PROFESSIONAL INFORMATION FOR

ACUZYRT SYRUP

SCHEDULING STATUS

S1

1. NAME OF THE MEDICINE

ACUZYRT SYRUP (Syrup)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of ACUZYRT SYRUP contains 1 mg cetirizine dihydrochloride.

Preservatives:

Methyl parahydroxybenzoate: 0,2 % *m/v*

Propyl parahydroxybenzoate: 0,02 % *m/v*

ACUZYRT SYRUP contains sugar (2,5 g sorbitol per 5 mL.)

ACUZYRT SYRUP contains sweetener (0,01 g monoammonium glycerrhizinate per 5 mL.)

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Syrup

A clear, colourless, pineapple and sweet orange flavoured syrup with a sweet taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ACUZYRT SYRUP is indicated for the treatment of allergic conditions responding to a histamine H1 receptor antagonist:

- Respiratory: Allergic rhinitis, hay fever.
- Cutaneous: Allergic skin conditions associated with pruritus, e.g. urticaria.

4.2 Posology and method of administration

Posology

Adults or children 12 years of age or older: 10 mg daily or 10 mL (two medicine measures), once daily.

Children 6 to 12 years old: 10 mg daily: either as a single dose (10 mL) (two medicine measures), or as divided doses of 5 mL (one medicine measure) in the morning and 5 mL (one medicine measure) in the evening.

Children 2 to 6 years old: 5 mg daily: either as a single dose (5 mL) (one medicine measure), or as divided doses of 2.5 mL (half a medicine measure) in the morning and 2.5 mL (half a medicine measure) in the evening.

Missed dose

Doctors should advise patients who forget to take ACUZYRT SYRUP to take a dose as soon as possible and then continue with the normal dose. Patients should not take a double dose to compensate for the missed dose.

Special populations

Elderly: At present there is no data to suggest that the dose needs to be reduced in elderly patients.

Renal impairment: In patients with renal insufficiency (creatinine clearance less than 40 mL/min), dosage should be reduced to half the usual recommended dose (see **section 4.3**.)

Hepatic impairment: The dosage should be reduced to half the recommended daily dose in patients with moderate to severe hepatic impairment.

Paediatric population

ACUZYRT SYRUP is contraindicated in children under the age of two years, as safety and efficacy have not been demonstrated (see **section 4.3.**)

Method of administration

Oral administration

4.3 Contraindications

ACUZYRT SYRUP is contraindicated in:

- Hypersensitivity to cetirizine, hydroxyzine, any piperazine derivatives or to any of the ingredients of ACUZYRT SYRUP.
- Patients with severe renal impairment at less than 30 mL/min creatinine clearance.
- Safety in pregnancy and lactation has not been established (see **section 4.6**).
- Children under the age of two years, as safety and efficacy have not been demonstrated.

4.4 Special warnings and precautions for use

- ACUZYRT SYRUP lacks significant sedative effects. Patients should, however, be warned that a small number of individuals may experience sedation. Sedative effects, when they occur, may diminish after a few days of treatment.
- 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 (see **section 4.5**). It is advisable to avoid excessive alcohol consumption. Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as ACUZYRT 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 ACUZYRT SYRUP and a wash-out period (of 3 days) is required before performing them.
- Elderly patients are more susceptible to many of the adverse effects of ACUZYRT SYRUP, including antimuscarinic effects, sedation and hypotension.
- Pruritus and/or urticaria may occur when ACUZYRT SYRUP is stopped, even if those symptoms were not present before treatment initiation. The symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.
- Because of their antimuscarinic properties, antihistamines should be used with care in conditions such as closed-angle glaucoma, urinary retention, prostatic hyperplasia, or pyloroduodenal obstruction. Other adverse effects of antihistamines suggest caution in patients with epilepsy and severe cardiovascular disorders.
- Antihistamines do not have a place in the treatment of asthma.

- Some antihistamines have been associated with foetal abnormalities when taken during pregnancy, but a number of large studies have failed to demonstrate any strong associations.

Special warnings about the excipients

ACUZYRT SYRUP contains sorbitol. Patients with the rare hereditary condition of sorbitol intolerance should not take ACUZYRT SYRUP.

The preservatives methyl parahydroxybenzoate and propyl parahydroxybenzoate included in ACUZYRT SYRUP may cause allergic reactions (possibly delayed).

4.5 Interaction with other medicines and other forms of interaction

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

Antihistamines may enhance the sedative effects of central nervous system depressants including alcohol, barbiturates, hypnotics, opioid analgesics, anxiolytic sedatives, and neuroleptics. MAOI's may enhance the antimuscarinic effects of antihistamines, and antihistamines have an additive antimuscarinic action with other antimuscarinic drugs, such as atropine and tricyclic antidepressants. It has been suggested that antihistamines could mask the warning signs of damage caused by ototoxic drugs such as aminoglycoside antibiotics.

Due to pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety in pregnancy has not been established (see **section 4.3**).

Breastfeeding

ACUZYRT SYRUP is contraindicated in lactating women since the active ingredient is excreted in breast milk.

Fertility

Limited data is available on human fertility, but no safety concern has been identified. Animal data show no safety concern for human reproduction.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Side effects
Psychiatric disorders	Frequent	Somnolence (may vary from slight drowsiness to deep sleep).
	Less frequent	Agitation.
Nervous system disorders	Frequent	Dizziness, headache.
	Less frequent	Paraesthesias.
	Frequency unknown	In-coordination, nervousness. In high doses, CNS stimulation may be attributed to antimuscarinic activity. Extra-pyramidal symptoms have been reported.
Respiratory, thoracic and mediastinal disorders	Frequent	Pharyngitis, rhinitis.
	Less frequent	Thickening of mucous, bronchospasm.
Gastrointestinal disorders	Frequent	Dry mouth, nausea.
	Less frequent	Epigastric pain, diarrhoea.
	Frequency unknown	Constipation, vomiting, increased appetite.
General disorders and administration site conditions	Frequent	Lassitude.
Ear and labyrinth disorders	Less frequent	Tinnitus.

Blood and lymphatic system disorders	Less frequent	Haemolytic anaemia, agranulocytosis, leucopenia, thrombocytopenia (these may have an immune basis.)
Skin and subcutaneous tissue disorders	Less frequent	Jaundice, hair loss, sweating, photosensitivity.
	Frequency unknown	Skin reactions (rash), angioedema (with cross sensitivity to related medicines).
Vascular disorders	Less frequent	Hypotension.

c. Description of selected adverse reactions

Skin reactions occurring after discontinuation of ACUZYRT SYRUP:

After discontinuation of ACUZYRT SYRUP, pruritis (intense itching) and/or urticaria have been reported (see **section 4.4**.)

d. Paediatric population

Children below 12 years of age

MedDRA system organ class	**Frequency**	**Side effects**
Gastro-intestinal disorders	Frequent	Diarrhoea.
Psychiatric disorders	Frequent	Somnolence.

	Less frequent	Nightmares, hallucinations and convulsions.
	Frequency unknown	Insomnia, nervousness, euphoria, irritability, tremors.
Respiratory, thoracic and mediastinal disorders	Frequent	Rhinitis.
General disorders and administration site conditions	Frequent	Fatigue.
Nervous system disorders	Frequency unknown	Paradoxical CNS stimulation.

Post-marketing data

MedDRA system organ class	**Frequency**	**Side effects**
Blood and lymphatic disorders	Less frequent	Thrombocytopenia.
Immune system disorders	Less frequent	Hypersensitivity, anaphylactic shock.
Metabolism and nutrition disorders	Frequency unknown	Increased appetite.
Psychiatric disorders	Less frequent	Agitation, aggression, confusion, depression, hallucination, insomnia, tics.
	Frequency unknown	Suicidal ideation, nightmare.

Nervous system disorders	Less frequent	Paraesthesia, convulsions, dysgeusia, dyskinesia, dystonia, syncope, tremor.
	Frequency unknown	Amnesia, memory impairment.
Eye disorders	Less frequent	Accommodation disorder, blurred vision, oculogyric crisis.
Ear and labyrinth disorders	Frequency unknown	Vertigo.
Cardiac disorders	Less frequent	Tachycardia.
Gastrointestinal disorders	Less frequent	Diarrhoea.
Hepatobiliary disorders	Less frequent	Abnormal hepatic function (increased transaminases, alkaline phosphatase, γ-GT and bilirubin).
	Frequency unknown	Hepatitis.
Skin and subcutaneous tissue disorders	Less frequent	Pruritus, rash, urticaria, angioneurotic oedema, fixed drug eruption.
	Frequency unknown	Acute generalized exanthematous pustulosis.
Musculoskeletal and connective tissue disorders	Frequency Unknown	Myalgia, arthralgia.

Renal and urinary disorders	Less frequent	Dysuria, enuresis.
	Frequency unknown	Urinary retention.
General disorders and administration site conditions	Less frequent	Asthenia, malaise, oedema.
Investigations	Less frequent	Weight increased.

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 or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Symptoms

Symptoms observed after an overdose of cetirizine, as in ACUZYRT SYRUP, are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect. Drowsiness is an expected symptom of overdosage. Overdosage may produce agitation, confusion, diarrhoea, dizziness, headache, malaise, mydriasis, restlessness, sedation, somnolence, stupor, pruritus, rash, urinary retention, fatigue, tremor and tachycardia.

Overdosage may be fatal especially in infants and children. In infants and children, central nervous system stimulation predominates over central nervous system depression, causing ataxia, excitement, tremors, psychoses, hallucinations and convulsions; hyperpyrexia may also occur. Deepening coma and cardiorespiratory collapse may follow. In adults, central nervous system depression is more common with drowsiness, coma and convulsions, progressing to respiratory failure or possible cardiovascular collapse.

Management

There is no specific antidote. Cetirizine is not effectively removed by dialysis. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 5.7.1 Antihistaminics

Pharmacotherapeutic group: Antihistamine for systemic use, Piperazine derivatives

ATC code: R06A E07

Mechanism of action

Cetirizine is a human metabolite of hydroxyzine, with a selective and potent histamine H1 receptor antagonism devoid of any significant anticholinergic and anti-serotonin effects as demonstrated in experimental and clinical pharmacology. At the present stage of research into the mode of action of cetirizine, the anti-allergic activity seems

to be exerted mainly via its effects on the release of certain mediators (mainly histamine) together with a selective action on the H1 receptors.

Pharmacodynamic effects

In addition to its anti-H1 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.

Clinical efficacy and safety

Studies in healthy volunteers show that cetirizine, at doses of 5 and 10 mg strongly inhibits the wheal and flare reactions induced by very high concentrations of histamine into the skin, but the correlation with efficacy is not established. In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and concomitant mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic patients with mild to moderate asthma. In a placebo-controlled study, cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of QT interval. At the recommended dosage, cetirizine has demonstrated that it improves the quality of life of patients with perennial and seasonal allergic rhinitis.

Paediatric population

In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic effect

(suppression of wheal and flare) of cetirizine was found. When a treatment with cetirizine is stopped after repeated administration, the skin recovers its normal reactivity to histamine within 3 days.

5.2 Pharmacokinetic properties

Absorption

Cetirizine is well absorbed from the gastrointestinal 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. The extent of bioavailability is similar when cetirizine is given as solutions or tablets.

No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. The distribution of pharmacokinetic parameters such as peak plasma concentration (Cmax) and area under curve (AUC), is unimodal.

Distribution

The apparent volume of distribution is 0,50 L/kg. A high proportion of cetirizine is bound to human plasma proteins (93 ± 0,3 %). Cetirizine does not modify the protein binding of warfarin.

Biotransformation

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.

Linearity/ non-linearity

Pharmacokinetics are linear over the range of 5 to 60 mg, with plasma concentrations increasing proportionately with increasing doses.

Pharmacokinetics in specific patient groups

Elderly

Following a single 10 mg oral dose in elderly patients, half-life increases by about 50 % and clearance decreases by 40 % compared to younger patients. The decrease in cetirizine clearance in these elderly patients appears to be related to their decreased renal function.

Renally impaired patients

The pharmacokinetics of cetirizine are similar in patients with mild impairment (creatinine clearance higher than 40 mL/min) and patients with normal renal function. Patients with moderate renal impairment have a 3-fold increase in half-life and 70 % decrease in clearance compared to patients with normal renal function.

Patients on haemodialysis (creatinine clearance less than 7 mL/min) given a single oral 10mg dose of cetirizine have a 3-fold increase in half-life and a 70 % decrease in

clearance compared to patients with normal renal function. Cetirizine is poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment (see **section 4.2**).

Hepatically impaired patients

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

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

Paediatric population

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sorbitol solution

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Glycerol

Pineapple Singapore

Sweet Orange No. 1

Monoammonium glycerrhizinate

Propylene glycol

Sodium citrate

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in a cool dry place below 25°C. Protect from light.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Packed in 150 mL amber glass or amber plastic bottles, into an outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Cipla Medpro (Pty) Ltd.

Building 9, Parc du Cap

Mispel Street

Bellville

7530

Customer Care: 080 222 6662

8. REGISTRATION NUMBER

37/5.7.1/0152

9. DATE OF FIRST AUTHORISATION/ RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7 May 2004

Date of latest renewal: Not applicable.

10. DATE OF REVISION OF THE TEXT

28 February 2024