SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Cetirizine Hydrochloride 10mg Tablets

Pollenshield Hayfever

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg Cetirizine hydrochloride.

Excipient with known effect: Each tablet contains 117.00mg lactose monohydrate
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

Film-coated, white or almost white convex, elliptical, tablets. 5.7 x 11.4 mm. The letter “C” on one side and the letters “J” and “E” on either side of a central division line on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine is indicated in adults and paediatric patients 6 year 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

10mg once daily (1 tablet).

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 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.

Dosing adjustments for adult patients with impaired renal function

Group	Estimated Glomerular Filtration Rate (eGFR) (ml/min)	Dosage and frequency
Normal renal function	≥ 90	10mg once daily
Mildly decreased renal function	60 - < 90	10mg once daily
Moderately decreased renal function	30 – < 60	5mg once daily
Severely decreased renal function	15 - < 30 not requiring dialysis treatment	5mg once every 2 days
End-stage renal disease	< 15 requiring dialysis treatment	Contra-indicated

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
The tablet formulation should not be used in children under 6 years of age as it does not allow the necessary dose adjustments.

Adolescents above 12 years: 10 mg once daily (1 tablet).
Children aged from 6 to 12 years: 5mg twice daily (a half tablet twice daily).

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
For oral use.
The tablets need to be swallowed with a glass of liquid.

4.3 Contraindications

- Hypersensitivity to the active substance, or 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 0.5g/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 is recommended in epileptic patients and patients at risk of convulsions.

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

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

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
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. It is recommended to use a paediatric formulation of cetirizine.

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 (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 (0.5 g/L blood levels).

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

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/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Breast-feeding
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. 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 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 ADRs*
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 reactions (WHO-ART)	**Cetirizine 10mg (n= 3260)**	**Placebo (n = 3061)**
Psychiatric disorders		
Somnolence	9.63%	5.00%
Nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Respiratory, thoracic and mediastinal disorders		
Pharyngitis	1.29%	1.34%
Gastro-intestinal disorders		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
General disorders and administration site conditions		
Fatigue	1.63%	0.95%

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 reactions (WHO-ART)	**Cetirizine 10 mg (n=1656)**	**Placebo (n =1294)**
Psychiatric disorders		
Somnolence	1.8%	1. 4%
Respiratory, thoracic and mediastinal disorders		
Rhinitis	1.4%	1.1%
Gastro-intestinal disorders		
Diarrhoea	1.0%	0.6%
General disorders and administration 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).

MEDRA SOC	*Uncommon*	*Rare*	*Very rare*	*Not known*
Blood and lymphatic system disorders			thrombocytopenia	
Immune system disorders		hypersensitivity	anaphylactic shock	
Metabolism and nutrition disorders				increased appetite
Psychiatric disorders	agitation	aggression, confusion, depression, hallucination, insomnia	tics	suicidal ideation, nightmares
Nervous system disorders	paraesthesia	convulsions	dysgeusia, syncope, tremor, dystonia, dyskinesia	amnesia, memory impairment
Eye disorders:			accommodation disorder, blurred vision, oculogyric crisis	
Ear and labyrinth disorders				vertigo
Cardiac disorders		tachycardia		
Gastro-intestinal disorders	diarrhoea			
Hepatobiliary disorders		hepatic function abnormal (increased transaminases,		hepatitis

		alkaline phosphatase, γ-GT and bilirubin)		
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria	angioneurotic oedema, fixed drug eruption	acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders				arthralgia, myalgia
Renal and urinary disorders			dysuria, enuresis	urinary retention
General disorders and administration site conditions	asthenia, malaise	oedema		
Investigations		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 website: 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 may be considered shortly after ingestion of the drug.
Cetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives, ATC code: R06A E07

Mechanism of action
Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1receptors.

Pharmacodynamic effects
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.

Clinical efficacy and safety
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 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.

Paediatric population
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.

5.2 Pharmacokinetic properties

Absorption
The steady-state peak plasma concentrations is approximately 300ng/ml and is achieved within 1.0 ± 0.5 h. The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) and area under curve (AUC), is unimodal.

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 third of the dose are excreted unchanged in urine.

Linearity/Non-linearity
Cetirizine exhibits linear kinetics over the range of 5 to 60mg.

Renal impairment: The pharmacokinetics of the drug was 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 haemodialysis (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 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 20mg 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 patients with hepatic impairment if concomitant renal impairment is present.

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 younger 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 and development.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose (E460), lactose monohydrate, crospovidone, colloidal anhydrous silica and magnesium stearate.

Film coat:

Hypromellose (E464), macrogol stearate, microcrystalline cellulose (E460), propylene glycol, titanium dioxide (E171).

6.2 Incompatibilities

None known

6.3 Shelf life

Aluminium laminate-aluminium blister pack

3 years.

HDPE tablet container with LDPE cap

2 years.

6.4 Special precautions for storage

Blister pack:

Do not store above 25^{o}C.

Store in the original package

6.5 Nature and contents of container

Blister pack
(i) 60µm PVC/45µm Al/25µm OPA
(ii) 20µm Al

HDPE tablet container with LDPE cap.

HDPE tablet container: 20, 28, 30, 56, 60, 100
Blister pack: 7, 20, 28, 30, 56, 60, 100

Not all pack sizes may be marketed

6.6 Special precautions for disposal

Not applicable

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER

PL 00142/0490

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/04/2011

10 DATE OF REVISION OF THE TEXT

12/07/2023