETAWAY SOLUTION contains maltitol and may have a laxative effect. Patients with the rare hereditary problems of fructose intolerance should not take CETAWAY SOLUTION.

## **Paediatric population**

### *Infants and children under 2 years*

The administration of CETAWAY SOLUTION to infants and toddlers aged less than 2 years is not recommended due to the lack of sufficient data in this age group (see sections 4.2 and 4.3).

## **4.5 Interaction with other medicines 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 antipyrine, ketoconazole, erythromycin, azithromycin, cimetidine, pseudoephedrine, glipizide and diazepam).

### ***Theophylline***

A 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.

### ***Ritonavir***

In a multiple dose study of 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 CETAWAY SOLUTION is not reduced with food, although the rate of absorption is decreased.

### ***Alcohol***

In sensitive patients the simultaneous administration of CETAWAY SOLUTION and alcohol or other central nervous system (CNS) depressants may have effects on the central nervous system. It is advisable to avoid excessive alcohol consumption (see section 4.4).

## **4.6 Fertility, pregnancy and lactation**

### **Pregnancy**

CETAWAY SOLUTION is contraindicated in pregnancy as safety has not been demonstrated (see section 4.3 and 5.3).

### **Breastfeeding**

CETAWAY SOLUTION is contraindicated in women who are breastfeeding their babies, since the active ingredient is excreted in breast milk.

### **Fertility**

No clinical data relating to levocetirizine effects on fertility is available.

## **4.7 Effects on ability to drive and use machines**

CETAWAY SOLUTION lacks significant sedative effects. Nevertheless, some patients could experience somnolence, fatigue, and asthenia under therapy with CETAWAY SOLUTION. Therefore, patients intending to drive, engage in potentially hazardous activities or operate machinery should take their response to the CETAWAY SOLUTION into account.

## **4.8 Undesirable effects**

### **a) Summary of the safety profile**

Mild to moderate side effects most frequently experienced in adults include, headache, somnolence, dry mouth, fatigue, with asthenia or abdominal pain occurring less frequently.

b) Tabulated summary of adverse reactions

| System Organ Class                              | Frequency                                                           | Side effects                                                                                              |
|-------------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Immune system disorders                         | <i>Frequency unknown</i>                                            | Angioedema, hypersensitivity including anaphylaxis                                                        |
| Metabolism and nutrition disorders              | <i>Frequency unknown</i>                                            | Increased weight, increased appetite                                                                      |
| Psychiatric disorders                           | <i>Frequency unknown</i>                                            | Aggression, agitation, hallucination, depression, insomnia, suicidal ideation, nightmare                  |
| Nervous system disorders                        | <i>Frequent</i><br><i>Frequency unknown</i>                         | Headache, somnolence<br>Convulsions, paraesthesia, dizziness, syncope, tremor, dysgeusia                  |
| Eye disorders                                   | <i>Frequency unknown</i>                                            | Visual disturbances, blurred vision                                                                       |
| Ear and labyrinth disorders                     | <i>Frequency unknown</i>                                            | Vertigo                                                                                                   |
| Cardiac disorders                               | <i>Frequency unknown</i>                                            | Palpitations, tachycardia                                                                                 |
| Respiratory, thoracic and mediastinal disorders | <i>Frequency unknown</i>                                            | Dyspnoea                                                                                                  |
| Gastrointestinal disorders                      | <i>Frequent</i><br><i>Less frequent</i><br><i>Frequency unknown</i> | Dry mouth, diarrhoea, constipation<br>Nausea, gastro-intestinal discomfort.<br>abdominal pain<br>Vomiting |
| Hepato-biliary disorders                        | <i>Frequency unknown</i>                                            | Hepatitis, abnormal liver function test                                                                   |



|                                                              |                                                         |                                                |
|--------------------------------------------------------------|---------------------------------------------------------|------------------------------------------------|
| <b>Skin and subcutaneous tissue disorders</b>                | <i>Frequency unknown</i>                                | Rash, urticaria, pruritus, fixed drug eruption |
| <b>Musculoskeletal, connective tissue and bone disorders</b> | <i>Frequency unknown</i>                                | Myalgia, arthralgia                            |
| <b>Renal and urinary disorders</b>                           | <i>Frequency unknown</i>                                | Dysuria, urinary retention                     |
| <b>General disorders and administrative site conditions</b>  | <i>Frequent<br/>Less frequent<br/>Frequency unknown</i> | Fatigue<br>Asthenia, malaise<br>Oedema         |

#### c) Description of selected adverse reactions

After levocetirizine discontinuation, pruritus has been reported.

#### d) Paediatric population

| <b>System Organ Class</b>         | <b>Frequency</b>                  | <b>Side effects</b>                 |
|-----------------------------------|-----------------------------------|-------------------------------------|
| <b>Psychiatric disorders</b>      | <i>Frequent</i>                   | Sleep disorders                     |
| <b>Nervous system disorders</b>   | <i>Frequent<br/>Less frequent</i> | Somnolence<br>Headache              |
| <b>Gastrointestinal disorders</b> | <i>Frequent<br/>Less frequent</i> | Diarrhoea, constipation<br>Vomiting |

#### *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. Healthcare 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**

#### **Signs and symptoms**

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

#### **Management of overdose**

There is no known specific antidote to CETAWAY SOLUTION. Should overdose occur, symptomatic or supportive treatment is recommended. Levocetirizine is not effectively removed by haemodialysis.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antihistamines for systemic use, piperazine derivatives.

ATC code: R06A E09

Pharmacological classification: A 5.7.1 Antihistaminics

## Mechanism of action

Levocetirizine is the R-enantiomer of cetirizine, which is a histamine H<sub>1</sub>-receptor antagonist.

Binding studies revealed that levocetirizine has high affinity for human H<sub>1</sub>-receptors ( $K_i = 3,2 \text{ nmol/l}$ ). Levocetirizine has an affinity 2-fold higher than that of cetirizine ( $K_i = 6,3 \text{ nmol/l}$ ).

Levocetirizine dissociates from H<sub>1</sub>-receptors with a half-life of  $115 \pm 38 \text{ min}$ .

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.

## 5.2 Pharmacokinetic properties

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. In adults, peak plasma concentrations are achieved 0,9 hours 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 once daily. 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.

In humans, 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 approximately 8 hours in adults. The half-life is shorter in small children. The mean apparent total body clearance in adults is 0,63 ml/min/kg. The main route of excretion of levocetirizine and metabolites is via urine, accounting for approximately 85 % of the dose. Approximately 13 % is excreted in the faeces. Levocetirizine is excreted both by glomerular filtration and active tubular secretion.

## **Linearity**

The pharmacokinetics of levocetirizine are linear with dose- and time-independent with low inter-subject variability.

## **Pharmacokinetics in special patient groups**

### ***Renal impairment***

The apparent body clearance of levocetirizine is correlated to 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 patients, the total body clearance is decreased by approximately 80 % when compared to normal patients. The amount of levocetirizine removed during a standard 4-hour haemodialysis procedure was < 10 %.

### ***Elderly***

Limited pharmacokinetic data are available in elderly subjects. Total body clearance in the elderly is approximately 33 % lower compared to younger adults. The disposition of racemic cetirizine has been shown to be dependent on renal function rather than age. This would also be applicable for levocetirizine, as both cetirizine and levocetirizine are both predominantly excreted in urine. Therefore, the dose of levocetirizine should be adjusted in accordance with renal function in elderly patients.

### ***Hepatic impairment***

The pharmacokinetics of levocetirizine in hepatically impaired patients have not been tested. Patients with chronic liver diseases (hepatocellular, cholestatic and biliary cirrhosis) given 10 or 20 mg of the racemic compound cetirizine as a single dose had a 50 % increase in half-life along with a 40 % decrease in clearance compared to healthy patients.

### ***Gender***

The same daily doses and dosing intervals are applicable for men and women with normal renal function.

### ***Race***

The effect of race on levocetirizine has not been studied. As levocetirizine is primarily renally excreted, and there are no important racial differences in creatinine clearance, pharmacokinetic characteristics of levocetirizine are not expected to be different across races. No race-related differences in the kinetics of racemic cetirizine have been observed.

### ***Paediatric population***

In children aged 6 to 11 years with body weight ranging between 20 and 40 kg the  $C_{max}$  and AUC values are about 2-fold greater than in healthy adults, following oral administration of a

single dose of 5 mg levocetirizine. Total body clearance is 30 % greater and the elimination half-life 24 % shorter in the paediatric population than in adults. 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.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Maltitol liquid (E965)

Glycerol (E422)

Saccharin sodium

Sodium acetate trihydrate

Glacial acetic acid

Sodium benzoate (E211)

Wild strawberry aroma PHL-101104

Water (purified)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

36 months

Shelf-life after first opening of the pack: 3 months

### **6.4 Special precautions for storage**

Store at or below 25 °C. Keep the bottle tightly closed.

Do not refrigerate.

Keep in the original package.

## 6.5 Nature and contents of container

CETAWAY SOLUTION is packed in brown Type III glass bottles containing 60 ml, 100 ml, 150 ml or 200 ml solution and closed with a white polypropylene childproof screw cap.

The bottle is labelled and packed in a cardboard box with or without a calibrated oral syringe for dosing. The main graduation per 1 ml is marked on the syringe by bold line and number. Additional graduation per 0,5 ml is marked by a thin line.

Not all pack sizes are necessarily marketed.

## 6.6 Special precautions for disposal

Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Abex Pharmaceutica (Pty) Ltd  
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617 Rubenstein Drive  
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0181  
South Africa

## 8. REGISTRATION NUMBER

47/5.7.1/0953.952

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

23 August 2022

## 10. DATE OF REVISION OF THE TEXT

Not applicable.