

Histazine Syrup

Summary of Product Characteristics

1. Name of the medicinal product

Histazine Syrup

2. Qualitative and quantitative composition

Each ml of solution contains 1 mg cetirizine dihydrochloride.

Excipients with known effect:

- one ml of solution contains 400 mg sorbitol
- one ml of solution contains 0.34 mg methylparahydroxybenzoate
- one ml of solution contains 0.16 mg propylparahydroxybenzoate

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Clear colorless to pale yellow Syrup.

4. Clinical particulars

4.1 Therapeutic indications

Antihistaminic drug for the treatment of allergies.

For the treatment of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria in children aged over 2 years and adults.

4.2 Posology and method of administration

Posology

Children over 6 years old and adults: 10 ml once daily or 5 ml twice daily.

Special population

Elderly

Data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

Renal impairment

There are no data to document the efficacy/safety ratio in patients with renal impairment. Since cetirizine is mainly eliminated via renal route (see section 5.2), in cases no alternative treatment can be used, the dosing intervals must be individualized 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_{Cr}) in ml/min is needed. The CL_{Cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{Cr} = \frac{[140 - \text{age}(\text{years})] \times \text{weight}(\text{kg})}{72 \times \text{serum creatinine}(\text{mg/dl})} (\times 0.85 \text{ for women})$$

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	≥80	10 mg once daily

Mild	50 – 79	10 mg once daily
Moderate	30 – 49	5 mg once daily
Severe	<30	5 mg once every 2 days
End-stage renal disease - Patients undergoing dialysis	<10	Contraindicated

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 Renal impairment above).

Paediatric population

Children 2-6 years old: 2.5 ml twice daily.

Children over 6 years old and adults: 10 ml once daily or 5 ml twice daily.

Method of administration:

The Syrup can be swallowed as such.

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, to hydroxyzine or to any piperazine derivatives.

Patients with severe renal impairment with a creatinine clearance below 10 ml/min.

4.4 Special warnings and precautions for use

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

Caution is recommended in epileptic patients and patients at risk of convulsions.

Methylparahydroxybenzoate and propylparahydroxybenzoate may cause allergic reactions (possibly delayed). Patients with rare hereditary problems of fructose intolerance should not take cetirizine.

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

Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Paediatric population

The use of the product is not intended in children aged less than 2 years.

4.5 Interaction with other medicinal products and other forms of interaction

Due to the 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).

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

In sensitive patients, the concurrent use of alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance although cetirizine does not potentiate the effect of alcohol (0.5 g/l blood levels).

4.6 Fertility, pregnancy and lactation

Pregnancy

For cetirizine prospectively collected data on pregnancy outcomes do not suggest potential for maternal or foetal/embryonic toxicity above background rates.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should nevertheless be exercised when prescribing to pregnant women.

Breast-feeding

Cetirizine passes into breast milk. A risk of side effects in breastfed infants cannot be excluded. Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

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

Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 10 mg. However, patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery. They should not exceed the recommended dose and should take their response to the medicinal product into account.

4.8 Undesirable effects

Clinical studies

• *Overview*

Clinical studies have shown that cetirizine at the recommended dosage has minor undesirable effects on the CNS, including somnolence, fatigue, dizziness and headache. In some cases, paradoxical CNS stimulation has been reported.

Although cetirizine is a selective antagonist of peripheral H₁-receptors and is relatively free of anticholinergic activity, isolated cases of micturition difficulty, eye accommodation disorders and dry mouth have been reported.

Instances of abnormal hepatic function with elevated hepatic enzymes accompanied by elevated bilirubin have been reported. Mostly this resolves upon discontinuation of the treatment with cetirizine dihydrochloride.

• *Listing of ADRs*

Double blind controlled clinical trials comparing cetirizine to placebo or other antihistamines at the recommended dosage (10 mg daily for cetirizine), of which quantified safety data are available, included more than 3200 subjects exposed to cetirizine.

From this pooling, the following adverse reactions were reported for cetirizine 10 mg in the placebo-controlled trials at rates of 1.0 % or greater:

Adverse reactions (WHO-ART)	Cetirizine 10 mg (n= 3260)	Placebo (n = 3061)
General disorders and administration site conditions Fatigue	1.63 %	0.95 %
Nervous system disorders Dizziness Headache	1.10 % 7.42 %	0.98 % 8.07 %
Gastro-intestinal disorders Abdominal pain Dry mouth Nausea	0.98 % 2.09 % 1.07 %	1.08 % 0.82 % 1.14 %
Psychiatric disorders Somnolence	9.63 %	5.00 %
Respiratory, thoracic and mediastinal disorders Pharyngitis	1.29 %	1.34 %

Although statistically more common than under placebo, somnolence was mild to moderate in the majority of cases. Objective tests as demonstrated by other studies have demonstrated that usual daily activities are unaffected at the recommended daily dose in healthy young volunteers.

Paediatric population

Adverse reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled clinical trials are:

Adverse reactions (WHO-ART)	Cetirizine (n=1656)	Placebo (n =1294)
Gastro-intestinal disorders Diarrhoea	1.0 %	0.6 %
Psychiatric disorders Somnolence	1.8 %	1.4 %
Respiratory, thoracic and mediastinal disorders Rhinitis	1.4 %	1.1 %
General disorders and administration site conditions Fatigue	1.0 %	0.3 %

Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following undesirable effects have been reported in post-marketing experience.

Undesirable effects are described according to MedDRA System Organ Class and by estimated frequency based on post-marketing experience.

Frequencies are defined as follows: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data)

Blood and lymphatic disorders

Very rare: thrombocytopenia

Immune system disorders

Rare: hypersensitivity

Very rare: anaphylactic shock

Metabolism and nutrition disorders

Not known: increased appetite

Psychiatric disorders

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tics

Not known: suicidal ideation, nightmare

Nervous system disorders

Uncommon: paraesthesia

Rare: convulsions

Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia

Not known: amnesia, memory impairment

Eye disorders

Very rare: accommodation disorder, blurred vision, oculogyration

Ear and labyrinth disorders

Not known: vertigo

Cardiac disorders

Rare: tachycardia

Gastro-intestinal disorders

Uncommon: diarrhoea

Hepatobiliary disorders

Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ -GT and bilirubin)

Not known: hepatitis

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash

Rare: urticaria

Very rare: angioneurotic oedema, fixed drug eruption

Not known: acute generalized exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Not known: arthralgia

Renal and urinary disorders

Very rare: dysuria, enuresis

Not known: urinary retention

General disorders and administration site conditions

Uncommon: asthenia, malaise

Rare: oedema

Investigations

Rare: weight increased

Description of selected adverse reactions

After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

Side effects can also be reported to the following email: safety@trima.co.il

4.9 Overdose

Symptoms

Symptoms observed after an overdose of cetirizine are mainly associated with CNS effects or with effects that could suggest an anticholinergic effect.

Adverse events reported after an intake of at least 5 times the recommended daily dose are: confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

Management

There is no known specific antidote to cetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug.

Cetirizine is not effectively removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives, ATC code: R06A E07

Mechanism of action

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H₁-receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than 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

The steady - state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.. The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) and area under curve (AUC) is unimodal.

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, capsules or tablets.

Distribution

The apparent volume of distribution is 0.50 l/kg. Plasma protein binding of cetirizine is 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 is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. About two third of the dose are excreted unchanged in urine.

Linearity/Non-linearity

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Renal impairment: The pharmacokinetics of the drug was 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 hemodialysis (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 normals. Cetirizine was poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment (see section 4.2).

Hepatic impairment: 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 patients with hepatic impairment if concomitant renal impairment is

present.

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.

Paediatric population: The half-life of cetirizine was about 6 hours in children of 6-12 years and 5 hours in children 2-6 years. In infants and toddlers aged 6 to 24 months, it is reduced to 3.1 hours.

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

6.1 List of excipients

- sorbitol
- glycerin
- propylene glycol
- strawberry flavor
- sodium citrate
- citric acid anhydrous
- methyl hydroxybenzoate
- propyl hydroxybenzoate
- purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

- Store in a cool place below 25°C.
- Use within 6 months of first opening the bottle and no later than the expiry date.

6.5 Nature and contents of container

Amber glass bottle containing volume of 115 ml, closed with a "child-proof" cap.

6.6 Special precautions for disposal and other handling

No special requirements

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

7. Manufacturer and License holder

Trima Israel Pharmaceutical Products Maabarot Ltd., Maabarot 4023000, Israel.

8. Licence number(s)

109-59-29304-00

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