

## **ZYRTEC 0.1%**

Cetirizine dihydrochloride 0.1%

### **NAME OF THE MEDICINAL PRODUCT**

Cetirizine dihydrochloride, 1 mg/ml, oral solution

### **QUALITATIVE AND QUANTITATIVE COMPOSITION**

*Cetirizine dihydrochloride, 1 mg/ml, oral solution*

Each 1 ml contains 1 mg of cetirizine dihydrochloride.

### **Excipients**

Sorbitol solution at 70% (non-crystallizing), Glycerol (85%), Propylene glycol, Sodium saccharinate, Methyl parahydroxybenzoate, Propyl parahydroxybenzoate, Banana flavour 54.330/A, Sodium Acetate, Glacial Acetic Acid, Purified water.

### **PHARMACEUTICAL FORM**

*Cetirizine dihydrochloride, 1 mg/ml, oral solution*

Banana flavoured clear colourless liquid.

### **CLINICAL INFORMATION**

#### **Indications**

For the relief of:

- nasal and ocular symptoms of seasonal and perennial allergic rhinitis,
- symptoms of urticaria.

#### **Dosage and Administration**

##### **Route of Administration**

For oral use.

##### **Adults**

10 mg (10 ml of oral solution) once daily.

A 5 mg starting dose (5 ml of oral solution) may be proposed if this leads to satisfactory control of the symptoms.

##### **Children**

*Children aged from 2 to 6 years*  
2.5 mg (2.5 ml of oral solution) twice daily.

*Children aged from 6 to 12 years*  
5 mg (5 ml of oral solution) twice daily.

*Children over 12 years of age*  
10 mg (10 ml of oral solution) once daily.

### **Elderly**

Data does not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

### **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.

Dosing adjustments for adult patients with impaired renal function

<b>Group</b>	<b>Estimated Glomerular Filtration Rate (eGFR) (ml/min)</b>	<b>Dosage and frequency</b>
Normal renal function	$\geq 90$	10 mg once daily
Mild decrease 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

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.

### **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 Renal impairment above*).

## Contraindications

Cetirizine is contraindicated in:

- hypersensitivity to any of the constituents of this formulation, to hydroxyzine or to any piperazine derivatives,
- patients with end-stage renal disease with eGFR (Estimated Glomerular Filtration Rate) below 15 ml/min.

## Warnings and 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 [*Please be aware that in some markets, film-coated tablets may be indicated in children 12 years and above.*]

The use of the hard capsules formulation is not recommended in children aged less than 12 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.

## **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 interactions 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**

Caution should be exercised when prescribing to pregnant women.

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.

### **Lactation**

Cetirizine passes into breast milk. A risk of side effects in breastfed infants cannot be excluded. Caution should be exercised when prescribing cetirizine to lactating women.

Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration.

## **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.

## **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 H<sub>1</sub>-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:

<b>Adverse reactions (WHO-ART)</b>	<b>Cetirizine 10 mg (n= 3260)</b>	<b>Placebo (n = 3061)</b>
<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:

<b>Adverse reactions (WHO-ART)</b>	<b>Cetirizine (n=1656)</b>	<b>Placebo (n =1294)</b>
<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%

**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  $\geq 1/1000$  to  $< 1/100$

Rare  $\geq 1/10000$  to  $< 1/1000$

Very rare  $< 1/10000$

Not known (cannot be estimated from the available data).

*Blood and lymphatic system 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, oculogyric crisis

*Ear and labyrinth disorders*

*Not known:* vertigo

*Cardiac disorders*

*Rare:* tachycardia

*Gastrointestinal disorders*

*Uncommon:* diarrhoea

*Hepatobiliary disorders*

*Rare:* hepatic function abnormal (transaminases increased, blood bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased)

*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, myalgia

*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 urticaria have been

reported (*see Section Warnings and Precautions*).

## **Overdosage**

### **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.

### **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**

#### **Pharmacotherapeutic group**

Antihistamines for systemic use, piperazine derivatives

#### **ATC Code**

R06AE07

### **Mechanism of Action and Pharmacodynamic effects**

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H<sub>1</sub>-receptors. *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H<sub>1</sub>-receptors.

*Ex vivo* experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H<sub>1</sub>-receptors.

In addition to its anti-H<sub>1</sub> 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 peak plasma concentration is approximately 300 ng/ml and is achieved within  $1.0 \pm 0.5$  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  $93 \pm 0.3\%$ . Cetirizine does not modify the protein binding of warfarin.

### **Metabolism and Elimination**

Cetirizine does not undergo extensive first pass metabolism. About two-thirds of the dose is excreted unchanged in 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 to 60 mg.

### **Special patient populations**

### **Children**

The half-life of cetirizine was about 6 hours in children of 6-12 years and 5 hours in children 2-6 years.

### **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.

### **Renal impairment**

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

### **Hepatic impairment**

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.

## **NON-CLINICAL INFORMATION**

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.

## **PHARMACEUTICAL INFORMATION**

### **Shelf-Life**

*Please refer to the packaging.*

### **Storage**

*Please refer to the packaging.*

### **Nature and Contents of Container**

*Box/ 1 bottle/ 75 ml.*

### **Incompatibilities**

There are no relevant data available.

### **Use and Handling**

There are no special requirements for use or handling of this product.

### **Manufactured by**

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