SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cetirizine 1mg/ml Oral Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 10ml of solution contains 10mg of cetirizine dihydrochloride

Excipients with known effect:
- one ml of solution contains 250 mg sorbitol (solution at 70 %, non crystallising)
- one ml of solution contains 1.8 mg methylparahydroxybenzoate
- one ml of solution contains 0.2 mg propylparahydroxybenzoate

For the full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Oral solution
Clear solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults and children 2 years of age and above
For the symptomatic treatment of seasonal allergic rhinitis (hayfever), perennial rhinitis and chronic idiopathic urticaria in adults and children aged 6 years and over, and for seasonal rhinitis in children aged between 2 and 6 years.

4.2 Posology and method of administration

Posology
Adults and adolescents over 12 years of age: 10mg (10ml oral solution 2 full spoons) once a day.

Children aged from 6 and 12 years: 5 mg (5 ml a full spoonful) twice a day.

Children between 2 and 6 years for seasonal rhinitis (hayfever): (2.5 ml oral solution twice daily) a half spoonful twice a day.
At present there are insufficient clinical data to recommend use of cetirizine in children under 2 years of age.

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

$$CLcr = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{772 \times \text{serum creatinine (mg/dl)}} \quad (\times 0{,}85 \text{ for women})$$

Dosing adjustments for adult patients with impaired renal function

Group	**Creatinine clearance (ml/min)**	**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 -	< 10	contraindicated
Patients undergoing dialysis		

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, his age and his body weight.

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

Patients with hepatic impairment and renal impairment

Dose adjustment is recommended (see Patients with moderate to severe renal impairment above).
Cetirizine dihydrochloride is contraindicated in patients with severe renal impairment. In patients with moderate renal impairment the dose should be adjusted to 5 mg (1/2 tablet per day). Caution should be exercised in patients with mild to moderate renal impairment or impaired liver function (see section 4.4 Special warnings and precautions for use).

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

4.3 Contraindications

Hypersensitivity to any of the constituents of the formulation listed in section 6.1, to hydroxyzine or to any piperazine derivatives.
- Patients with severe renal impairment at less than 10 ml/min creatinine clearance
- Patients with rare hereditary problems of fructose intolerance should not take cetirizine 1 mg/ml oral solution.

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

Methylparahydroxybenzoate and propylparahydroxybenzoate may cause allergic reactions (possibly delayed).

Patients with rare hereditary problems of fructose intolerance should not take cetirizine 1 mg/ml oral solution.

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

Paediatric population

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation.

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

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/fetal 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. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

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.

Patients intending to drive, engaging in potentially hazardous activities or operating machinery 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 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 H_1-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.

Clinical trials

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)**
Body as a whole - general disorders		
Fatigue	1.63%	0.95%
Central and peripheral nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07 %
Gastro-intestinal system disorders		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
Psychiatric disorders		

Somnolence	9.63%	5.00%
Respiratory system 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.

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 system disorders Diarrhoea	1.0%	0.6%
Psychiatric disorders Somnolence	1.8%	1.4%
Respiratory system disorders Rhinitis	1.4%	1.1%
Body as a whole - general disorders 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 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

Nervous system disorders

Uncommon: paraesthesia

Rare: convulsions

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

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)

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash

Rare: urticaria

Very rare: angioneurotic oedema, fixed drug eruption

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

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: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

a) 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: 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.

b) 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.

Cetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

Cetirizine a metabolite of hydroxyzine, is a potent and 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 displays an 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 and 10 mg strongly inhibits the wheal and flare reactions induced by very high concentrations of histamine in the skin but this correlation with efficacy has not been established.

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.

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 do 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 improves the quality of life of patients with perennial and seasonal allergic rhinitis.

5.2 Pharmacokinetic properties

The steady- state peak plasma concentrations of approximately 300 ng/ml is achieved within 1.0 ± 0.5 h. 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 (C_{max}) and area under curve (AUC), is unimodal in volunteers.

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased. The extent of bioavailability is similar whether the cetirizine its given as a solution, capsules or tablet.

The apparent volume of distribution is 0.50 l/kg. The plasma protein binding of cetirizine is 93 ± 0.3 %. Cetirizine does not modify the protein binding of warfarin.

Cetirizine does not undergo extensive first pass metabolism, approximately two thirds of the dose are excreted unchanged in urine. The terminal half-life is approximately 10 hours.

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

Special populations:

Older people: Following a single 10 mg oral dose the 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 aged 6-12 years and 5 hours in children 2-6 years. In infants and toddlers aged 6 to 24 months its reduced to 3.1 hours.

Renal impairment: The pharmacokinetics of the drug 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 patients. Cetirizine was poorly cleared by haemodialysis. A 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 hepatic impairment patients if concomitant renal impairment is present.

5.3 Preclinical safety data

Non-clinical data revealed 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

Liquid sorbitol (non-crystallising)

Glycerol

Propylene glycol

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Sodium acetate

Glacial acetic acid

Saccharin sodium

Mixed Fruit Flavour ID 21533 (which contains vanillin, orange oil, ethyl vanillin, amyl acetate, amyl butyrate, amyl propionate, ethyl butyrate, ethyl propionate, citral, allyl heptylate, linalool, terpeneol, lemon oil, geraniol, butyric acid and propylene glycol)

Raspberry flavour 249 (which contains raspberry aldehyde, amyl acetate, amyl butyrate, ethyl acetate, ethyl butyrate, hexanyl butyrate, alpha ionone, geraniol, clove oil, cinnamon oil, orris oil, geranium oil and propylene glycol)

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Unopened: 24 months.

After first opening: 3 months.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

Type III Amber glass bottles fitted with EPE lined child resistant closures or amber PET containers fitted with EPE lined child resistant closures.

6.6 Special precautions for disposal

Not applicable.

7 MARKETING AUTHORISATION HOLDER

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