SUMMARY OF PRODUCT CHARACTERISTICS

Hayzine Syrup

Summary of Product Characteristics (SmPC) Updated 04/06/2020| Phyto-Riker (GIHOC) Pharma. L.t.d.

1. NAME OF THE MEDICINAL PRODUCT

Hayzine Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of syrup contains 5mg of cetirizine hydrochloride.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Slightly cloudy to clear orange flavoured syrup.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hayzine is indicated for the relief of symptoms associated with seasonal and perennial allergic rhinitis due to allergens such as pollen, dust mites and moulds and treatment of uncomplicated skin manifestations of chronic urticaria in adults and children above 2 years of age. Symptoms treated effectively include sneezing, nasal pruritis, ocular pruritis, tearing and redness of the eyes.

4.2 Posology and method of administration

Posology

Hayzine can be taken with or without food.
Adults and Children 12 years and older: 10mg daily as a single daily dose (10 ml once daily).
The time of administration may be varied to suit individual patient need.

Children aged between 6 to 11 years: 10 mg daily in two divided doses (5 ml twice daily).
The time of administration may be varied to suit individual patient needs.

Children aged between 2-5 years: 5 mg daily in two divided doses (2.5 ml twice daily).

At present there is insufficient clinical data to recommend the use of Cetirizine in children under 2 years of age.

Elderly patients do not require any dose reduction unless renal impairment is present

For patients with moderate to severe 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 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 (CrCL) in ml/min is needed. The CrCL (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$

Group	Creatine Clearance	Posology 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

Method of administration

For oral use only

4.3 Contraindications

Hayzine is contraindicated in patients who are hypersensitive to cetirizine, to its parent drug hydroxyzine, to any piperazine derivatives or to any of the excipients listed in section 6.1
Patients with severe renal impairment with a creatinine clearance below 10 ml/min.

4.4 Special warnings and precautions for oral use

Keep all medicines out of the reach and sight of children.

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.

Methylhydroxybenzoate and Propylhydroxybenzoate may cause allergic reactions (possibly delayed).

Patients with rare hereditary problems of fructose intolerance should not take this medicinal product as it contains Liquid Sorbitol

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
Due to the amount of some excipients in the formulation, the use of the product is not recommended 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). As with other antihistamines, it is advisable to avoid excessive alcohol consumption.

4.6 Pregnancy and lactation

Pregnancy:
Animal studies have not revealed any teratogenicity or foetal toxicity. However, since human data are not adequate, Hayzine should be used during pregnancy only if the expected benefit outweighs any possible risk to the foetus.

Lactation:
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. Recommended dosage should not be exceeded.

4.8 Undesirable effects

Clinical studies

• *Overview*
Clinical studies have shown that cetirizine at the recommended dosage has minor adverse 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. Affected patients may divide their daily dose, i.e. take as 5 mg in the morning and 5 mg in the evening. 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 hydrochloride.

• *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 events 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.

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

Adverse reactions (WHO-ART)	Cetirizine (n=1656)	Placebo (n=1294)
General disorders Diarrhoea	1.0%	0.6%
Psychiatric disorders Somnolence	1.80%	1.4%
Respiratory, thoracic and mediastinal disorders Rhinitis	1.4%	1.1%
Psychiatric disorders Somnolence	9.63%	5.00%
General disorders and administrative 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 (1/10); common (1/100 to <1/10); uncommon (1/1,000 to <1/100); rare (1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data)

Blood and lymphatic system 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: syncope, dysgeusia, 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

Gastrointestinal disorders
Uncommon: diarrhea

Hepatobiliary disorders:
Rare: abnormal hepatic function (increased transaminases, alkaline phosphatase, gamma-GT and bilirubin)
Not known: hepatitis

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus
Rare: urticaria
Very rare: angioneurotic oedema, fixed drug eruption
Not known: acute generalized exanthematous pustulosis

Musculosk eletal 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. Healthcare providers and patients are asked to report any suspected adverse reactions to Hayzine via info@phyto-riker.com.gh or www.phyto-riker.com.gh or using the Patient Report Form

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 specific antidote to Hayzine. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. 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 classification: Piperazine derivatives, R06A E07 (ATC classification system)

Cetirizine, a human metabolite of hydroxyzine, is a potent antihistamine, selective H1 receptor antagonist. Thehistamine-mediated 'early' phase of the allergic reaction is inhibited by cetirizine, which also reduces the migration of inflammatory cells and the release of mediators associated with the 'late' allergic responses. Effects on other receptors are negligible and consequently cetirizine is unlikely to cause undesirable anti-cholinergic and anti-serotonin effects. At the recommended therapeutic dose of 10 mg daily, impairment of CNS function has not been found to be greater than with the placebo.
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.
Studies in healthy volunteers show that cetirizine, at doses of 5 mg 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 35-day study in children aged 5 to 12, no tolerance to the antihistaminic effect (suppression of the 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.
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 the QT interval.
At the recommended dosage, cetirizine has demonstrated that it improves the quality of life of patients with perennial and seasonal allergic rhinitis.

5.2 Pharmacokinetic properties

Cetirizine is rapidly absorbed from the gastrointestinal tract; absorption is not reduced by food, though the rate may be decreased slightly. Peak blood levels in the order of 0.3 micrograms/ml are attained between 30 and 60 minutes following administration of a 10 mg oral dose of cetirizine. Apparent plasma clearance is greater in children than in adults: the terminal elimination half-life in healthy adult volunteers ranges between 6.7 – 10.7 hours; in children 6.1 – 7.1 hours; and in children aged under 4 years 5.55 hours. Cetirizine is mainly excreted unchanged in the urine (approximately 70% over 5 days compared with 10% in the faeces). The half-life is increased in renal dysfunction: half lives of 19 and 21 hours in patients with mild to moderate renal impairment respectively have been reported. This may have implications for elderly patients. Cetirizine binds strongly to plasma proteins.

5.3 Preclinical safety data

There are no new preclinical data of relevance to the prescriber which are additional to the data already presented in this Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose, Sodium Methylhydroxybenzoate, Sodium Propylhydroxybenzoate , Propylene Glycol, Glycerin, Liquid Sorbitol, Glacial Acetic Acid, Sodium Acetate, Orange Flavour

6.2 Incompatibilities

There are no relevant data available.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store away from light in a cool dry place (below 30^0c).

6.5 Nature and contents of container

Type III amber glass bottle (30ml) with ROPP (Roll-On-Pilfer-Proof) cap to fit 25mm diameter bottle neck. Polypropylene plastic measuring cup with at least 2.5ml mark.

6.6 Special precautions for disposal

No special requirements
Any unused product or waste material should be disposed of in accordance with local requirements

7. APPLICANT

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