Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cetirizine dihydrochloride Haleon 1 mg/ml oral solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of solution contains 1 mg of cetirizine dihydrochloride.
Excipients with known effect

- One ml of solution contains 315 mg of sorbitol.
- One ml of solution contains 1.35 mg methylparahydroxybenzoate (E 218)
- One ml of solution contains 0.15 mg propylparahydroxybenzoate (E 216)
- One ml of solution contains 50 mg propylene glycol (E 1520)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oral solution.
Clear and colourless liquid with a slightly sweet taste and a banana flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine is indicated in adults and children aged 2 years and above:

- for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis
- for the relief of symptoms of chronic idiopathic urticaria

4.2 Posology and method of administration

Posology
10 mg once daily (10 ml oral solution (2 full spoons)).

Special populations
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.

Dosing adjustments for adult patients with impaired renal function

Group	Estimated Glomerular Filtration Rate (eGFR) (ml/min)	Dosage and frequency
Normal renal function	≥90	10 mg once daily
Mildly decreased renal function	60 - < 90	10 mg once daily
Moderately decreased renal function	30 – < 60	5 mg once daily
Severely decreased renal function	15 - <30 not requiring dialysis	5 mg once every 2 days
End-stage renal disease	<15 requiring dialysis treatment	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 aged from 2 to 6 years: 2.5 mg twice daily (2.5 ml oral solution twice daily (a half spoon twice daily)).

Children aged from 6 to 12 years: 5 mg twice daily (5 ml oral solution twice daily (a full spoon twice daily).

Adolescents over 12 years of age: 10 mg once daily (10 ml oral solution (2 full spoons)).

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance, age and body weight of the patient.

Method of administration:
The solution 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 end-stage renal disease with an eGFR (estimated Glomerular Filtration Rate) below 15 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 (see Section 4.8).
Caution in epileptic patients and patients at risk of convulsions is recommended.
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.

Excipients
This medicinal product contains 1575 mg sorbitol (E 420) in each 5 ml which is equivalent to 315 mg/ml. Patients with hereditary fructose intolerance (HFI) should not take / be given this medicinal product. Sorbitol may cause gastrointestinal discomfort and mild laxative effect.
This medicinal product contains methylparahydroxybenzoate (E 218) and propylparahydroxybenzoate (E 216) which may cause allergic reactions (possibly delayed).
This medicinal product contains 250 mg propylene glycol (E 1520) in each 5 ml which is equivalent to 50 mg/ml.
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially `sodium-free'.

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. No pharmacodynamic or significant pharmacokinetic interaction has been 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.
Alcohol and other CNS depressants
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 post-natal development (see 5.3). Caution should be exercised when prescribing to pregnant women.

Breast feeding
Caution should be exercised when prescribing cetirizine to lactating women. Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration.

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 hydrochloride.

Listing of ADRs
Double blind controlled clinical or pharmacoclinical 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 event (WHO-ART)	**Cetirizine 10mg (n=3260)**	**Placebo (n=3061)**
General disorders and administration site conditions:		
Fatigue	1.63%	0.95%
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, 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.

Pediatric population

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

Adverse event (WHO-ART)	**Cetirizine 10 mg (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 effects reported during clinical studies and listed above, the following adverse drug reactions 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):

System Organ Class and Undesirable Effect	**Frequency**
Blood and lymphatic disorders:	
Thrombocytopenia	*Very rare*
Immune system disorders:	
hypersensitivity	*Rare*
anaphylactic shock	*Very rare*
Metabolism & nutrition disorders:	
increased appetite	*Not known:*
Psychiatric disorders:	
agitation	*Uncommon*
aggression, confusion, depression, hallucination, insomnia	*Rare*
tics	*Very rare*
suicidal ideation	*Not known*
Nervous system disorders:	
paraesthesia	*Uncommon*
convulsions	*Rare*
dysgeusia, dyskinesia, dystonia, syncope, tremor	*Very rare*
amnesia, memory impairment	*Not known*
Eye disorders:	
accommodation disorder, blurred vision, oculogyration	*Very rare*
Ear and labyrinth disorders:	
vertigo	*Not known*
Cardiac disorders:	
tachycardia	*Rare*
Gastro-intestinal disorders:	
diarrhoea	*Uncommon*
Hepatobiliary disorders:	
hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)	*Rare*
Skin and subcutaneous tissue disorders:	
pruritus, rash	*Uncommon*
urticaria	*Rare*
angioneurotic oedema, fixed drug eruption	*Very rare*
Renal and urinary disorders:	
dysuria, enuresis	*Very rare*
urinary retention	*Not known*
General disorders and administration site conditions:	
asthenia, malaise	*Uncommon*

oedema	*Rare*
Investigations:	
weight increase	*Rare*

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 HPRA Pharmacovigilance website: www.hpra.ie.

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. Cetirizine is not effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07
Mechanism of action
Cetirizine, a human metabolite of hydroxyzine, is a potent and selective, non-sedating 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.

Pediatric population
In a 35-day study in children aged 5 to 12, no tolerance to the antihistamine 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. 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 in human 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 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 thirds 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 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 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 hepatically impaired patients 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

- Glycerol (E 422)
- Propylene glycol (E 1520)
- Liquid Sorbitol (non- crystallising) (E 420)
- Methyl Parahydroxybenzoate (E 218)
- Propyl Parahydroxybenzoate (E 216)
- Sodium acetate
- Acetic acid
- Saccharin sodium
- Banana flavour
- Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years
Once opened, use within 1 month.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

70 ml fill bottle.
Amber glass bottle with child-resistant polypropylene screw cap incorporating a tamper evident seal (yellow polyethylene)
Measuring device: 5 ml plastic PP measuring spoon graduated at 2.5 ml

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0678/162/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT