Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zirtek 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg cetirizine dihydrochloride.

Excipients with known effect: one film-coated tablet contains 66.40 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

White, oblong, film-coated tablet, with breakline and Y-Y logo.
The tablet can be divided into 2 equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine dihydrochloride 10 mg film-coated tablets are 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
10 mg once daily (1 tablet).

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

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

Adolescents above 12 years: 10 mg once daily (1 tablet).

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 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 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.

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, the Lapp lactase deficiency or glucose- galactose malabsorption should not take cetirizine film-coated tablets.

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 (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 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 (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)**
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 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 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 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 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, 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, oculogyric crisis

- *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 generalized exanthematous pustulosis

- *Musculoskeletal and connective tissue disorders*

Not known: arthralgia, myalgia

- *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
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 may be considered shortly after ingestion of the drug.
Cetirizine is not effectively removed by haemodialysis.

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_1-receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1-receptors.

Pharmacodynamic effects
In addition to its anti-H_1 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.

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
Thesteady -state peak plasma concentrations is approximately 300 ng/ml and is achievedwithin 1.0 ±0.5 h.Thedistributionofpharmacokineticparameterssuchaspeakplasmaconcentration (Cmax)and area under curve (AUC), is unimodal. Theextentofabsorptionofcetirizineisnotreducedwithfood,althoughtherateofabsorptionis decreased. Theextentofbioavailabilityissimilarwhencetirizineisgivenassolutions,capsulesor tablets.

Distribution
Theapparentvolumeofdistributionis0.50 l/kg. Plasma protein binding of cetirizine is 93 ±0.3 %. Cetirizine does not modify theproteinbindingofwarfarin.

Biotransformation
Cetirizine does not undergo extensive first pass metabolism.

Elimination
Theterminalhalf-life is approximately 10 hoursand no accumulation is observed forcetirizine following daily doses of 10 mgfor 10 days. Abouttwothirdofthedoseareexcretedunchangedin urine.

Linearity/Non-linearity
Cetirizineexhibitslinearkineticsovertherangeof5to60 mg.

Renalimpairment: The pharmacokinetics of the drug wassimilar in patients with mild impairment (creatinineclearancehigherthan40 ml/min) and healthy volunteers. Patients with moderate renal impairment had a 3-foldincreaseinhalf-lifeand70 %decreaseinclearancecomparedtohealthy volunteers. Patientsonhemodialysis(creatinineclearancelessthan7 ml/min) given a single oral 10 mgdoseof cetirizinehada3-foldincreaseinhalf-lifeanda70 % 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).

Hepaticimpairment:Patientswithchronicliverdiseases(hepatocellular,cholestatic,andbiliary cirrhosis) given 10 or 20 mg of cetirizine as a single dose had a 50%increaseinhalf-life along with a 40 %decreaseinclearancecomparedtohealthy subjects. Dosing adjustment is only necessary in patients with hepatic impairment ifconcomitantrenal impairment is present.

Elderly: Following a single 10 mg oral dose, half-lifeincreasedbyabout50 %andclearance decreased by 40 %in16elderlysubjectscomparedtotheyoungersubjects. Thedecreasein cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Paediatricpopulation: The half-lifeofcetirizinewasabout6 hoursinchildrenof6-12 years and 5 hoursinchildren2-6 years. In infants and toddlers aged 6 to 24months, 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

Core

Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate
Opadry –Y-1-7000 which consists of
- Hydroxypropylmethylcellulose (E464)
- Titanium dioxide (E171)
- Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

The tablets are enclosed in a transparent, colourless, inert PVC blister strip thermo-sealed with a lacquered aluminium foil. These blister strips are housed in a carton box.
Boxes of 1, 4, 5, 7, 10, 14, 15, 20, 21, 30, 40, 45, 50, 60, 90, 100 or 100 (10x10) tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Nospecialrequirements.
Any unused medicinal product orwastematerialshouldbedisposedofinaccordancewithlocal requirements.

7 MARKETING AUTHORISATION HOLDER

UCB (Pharma) Ireland Limited
United Drug House
Magna Drive, Magna Business Park
Citywest Road
Dublin 24
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0891/008/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 8th August 1988

Date of last renewal: 14th November 2011

10 DATE OF REVISION OF THE TEXT

June 2022