

Zyrtec®

Cetirizine dihydrochloride

Film-coated tablets drops oral solution

QUALITATIVE AND QUANTITATIVE COMPOSITION

Zyrtec tablets are white oblong film-coated tablets, each containing 10 mg cetirizine dihydrochloride. It contains 66.40 mg lactose per film-coated tablet. Each tablet has a bisect line and a Y-Y logo.

Zyrtec oral drops containing 10 mg cetirizine dihydrochloride per ml. It contains preservatives methylparaben 1.35 mg/ml and propylparaben 0.15 mg/ml. The solution is clear and colourless.

Zyrtec oral solution containing 1 mg cetirizine dihydrochloride per ml. It contains preservatives methylparaben 1.35 mg/ml and propylparaben 0.15 mg/ml. The solution is clear and colourless with slightly sweet taste and a banana flavour.

EXCIPIENTS

Zyrtec Tablet 10 mg:

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

Zyrtec Oral Drops 10 mg/ml:

Glycerol (85%), Propylene glycol, Saccharin sodium, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Sodium acetate, Glacial acetic acid, Purified water.

Zyrtec Oral Solution 1 mg/ml:

Sorbitol solution at 70% (non-crystallising), Glycerol (85%), Propylene glycol, Saacharin sodium, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Banana flavor 54.330/A, Sodium acetate, Glacial acetic acid, Purified water.

CLINICAL INFORMATION

INDICATIONS

For relief of:

- nasal and ocular symptoms of seasonal and perennial allergic rhinitis;
- symptoms of chronic idiopathic urticaria

DOSAGE AND DIRECTIONS FOR USE

Children aged from 2 to 6 years: 2.5 mg twice daily [5 drops twice daily or 2.5 ml of oral solution twice daily (half of a spoon twice daily)].

Children aged from 6 to 12 years: 5 mg [10 drops, or 5 ml oral solution (1 full spoon) or half of the tablet] twice daily.

Adolescents 12 years and above, and adults: 10 mg once daily [1 tablet, 20 drops, or 10 ml oral solution (2 full spoons)]. A 5 mg starting dose (half of the tablet, 10 drops, or 5 ml oral solution) may be proposed if this leads to satisfactory control of the symptoms.

The tablets need to be swallowed with a glass of liquid. The drops have to be diluted in liquid, while the solution can be swallowed as such.

Elderly subjects: 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: Since cetirizine is mainly excreted via renal route, 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 this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in ml/min is needed. The CL_{cr} (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - \text{age}(\text{years})] \times \text{weight}(\text{kg})}{2 \times \text{serum creatinine}(\text{mg/dl})} \quad (\times 0.85 \text{ for women})$$

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 - 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 age and body weight of the patient.

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

Patients with hepatic impairment and renal impairment: adjustment of the dose is recommended (*see Patients with renal impairment above*).

CONTRAINDICATIONS

ZYRTEC is contraindicated during lactation.

Hypersensitivity to any of the constituents of the formulation, 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 galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take cetirizine film-coated tablet.

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

WARNINGS & PRECAUTIONS

Alcohol

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 (see Section *Interactions*).

Increased risk of urinary retention

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 *Adverse Reactions*)

Patients at risk of convulsions

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

Skin reactions

Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation (see Section *Adverse Reactions*). In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Children

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.

Allergy skin tests

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

Food

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased by 1 hour.

ABILITY TO PERFORM TASKS THAT REQUIRE JUDGEMENT, MOTOR OR COGNITIVE SKILLS

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.

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.

Activities requiring mental alertness. In clinical trials, the occurrence of somnolence has been reported in some patients taking ZYRTEC. Due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.

DRUG INTERACTIONS

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interaction studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

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) (see Section *Warnings and Precautions*).

PREGNANCY AND LACTATION

Fertility

Limited data is available on human fertility but no safety concern has been identified. Animal data show no safety concern for human reproduction.

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.

Caution should be exercised when prescribing to pregnant women. ZYRTEC should not be administered to pregnant women during the first three months of pregnancy.

Lactation

Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, ZYRTEC is contraindicated in lactating women since the active ingredient, cetirizine is excreted in breast milk.

ADVERSE REACTIONS

Clinical trial data

Clinical studies have shown that cetirizine at the recommended dosage has minor adverse 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.

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)
<i>General disorders and administration site conditions</i> Fatigue	1.63 %	0.95 %
<i>Nervous system disorders</i> Dizziness Headache	1.10 % 7.42 %	0.98 % 8.07 %
<i>Gastro-intestinal system disorders</i> Abdominal pain Dry mouth Nausea	0.98 % 2.09 % 1.07 %	1.08 % 0.82 % 1.14 %
<i>Psychiatric disorders</i> Somnolence	9.63 %	5.00 %
<i>Respiratory thoracic and mediastinal disorders</i> 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)
<i>Gastro-intestinal system disorders</i> Diarrhoea	1.0 %	0.6 %
<i>Psychiatric disorders</i> Somnolence	1.8 %	1.4 %
<i>Respiratory thoracic and mediastinal disorders</i> Rhinitis	1.4 %	1.1 %

<i>General disorders and administration site conditions</i> Fatigue	1.0 %	0.3 %
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Post-marketing data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

Very common $\geq 1/10$

Common $\geq 1/100$ to $< 1/10$

Uncommon $\geq 1/1,000$ to $< 1/100$

Rare $\geq 1/10,000$ 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, 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, gamma-glutamyl transferase and bilirubin)
Not known: hepatitis

- Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioedema, fixed drug eruption
Not known: acute generalized exanthematous pustulosis (AGEP)
- Musculoskeletal and connective tissue disorders:
Not known: arthralgia
- Renal and urinary disorders:
Very rare: dysuria, enuresis
Not known: urinary retention (see Section *Warnings and Precautions*)
- General disorders and administration site conditions:
Uncommon: asthenia, malaise
Rare: oedema
- Investigations:
Rare: weight increased

Skin reactions occurring after discontinuation of cetirizine

After discontinuation of cetirizine, pruritus (intense itching) and/or urticarial have been reported (see Section *Warnings and Precautions*).

OVERDOSAGE

a) Symptoms and signs

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) Treatment

There is no known specific antidote to cetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Cetirizine is not effectively removed by haemodialysis.

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Cetirizine (ATC code R06A E07), a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H₁-receptors. *In vitro* receptor binding studies have

shown no measurable affinity for receptors other than H₁-receptors. *Ex vivo* experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H₁-receptors.

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 inflammatory cells, notably eosinophils, in the skin and conjunctiva of atopic subjects submitted to antigen challenge, and the dose of 30 mg/day inhibits the influx of eosinophils in the bronchoalveolar lavage fluid during a late-phase bronchial constriction induced by allergen inhalation in asthmatic subjects. Moreover, cetirizine inhibits the late-phase inflammatory reaction induced in chronic urticaria patients by intradermal administration of kallikrein. It also down-regulates the expression of adhesion molecules, such as ICAM-1 and VCAM-1, which are markers of allergic inflammation.

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. The onset of activity after a single 10 mg dose occurs within 20 minutes in 50 % of the subjects and within one hour in 95 %. This activity persists for at least 24 hours after a single administration.

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.

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.

PHARMACOKINETICS

Absorption

The steady-state maximum plasma concentration is approximately 300 ng/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 (AUC) of cetirizine is not reduced with food, although the rate of absorption (T_{max} and C_{max}) 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 $93 \pm 0.3\%$. Cetirizine does not modify the protein binding of wafarin.

Metabolism and Elimination

Cetirizine does not undergo extensive first pass metabolism. About two-thirds of the dose is excreted unchanged in the urine. The terminal half-life is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. Cetirizine exhibits linear kinetics over the range 5 – 60 mg.

Special populations

Elderly: 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 younger 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 was 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. Cetirizine was poorly cleared by haemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment.

Hepatically impaired patients: 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.

SHELF-LIFE

The expiry date is stated on the outer packaging.

STORAGE

Refer to the storage condition on the outer packaging.
Keep tablets in a dry place.

PRESENTATION

Tablet: Boxes containing 10, 50 and 500 film-coated tablets in blister strips
Oral drops: Bottle containing 10 or 20 ml drops
Oral solution: Bottle containing 75 ml solution

Not all presentations will be available locally.

Version: **NCDS05SI**

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Manufacturer for tablets:
UCB FARCHIM SA
BULLE - SWITZERLAND

Manufacturer for oral
solution and drops:
AESICA PHARMCEUTICALS
S.R.L.
PIANEZZA (TO) - ITALY

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