Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cetrine 10 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg cetirizine dihydrochloride.

Excipients with known effect: Also contains 81.8mg lactose monohydrate

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
White, oblong film-coated tablet, scored on one side.
The scoreline is to allow the tablet to be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cetrine is indicated in adults and paediatric patients 6 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

Children aged from 6 to 12 years: 5mg twice daily (a half a tablet twice daily)

Adults and adolescents over 12 years of age: 10 mg once daily (1 tablet).

Elderly patients: data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

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 individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use the 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;

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

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine Clearance (ml/min)	Dosage and frequency
Normal	≥80	10mg once daily
Mild	50 – 79	10mg once daily
Moderate	30 – 49	5mg 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 and the 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).

Method of administration
The tablets need to be swallowed with a glass of liquid.

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 of less than 10ml/min creatinine clearance.

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 0.5g/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.

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 re-started. The symptoms should resolve when the treatment is restarted.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 interactions

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 (400mg/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 (0.5g/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/foetal development, parturition or postnatal development (see 5.3).

Caution should be exercised when prescribing to pregnant women.

Breast-feeding
Cetirizine is excreted in human milk at concentrations representing 25% to 90% 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 10mg.

However, patients who experience somnolence should refrain from driving, 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.

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 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.

- Listing of ADR's

Double blind controlled clinical trials comparing cetirizine to placebo or other antihistamines at the recommended dosage (10mg 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 10mg 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 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 mediastinaldisorders		
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 event (WHO-ART)	**Cetirizine 10mg (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 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 postmarketing 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, 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 generalised 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie

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: 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 the medicinal product.
Cetirizine is not effectively removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code : R06A E07: Antiallergic Agent

Pharmacotherapeutic group: Antihistamines for systemic use. Piperazine derivatives

Cetirizine, a human 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 was shown to display anti-allergic activities: at a dose of 10mg 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 10mg 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 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 10mg 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 60mg 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.

5.2 Pharmacokinetic properties

The steady-state peak plasma concentrations is approximately 300ng/ml and is achieved within 1.0 ± 0.5h. No accumulation is observed for cetirizine following daily doses of 10mg for 10 days. The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) 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.

The apparent volume of distribution is 0.50l/kg. 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. About two third of the dose are excreted unchanged in urine. The terminal half-life is approximately 10 hours.

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

Special populations

Elderly: Following a single 10mg 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.

Children, infants and toddlers: 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.

Renally impaired patients: The pharmacokinetics of the drug were similar in patients with mild impairment (creatinine clearance higher than 40ml/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 7ml/min) given a single oral 10mg dose of cetirizine had a 3-fold increase in half-life and a 70% decrease in clearance compared to normal. Cetirizine was poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment (see section 4.2).

Hepatically impaired patients: Patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given 10 or 20mg of cetirizine as a single dose had a 50% increase in half-life along with 40% decrease in clearance compared to healthy subjects.
Dosing adjustment is only necessary in hepatically impaired patients if concomitant renal impairment is present.

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

Lactose Monohydrate
Microcrystalline Cellulose
Silica, Colloidal Anhydrous
Magnesium Stearate

For film-coating
Lactose Monohydrate
Titanium Dioxide (E171)
Hypromellose
Macrogol 4000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Cetrine 10 mg tablets are packed into PVC/Al strips and inserted into a carton.

Cetrine 10 mg tablets are available in packs of 30 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Not applicable.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry

Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/075/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 August 2004
Date of last renewal: 06 August 2009

10 DATE OF REVISION OF THE TEXT

April 2019