Zyrtec®

Cetirizine dihydrochloride

film-coated tablets/oral drops/oral solution

CP135/02

NAME OF THE MEDICINAL PRODUCT
Zyrtec 10 mg per film-coated tablet
Zyrtec 1 mg/ml, oral solution
Zyrtec 10 mg/ml, oral drops, solution
Generic name: Cetirizine hydrochloride.
CLINICAL PARTICULARS
Therapeutic indications
In adults, children, infants:
- Cetirizine is indicated for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- Cetirizine is indicated for the relief of symptoms of urticaria.

Posology and method of administration
Children aged from 2 to 6 years: 2.5 mg twice daily (5 drops bid or 2.5 ml oral solution bid (a half spoon bid)).
Children aged from 6 to 12 years: 10 mg once daily (1 tablet, 20 drops, or 10 ml oral solution (2 full spoons)). A 5 mg starting dose (1 half tablet, 10 drops, or 5 ml oral solution) may be proposed if this leads to satisfactory control of the symptoms.
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 (1 half 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: 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 (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula :

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

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	Contra-indicated

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 his body weight.
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).
Contra-indications
History of 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.
Special warnings and precautions for use
Cetirizine should not be used for children at less than 2 years of age, and this due to the potential side effects that may happen if misused e.g.: Irritability, irritation, drowsiness, lack of concentration.
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 in epileptic patients and patients at risk of convulsions is recommended.
Methyl parahydroxybenzoate and propyl parahydroxybenzoate included in the 10 mg/ml oral drops and in the 1 mg/ml oral solution may cause allergic reactions (possibly delayed).
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.
Due to the amount of some excipients in the formulation, the oral solution is not recommended in children aged less than 2 years.
Interactions with other medicinal products and other forms of interaction
Pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, cimetidine, ketoconazole, erythromycin, and azithromycin; no pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once a day) and cetirizine, there was a small (16%) decrease in clearance of cetirizine, while the disposition of theophylline was not altered by concomitant cetirizine administration.
Studies with cetirizine and cimetidine, glipizide, diazepam, and pseudoephedrine have revealed no evidence of adverse pharmacodynamic interactions.
Studies with cetirizine and azithromycin, erythromycin, ketoconazole, theophylline, antipyrine, and pseudoephedrine have revealed no evidence of adverse clinical interactions. In particular, concomitant administration of cetirizine with macrolides or ketoconazole has never resulted in clinically relevant ECG changes.
In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.
The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased by 1 hour.
Allergy skin tests are inhibited by antihistamines and a wash-out period of 3 days is recommended before performing them.
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/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.
Lactation
Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.
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.
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.
In sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.
Undesirable effects
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 drug.
A) Clinical trials
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)
Body as a whole - general disorders Fatigue	1.63%	0.95%
Central and peripheral nervous system disorders Dizziness Headache	1.10% 7.42%	0.98% 8.07%
Gastro - intestinal system disorders Abdominal pain Dry mouth Nausea	0.98% 2.09% 1.07%	1.08% 0.82% 1.14%
Psychiatric disorders Somnolence	9.63%	5.08%
Respiratory system 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.

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 system disorders Diarrhoea	1.0%	0.6%
Psychiatric disorders Somnolence	1.8%	1.4%
Respiratory system disorders Rhinitis	1.4%	1.1%
Body as a whole - general disorders Fatigue	1.0%	0.3%

B) 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
• Psychiatric disorders:
Uncommon: agitation
Rare: aggression, confusion, depression, hallucination, insomnia
Very rare: tic
• Nervous system disorders:
Uncommon: paraesthesia
Rare: convulsions
Very rare: dyskinesia, dystonia, vertigo, syncope, tremor
Not known: amnesia, memory impairment
• Eye disorders:
Very rare: accommodation disorder, blurred vision, oculogyration
• Cardiac disorders:
Rare: tachycardia
• Gastro-intestinal disorders:
Uncommon: diarrhoea
• Hepatobiliary disorders:
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)
• Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioneurotic oedema, fixed drug eruption
• Renal and urinary disorders:
Very rare: dysuria, enuresis
• General disorders and administration site conditions:
Uncommon: asthenia, malaise
Rare: oedema
• Investigations:
Rare: weight increased
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 a short occurrence.
Cetirizine is not effectively removed by dialysis.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
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 other 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/kg inhibits the influx of eosinophils in the broncho alveolar 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 downregulates 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 various doses of histamine into the skin. 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 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 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.
Chronic idiopathic urticaria was studied as a model for urticarial conditions. Since histamine release is a causal factor in urticarial diseases, cetirizine is expected to be effective in providing symptomatic relief for other urticarial conditions, in addition to chronic idiopathic urticaria. 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.
Pharmacokinetic properties
Cetirizine exhibits linear kinetics over the range 5 to 60 mg. The terminal half-life is approximately 10 hours and the apparent volume of distribution is 0.50 l/kg. No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. The steady - state maximum plasma concentration is approximately 500 ng/ml and is achieved within 1.0 ± 0.5 h. 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 distribution of pharmacokinetic parameters as peak level and area under curve, is unimodal in human volunteer and no differences were observed in the kinetics of cetirizine between white and black adult males. 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.
Special populations
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.
Children, infants: 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 normal volunteers.
Moderately renally impaired patients had a 3-fold increase in half-life and 70% decrease in clearance compared to normal volunteers.
Patients on hemodialysis (creatinine clearance less than 7 ml/min) given a single oral 10 mg dose of cetirizine had a 5-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 § 4.2).
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.
PHARMACEUTICAL PARTICULARS
List of excipients
1 Film-coated tablet
- Microcrystalline cellulose
- Lactose
- Colloidal anhydrous silica
- Magnesium stearate
- Opadry Y-1-7000
- Hydroxypropylmethylcellulose (E464)
- Titanium dioxide (E 171)
- Macrogol 400

2 Oral drops at 10 mg/ml
- Glycerol
- Propylene glycol
- Sodium saccharinate
- Methylparahydroxybenzoate
- Propylparahydroxybenzoate
- Sodium acetate
- Glacial acetic acid
- Purified water

3 Oral solution at 1 mg/ml
- Sorbitol solution at 70 % (non crystallizing)
- Glycerol
- Propylene glycol
- Sodium saccharinate
- Methylparahydroxybenzoate
- Propylparahydroxybenzoate
- Banana flavor 54.12GIA (Firmenich)
- Sodium acetate
- Glacial acetic acid
- Purified water

Storage: store in temperature not exceeding 30°C
Nature and contents of container
Tablets: carton box containing 2 ALU/PVC strips each of 10 tablets and inner leaflet.
Oral drops: carton box containing 1 bottle of 10 ml and inner leaflet.
Oral solution: carton box containing 1 bottle of 100 ml and inner leaflet.
Manufactured by : GLAXOSMITHKLINE - EL SALAM CITY-CAIRO, EGYPT
KEEP OUT OF REACH OF CHILDREN
DATE OF REVISION OF THE TEXT
June 2010
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keep all medicines out of the reach of children

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