SUMMARY PRODUCT CHARACTERISTICS

1. Name of the medicinal product

CETIRIZINE HYDROCHLORIDE SYRUP 5 MG/5 ML

2. Qualitative and quantitative composition

Each 5 ml contains

Cetirizine hydrochloride 5 mg .

RM Code	Name of Ingredients	Spec.	Quantity Per 5ml	% Over ages	Quantity Per 5ml with Overages	Quantity Per Batch for 1200Lit	Category
RN369	Cetirizine Hcl	BP	5.00 mg	NA	5.00 mg	1.2 kg	Active
RS225	Sodium Benzoate	BP	1.00 mg	NA	1.00 mg	0.24 kg	Preservative
RS226	Sorbitol 70%	BP	250.00 mg	NA	250.00 mg	60 kg	Sweetener
RM165	Liquid glucose	BP	100.00 mg	NA	100.00 mg	24 kg	Sweetener
RP192	Potassium sorbate	BP	1.50 mg	NA	1.50 mg	0.36 kg	Preservative
RS218	Sodium Saccharin	BP	15.00 mg	NA	15.00 mg	3.6 kg	Sweetener
RD061	Disodium EDTA	BP	1.25	NA	1.25	0.3 kg	Chelating agent
RG135	Sugar	BP	500.00	NA	500.00	120 kg	Sweetener
RX280	Citric acid	BP	8.30	NA	8.30	1.992 kg	Buffer
RE453	Carmoisine color	**IH**	0.500	NA	0.500	0.12 kg	Colour
RE104	Mixed fruit flavor	IH	10.00	NA	10.00	2.4 kg	Flavour
RE523	**PW water to make up to volume**	BP	QS		QS	QS	Diluents

3. Pharmaceutical form

Oral Syrup

A red coloured syrup with mixed-fruit flavour free from visible evidence of contamination.

4. Clinical particulars

4.1 Therapeutic indications

For the treatment of perennial rhinitis, seasonal allergic rhinitis (hay fever) and chronic idiopathic urticaria in adults and children aged 6 years and over, and for seasonal rhinitis (hay fever) in children aged between 2 to 5 years.

4.2 Posology and method of administration

For oral use only.

Adults and children 6 years and above: 10 mg daily.

Adults and children aged 12 years and above: 10 ml once daily.

Children aged between 6 to 11 years: Either 5 ml twice daily or 10 ml once daily.

Children aged between 2-5 years: 5 mg daily.

Either 5 ml once daily or 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 subjects: There is no data to suggest that the dose should be reduced in elderly patients, provided that the renal function is normal.

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 (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine clearance (ml/min)	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

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, their age and their body weight.

Patients with hepatic impairment: no dose adjustment is needed in patients with solely hepatic impairment.

Patients with hepatic and renal impairment: dose adjustment is recommended (see Patients with moderate to severe hepatic impairment above).

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.

Cetirizine is also contraindicated in patients with severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings and precautions for use

(See also section 4.7 Effects on Ability to Drive and Use Machines).

Dosage adjustment is necessary in patients with moderate or severe renal impairment (*see section 4.2 Posology and Method of Administration*).

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.

This medicinal product contains propylene glycol which may cause alcohol-like symptoms.

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

This medicinal product also contains Methyl parahydroxybenzoate and Propyl parahydroxybenzoate which 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 (E420).

For patients whose symptoms persist, it is advised to consult a doctor or pharmacist.

At therapeutic doses, no clinically signification 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.

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).

4.6 Fertility, pregnancy and lactation

Pregnancy

For cetirizine, very rare clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Breast-feeding

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

In sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

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 H_1-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.

Paediatric population

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

Adverse drug 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 administrative site conditions	 1.0%	 0.3%

Fatigue		

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: diarrhoea

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

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 should be considered following ingestion of a short occurrence. In addition active charcoal should be considered if cetirizine has been ingested within 1 hour.

Cetirizine is not effectively removed by dialysis.

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. The histamine-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
No relevant information additional to that contained elsewhere in the SPC.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium Benzoate
Sorbitol 70%
Liquid glucose
Potassium sorbate
Sodium Saccharin
Disodium EDTA
Sugar
Citric acid
Carmoisine color
Mixed fruit flavor
PW water to make up to volume

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf life before opening – 36 months

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container
Type III amber Pet bottles with a tamper evident screw cap having a polypropylene outer layer and a polyethylene inner layer.

Polystyrene/polyethylene measuring device.

60ml, 75ml, 80ml, 100ml, 150ml and 200 ml

6.6 Special precautions for disposal and other handling
None.

7. Date of revision of the text

28/09/2020