PROFESSIONAL INFORMATION for ZELARY SYRUP

SCHEDULING STATUS:

S2

PROPRIETARY NAME AND DOSAGE FORM:

ZELARY SYRUP (syrup)

COMPOSITION:

Active ingredients:

Each 1 ml syrup contains 1 mg cetirizine dihydrochloride.

Inactive ingredients:

Acetic acid, banana flavouring, glycerol, propylene glycol, purified water, saccharin sodium, sodium acetate and sorbitol.

Preservatives: Methyl hydroxybenzoate 0,135 % m/v and propyl hydroxybenzoate 0,015 % m/v.

Contains sorbitol.

PHARMACOLOGICAL CLASSIFICATION:

A 5.7.1 Antihistaminics

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties

Cetirizine, a metabolite of hydroxyzine, is a selective antagonist of peripheral H_1-receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1-receptors. In addition to its anti-H_1 effect, cetirizine was shown to display anti-allergic activities: at a dose of 10 mg once or twice daily, it inhibits the late phase recruitment of eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

Pharmacokinetic properties:

Absorption:

Cetirizine is well absorbed from the gastro-intestinal tract and peak plasma concentrations of 300 ng/ml are reached within 1 hour after oral administration. The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.

No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. A high proportion of cetirizine is bound to human plasma proteins.

Distribution:

The apparent volume of distribution is 0,50 l/kg. Plasma protein binding of cetirizine is 93 ± 0,3 %. Pharmacokinetics are linear over the range of 5 to 60 mg, with plasma concentrations increasing proportionately with increasing doses.

Metabolism:

Cetirizine does not undergo extensive first- pass metabolism.

Elimination:

The terminal half-life in adults is approximately 10 hours; in children aged 6 to 12 years, 6 hours; in children aged 2 to 6 years, 5 hours.

Cetirizine is eliminated faster in children, and slower in patients with hepatic or renal impairment (creatinine clearance < 40 ml/min), with a resultant increase in half-life and decrease in clearance.

The cumulative urinary excretion represents about two thirds of the dose given in both adults and children.

Special Populations

Elderly:

Following a single 10 mg oral dose, half-life increased by about 50 % and clearance decreased by 40 % in 16 elderly subjects compared to the normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Children, infants and toddlers:

The terminal half-life in adults is approximately 10 hours; in children aged 6 to 12 years, 6 hours; in children aged 2 to 6 years, 5 hours.

This is consistent with the urinary excretion half-life of the medicine.

In infants and toddlers aged 6 to 24 months, it is reduced to 3,1 hours.

***Renally impaired patients**:*

The pharmacokinetics of cetirizine were similar in patients with mild impairment (creatinine clearance higher than 40 ml/min) and healthy volunteers. Patients with moderate renal impairment had a 3-fold increase in half-life and 70 % decrease in clearance compared to healthy volunteers.

Patients on haemodialysis (creatinine clearance less than 7 ml/min) given a single oral 10 mg dose of cetirizine had a 3-fold increase in half-life and a 70 % decrease in clearance compared to normal renal function. Cetirizine was poorly cleared by haemodialysis.

Dosing adjustment is necessary in patients with moderate or severe renal impairment (see **DOSAGE AND DIRECTIONS FOR USE**).

***Hepatically impaired patients**:*

Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20 mg of cetirizine as a single dose had a 50 % increase in half-life along with a 40 % decrease in clearance compared to healthy subjects.

Dosing adjustment is only necessary in hepatically impaired patients if concomitant renal impairment is present.

INDICATIONS:

ZELARY SYRUP is indicated for symptomatic relief of allergic conditions such as allergic rhinitis, hay fever and allergic skin conditions associated with pruritus such as urticaria.

CONTRAINDICATIONS:

- Hypersensitivity to cetirizine, hydroxyzine, any piperazine derivatives, or any of the ingredients of **ZELARY SYRUP**.
- Patients with severe renal impairment at less than 30 ml/min creatinine clearance.
- Asthma, as it may cause airway obstruction in patients who have previously experienced adverse reactions to antihistamines.
- Safety in pregnancy and lactation has not been established (see **HUMAN REPRODUCTION**).
- Children under the age of two years, as safety and efficacy have not been demonstrated.

WARNINGS AND SPECIAL PRECAUTIONS:

- **ZELARY SYRUP** lacks significant sedative effects. Patients should be warned, however, that a small number of individuals may experience sedation.
- At therapeutic doses, no clinically significant interactions have been demonstrated with alcohol (for blood alcohol level of 0,5 g/ℓ). Nevertheless, precaution is recommended if alcohol is taken concomitantly (see **INTERACTIONS**).
- Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as **ZELARY SYRUP** may increase the risk of urinary retention.
- Caution in epileptic patients and patients at risk of convulsions is recommended.

- Allergy skin tests are inhibited by **ZELARY SYRUP** and a washout period (of 3 days) is required before performing them.
- Methyl parahydroxybenzoate and propyl parahydroxybenzoate as contained in **ZELARY SYRUP** may cause allergic reactions (possibly delayed).
- Elderly patients are more susceptible to many of the adverse effects of **ZELARY SYRUP** and, in particular their inappropriate use for postural giddiness should be avoided.

Effects on ability to drive and use machines:

ZELARY SYRUP can lead to drowsiness and patients should be aware how they react to **ZELARY SYRUP** and exercise caution before driving, operating hazardous machinery or performing hazardous tasks.

Information on excipients of ZELARY SYRUP:

ZELARY SYRUP contains sorbitol and may have a laxative effect. Patients with the rare hereditary condition of sorbitol intolerance should not take **ZELARY SYRUP**.

INTERACTIONS:

Concomitant use of alcohol and other sedating agents should be avoided.

There is no evidence of an interaction between cetirizine and cimetidine, ketoconazole, erythromycin, azithromycin, diazepam, glipizide, and pseudoephedrine.

HUMAN REPRODUCTION:

Safety in pregnancy and lactation has not been established (see **"CONTRAINDICATIONS"**).

Cetirizine is excreted in human milk at concentrations representing 25 % to 90 % of those measured in plasma, depending on sampling time after administration.

DOSAGE AND DIRECTIONS FOR USE:

Adults or children 12 years of age or older:

10 mg (10 ml) once daily.

Children 6 to 12 years old:

10 mg (10 ml) daily, either as a single dose or as divided doses of 5 ml in the morning and 5 ml in the evening.

Children age 2 to 6 years:

5 mg (5 ml) may be given as a single dose or as divided doses of 2,5 ml in the morning and 2,5 ml in the evening.

No dose adjustment is necessary in healthy elderly patients with normal renal function.

Dosage in Renal impairment:

In patients with renal impairment, where the creatinine clearance is less than 40 ml/min, the recommended daily dose of cetirizine should be halved (see "**CONTRAINDICATIONS**").

Dosage in Hepatic impairment:

In moderate to severe hepatic impairment half the recommended daily dose should be used.

SIDE EFFECTS:

System Organ Class	**Frequency**	**Side Effects**
Blood and lymphatic system disorders:	Less frequent:	Thrombocytopenia, leucopoenia, haemolytic anaemia, agranulocytosis.
Immune system disorders:	Less frequent:	Angioedema, hypersensitivity reactions, anaphylaxis, bronchospasm.

Metabolism and nutrition disorders:	Frequency unknown:	Increased appetite.
Psychiatric disorders:	Less frequent:	Somnolence, depression, confusion, agitation, aggression, hallucinations, insomnia, tics.
	Frequency unknown:	Memory impairment.
Nervous system disorders:	Less frequent:	Drowsiness.
	Frequency unknown:	Headaches, dizziness, anxiety, nervousness, paraesthesia, convulsions, movement disorders, dysgeusia, syncope, tremor, dystonia, dyskinesia, amnesia.
Eye disorders:	Less frequent:	Accommodation disorder, blurred vision, oculogyration.
Ear and labyrinth disorders:	Less frequent:	Tinnitus, vertigo.
Cardiac disorders:	Less frequent:	Palpitations,

		dysrhythmias, tachycardia.
Vascular disorders:	Less frequent:	Hypotension.
Respiratory, thoracic and mediastinal disorders:	Frequent:	Pharyngitis, rhinitis.
	Less frequent:	Thickening of mucous, bronchospasm.
Gastrointestinal disorders:	Less frequent:	Nausea, gastro-intestinal discomfort, diarrhoea, constipation and dry mouth.
Hepato-biliary disorders:	Less frequent:	Hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin) jaundice.
Skin and subcutaneous tissue disorders:	Less frequent:	Pruritus, skin rash, urticaria, fixed drug eruption, photosensitivity, ~~hair loss~~ <u>alopecia</u>, sweating.
Musculoskeletal, connective tissue and bone disorders:	Less frequent:	Myalgia.
Renal and urinary	Less frequent:	Dysuria, enuresis,

disorders:		urinary retention.
General disorders and administrative site conditions:	Less frequent:	Fatigue, asthenia, malaise, oedema.
Investigations:	Less frequent:	Weight increased.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms observed after an overdosage of cetirizine are mainly associated with CNS effects or with effects that suggest an anticholinergic effect (see **SIDE EFFECTS**).

Drowsiness is an expected symptom of overdosage. Overdosage in children may produce agitation, somnolence, pruritus, rash, urinary retention, fatigue, tremor, and tachycardia. In the case of overdosage, the usual supportive measures should apply.

There is no specific antidote. **ZELARY SYRUP** is not effectively removed by dialysis.

Further treatment is symptomatic and supportive.

IDENTIFICATION:

Clear or almost clear colourless solution with taste and odour of banana.

PRESENTATION:

Type 3 amber glass bottle with a tamper evident, white coloured polyethylene closure, contained in a printed outer carton.

Pack sizes: 50 ml, 100 ml, 150 ml and 200 ml.

STORAGE INSTRUCTIONS:

Store in a cool (at or below 25ºC), dry place.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:

41/5.7.1/0085

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Unicorn Pharmaceuticals (Pty) Ltd

Corner Searle and Pontac Streets

Cape Town

8001

DATE OF PUBLICATION OF THE PROFESSIONAL INFORMATION:

Date of registration: 18 April 2008.

Date of the most recent amendment to the professional information as approved by the Authority: 24 Mar 2014.