

Product Information

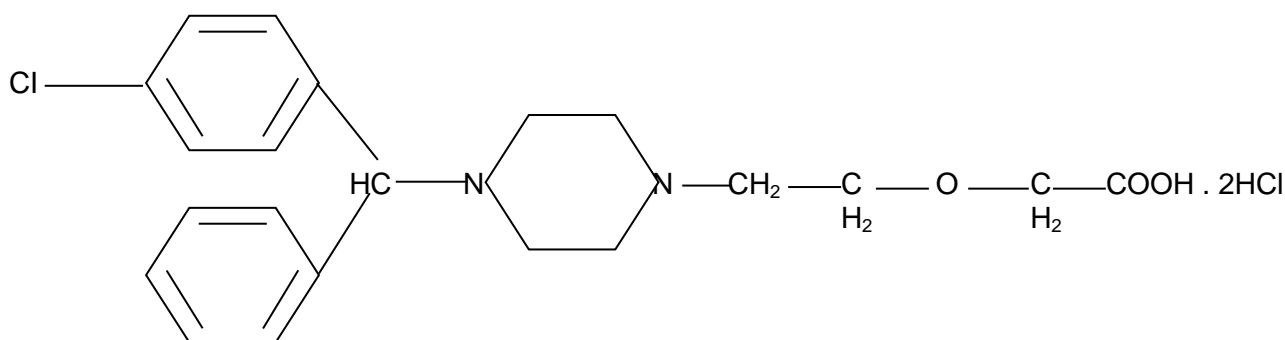
Zyrtec

NAME OF THE MEDICINE

Cetirizine hydrochloride

DESCRIPTION

Cetirizine hydrochloride is an orally active, H₁-receptor antagonist. Chemical name: 2-(2-(4-(4-chlorophenyl) phenylmethyl)-1-piperazinyl) ethoxy) acetic acid, dihydrochloride. The molecular weight is 461.8 and the chemical structure is shown below:



Cetirizine hydrochloride is a white, crystalline powder and is water-soluble (160 g/100 mL). It is formulated as white, film-coated, scored 10 mg tablets, oral liquid 1 mg/mL and oral drops 10 mg/mL.

PHARMACOLOGY

Mechanism of action: Cetirizine, a human metabolite of hydroxyzine, is an antiallergic compound; its principal effects are mediated via competitive occupancy of peripheral H₁-receptors.

In vitro receptor binding studies have shown no measurable affinity for receptors other than H₁-receptors.

CNS Effects: Autoradiographic studies with radiolabelled cetirizine in the rat have shown very low penetration of the brain. Sedation was observed in animal studies, but only at doses at least 1,000 times greater than those required for antagonism of histamine H₁-receptors. Studies in normal volunteers using objective measurements have, most of the time, shown no effect of cetirizine at the recommended dose of 10 mg on sleep latency time, cognitive function or motor performance. However, the occurrence of CNS effects has been observed in clinical trials in some patients (see Adverse Effects).

Studies using quantitative EEG recordings and various other tests of cognitive function confirmed that cetirizine does not cause CNS depression.

Pharmacodynamics: Studies in normal volunteers show that cetirizine at doses of 5 and 10 mg strongly inhibits the skin wheal and flare caused by the intradermal injection of histamine. The onset of activity corresponds with the occurrence of maximal plasma levels, and significant blockade persists for at least 24 hours after a single dose. The effects of intradermal injection of various other mediators or histamine releasers are also inhibited by cetirizine, as is cold-induced urticaria. The late phase recruitment of eosinophils, a component of the allergic inflammatory response, is inhibited by cetirizine following cutaneous antigen challenge.

Pharmacokinetics: Cetirizine is rapidly absorbed after oral administration. In adults, peak plasma levels after a 10 mg dose are approximately 300 ng/mL and occur at about one hour. Co-administration with food decreases the rate of absorption by 1.7 hour (lower C_{max} and greater T_{max}), but does not affect bioavailability as measured by the AUC. Plasma protein binding is 93%. The apparent volume of distribution is 0.45 L/kg, suggestive of significant extravascular distribution. The plasma elimination half-life in adults is approximately 8 hours and does not change with multiple dosing. Plasma levels are proportional to the dose administered over the range of 5 to 20 mg.

The bioavailability of cetirizine hydrochloride is similar from the different dosage forms of Zyrtec. The mean time taken to reach the peak serum cetirizine concentration (T_{max}) was 0.67 hour after a single 10 mg dose of the film coated tablets

In children, as with adults, cetirizine is eliminated mostly in the urine. Children over 6 years of age show peak plasma levels and times to peak similar to adults, with slightly more rapid elimination. Children younger than 6 years have more rapid clearance and a shorter half-life relative to adults. The half-life of cetirizine is approximately; 6 hours in children aged 6-12 years; 5 hours in children aged 2-6 years, and; 3 hours in infants and toddlers aged 6-24 months.

In contrast to other known antihistamines, cetirizine is less extensively metabolised, and approximately 2/3 of an administered dose is excreted unchanged in the urine. This results in high bioavailability with low inter- or intrasubject variation in blood levels. A study using 14-C-labelled cetirizine showed that most of the plasma radioactivity is associated with the parent compound. Only one metabolite has been identified in human plasma, the product of oxidative dealkylation of the terminal carboxymethyl group. The antihistaminic activity of this metabolite is negligible.

The total body clearance of cetirizine is reduced in subjects with renal dysfunction but below a creatinine clearance of about 30 to 50 mL/minute, little further change occurs. 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. Plasma levels of cetirizine are essentially unaffected by haemodialysis, and the plasma elimination half-life in dialysis patients is approximately 20 hours. The plasma AUC is increased about threefold in these patients. The clearance of cetirizine is reduced in elderly patients, but only in proportion to the decrease in creatinine clearance. Thus, in 16 patients with a mean age of 77 years, half-life increased to 12 hours. Cetirizine blood levels were monitored in a clinical trial of 59 patients, aged 60 to 82, who received 10 mg of cetirizine daily for three weeks, and no undue accumulation of cetirizine was found.

INDICATIONS

Seasonal allergic rhinitis: Cetirizine is indicated for the relief of symptoms associated with seasonal allergic rhinitis (hay fever) in adults and children aged 1-12 years. Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing and redness of the eyes.

Perennial allergic rhinitis: Cetirizine is indicated for the relief of symptoms associated with perennial allergic rhinitis in adults and children aged 1-12 years. Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Chronic idiopathic urticaria: Cetirizine is indicated for the treatment of the uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children aged 1-12 years. It significantly reduces the occurrence, severity and duration of hives and markedly reduces pruritus. As with other antihistamines, patients should be advised to seek medical advice about the possibility that their urticaria is associated with ingestion of certain foods.

CONTRAINDICATIONS

Zyrtec (cetirizine hydrochloride) is contraindicated:

- in patients with a known hypersensitivity to any of the ingredients of the Zyrtec formulations (see under PRESENTATION)
- in patients with a known hypersensitivity to hydroxyzine (the parent compound of cetirizine) or to any piperazine derivatives
- in patients with severe renal impairment (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 Zyrtec film-coated tablets.

Patients with rare hereditary problems of fructose intolerance should not take Zyrtec 1 mg/mL oral liquid.

PRECAUTIONS

Although it has been shown that cetirizine at the recommended dose of 10 mg does not potentiate the effect of alcohol, in sensitive patients, the simultaneous administration of cetirizine and alcohol or other CNS depressants may have effects on the CNS. Therefore, precaution is recommended if alcohol is taken concomitantly.

Activities requiring mental alertness: Some patients may experience a degree of drowsiness with cetirizine. Studies using objective measurements have shown no effect of cetirizine on cognitive function, motor performance or sleep latency. However, in clinical trials, the occurrence of CNS effects has been observed in some individual patients and due caution should be exercised when driving a car or operating potentially dangerous machinery.

In sensitive patients, concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

Patients with risk of urinary retention: Caution should be taken in patients with predisposing factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.

Patients with epilepsy: CNS stimulation may occur with antihistamines, especially in children. Therefore caution is recommended when treating patients suffering from epilepsy or patients at risk of convulsions.

Carcinogenic and mutagenic potential: Carcinogenicity studies over 24 months showed increased incidences of benign liver tumours in male mice (at the maximum dose of 16 mg/kg/day), but not in female mice or in rats. These benign tumours in mice are commonly found with compounds which cause liver enzyme induction. Since cetirizine does not induce liver enzymes in non-rodents and humans, this may be considered to be a species specific phenomenon. Cetirizine was devoid of mutagenic activity in a series of *in vitro* and *in vivo* assays.

Allergy skin tests are inhibited by antihistamines. Wash-out periods vary in individuals due to different rates of metabolism and different antihistamines. For cetirizine, a wash-out period of at least four days is generally recommended before performing the allergy skin tests.

Use in pregnancy: Category B2: Reproduction studies in mice, rats and rabbits failed to show evidence of teratogenicity using doses up to 96, 225, and up to 135 mg/kg/day respectively. However, the short half-life of cetirizine in these species suggests that fetal exposure may have been inadequate. In mice, post-natal development was inhibited after 96 mg/kg/day. Clinical data for cetirizine or other compounds of the class are inadequate to establish safety in pregnancy. Until such data are available, cetirizine should be used in pregnancy only if the expected benefits clearly outweigh potential risks to mother and fetus.

Use in lactation: Studies in beagle dogs indicate that approximately 3% of the dose is excreted in milk. Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration. Use of cetirizine in breastfeeding mothers is not recommended.

Use in Children: The use of the tablets is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation.

The oral liquid is not recommended in children aged less than 2 years as the amount of sorbitol (1.6 g/5 mL) in the formulation may cause diarrhoea in children under 2 years.

The oral drops should not be used in children aged less than 1 year.

Use in the Elderly: Cetirizine is well tolerated by patients 65 years of age and over. Clearance of cetirizine is reduced in proportion to creatinine clearance. In patients whose creatinine clearance is reduced (i.e. those with moderate renal impairment), a dose of 5 mg/day is recommended.

INTERACTIONS WITH OTHER MEDICINES

Studies with cetirizine demonstrated that there were no clinically relevant adverse interactions with pseudoephedrine, antipyrine, cimetidine, ketoconazole, erythromycin, azithromycin, glipizide and diazepam. A small decrease in the clearance of cetirizine (16%) was observed in a multiple dose study with theophylline (400 mg once a day); while the disposition of theophylline was not altered by concomitant cetirizine administration. 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.

ADVERSE EFFECTS

The more commonly observed untoward reactions reported during cetirizine administration and not associated with an equivalent incidence among placebo-treated patients are somnolence, dry mouth and fatigue.

The table below shows adverse events occurring with an incidence of greater than 1% after intake of cetirizine 5 to 20 mg cetirizine a day. It pools data obtained from American and European clinical studies (including open studies with access to rescue drug) in urticaria, perennial and seasonal rhinitis. The incidence of somnolence associated with Zyrtec was 14.3% (7.6% under placebo) and was predominantly mild to moderate in severity. After pooling the same studies in the three registered indications, sedation is reported more in the patients suffering from seasonal allergic rhinitis, than in the patients suffering from perennial allergic rhinitis and urticaria.

Adverse experience by WHO grouping	Number of Patients (%)	
	Cetirizine (n = 2,487)	Placebo (n = 1,577)
Somnolence	356 (14.3%)	120 (7.6%)
Headache	272 (10.2%)	177 (11.2%)
Dry mouth	122 (5.0%)	29 (1.8%)
Fatigue	85 (3.4%)	26 (1.6%)
Nausea	51 (2.1%)	48 (3.0%)
Dizziness	49 (2.0%)	26 (1.6%)
Pharyngitis	34 (1.4%)	15 (1.8%)
Insomnia	29 (1.2%)	17 (1.1%)
Dyspepsia	21 (0.8%)	23 (1.5%)
Pruritus	5 (0.2%)	16 (1.0%)

Assessment of severity of sedation in clinical trials indicates the mild nature of sedation associated with cetirizine.

The following events were observed infrequently (less than 1/100), but more than once, in 2,487 patients who received cetirizine in all US and European trials, a causal relationship with cetirizine administration has not been established. Events are listed in order of decreasing frequency within a given body system.

Autonomic nervous system. Increased appetite, anorexia, flushing, increased sweating.

Cardiovascular. Palpitations/tachycardia.

ENT. Earache, epistaxis, altered sense of taste, tinnitus, tongue disorder.

Vision. Eye abnormality, periorbital oedema, abnormal vision, eye pain, conjunctivitis.

Gastrointestinal. Abdominal pain, diarrhoea, vomiting, constipation, flatulence.

Genitourinary. Polyuria, urinary retention, urinary tract infection.

Musculoskeletal. Back pain, myalgia, arthralgia, bone disorder (fracture), leg cramps.

Neurologic. Nervousness, impaired concentration, confusion, paraesthesia, asthenia, hypertonia, tremor.

Respiratory System. Respiratory disorder, coughing, bronchospasm, upper respiratory tract infection, dyspnoea.

Miscellaneous. Weight increase (see comment below), fever, oedema, chest pain, pain, rigors, dysmenorrhoea, thirst, decreased libido.

Weight gain was reported as an adverse effect in 0.4% of cetirizine patients in placebo-controlled trials. In an open study of six months' duration, the mean gain in weight was 2.8% after 20 weeks, with no further increase at 26 weeks. This effect has been reported for other antihistamines.

Occasional instances of reversible liver function test (transaminase) elevations have occurred during cetirizine therapy, without evidence of jaundice, hepatitis or other clinical findings.

Adverse events at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled trials are:

Adverse events (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 system disorders</i> Rhinitis	1.4 %	1.1 %
<i>Body as a whole – general disorders</i> Fatigue	1.0 %	0.3 %

Methyl hydroxybenzoate and propyl hydroxybenzoate, included in the oral liquid and oral drops, may cause allergic reactions (possibly delayed).

Post Marketing Experience: In addition to the adverse events 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.

Experiences are defined as follows: 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

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

Renal and urinary disorders:

Very rare: dysuria, enuresis

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash

Rare: urticaria

Very rare: angioneurotic oedema, fixed drug eruption

General disorders and administration site conditions:

Uncommon: asthenia, malaise

Rare: oedema

Immune system disorders:

Rare: hypersensitivity

Very rare: anaphylactic shock

Hepatobiliary disorders:

Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ -GT and bilirubin)

Psychiatric disorders:

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tic

Not known: suicidal ideation

Cardiac disorders:

Rare: tachycardia

Gastro-intestinal disorders:

Uncommon: diarrhoea

Investigations:

Rare: weight increased

The following clinically significant adverse events have been reported: cholestasis, glomerulonephritis, haemolytic anaemia, hepatitis, severe hypotension and stillbirth. Data are insufficient to support an estimate of their incidence in the population to be treated.

DOSAGE AND ADMINISTRATION

Zyrtec Tablets

The use of Zyrtec tablets is not recommended in children less than 6 years since this formulation does not allow for appropriate dose adaptation.

Children 6 - 12 years: The recommended dose is 5 mg (half a tablet) twice daily with or without food.

Adults and children over 12 years: The recommended dose is 10 mg (one tablet) once a day, with or without food.

The time of administration may be varied to suit individual patient needs.

Zyrtec Oral Liquid

The use of Zyrtec Oral Liquid is not recommended in children aged less than 2 years as the amount of sorbitol (1.6 g/5 mL) in the formulation may cause diarrhoea in children under 2 years.

Children 2 - 12 years: The recommended dose is to be taken twice daily with or without food and should be calculated on the basis of body weight according to the following scale:

Zyrtec Oral Liquid (for use in children 2 years old and above)

Body weight (kg)	8-14	14-18	18-22	22-26	26-30	Over 30
mL of Oral Liquid	2.0	2.5	3.0	3.5	4.0	5.0

Adults and children over 12 years: The recommended dose is 10 mg (10 mL) once a day, with or without food.

Zyrtec Oral Drops

The oral drops should not be used in children aged less than 1 year.

Children from 1 year of age and over: The recommended dose is to be taken twice daily with or without food and should be calculated on the basis of body weight according to the following scale:

Zyrtec Oral Drops (for use in children 1 year and above)

Body weight (kg)	Up to 14	14-18	18-22	22-26	26-30	Over 30
No. drops of Oral Drops	4	5	6	7	8	10

Adults and children over 12 years: The recommended dose is 10 mg (20 drops) once a day, with or without food.

Use in the elderly

There are no data to suggest that elderly who have normal renal function require a lower dose. However, as advancing age may be associated with declining renal function, dosage may need to be reduced in the elderly if creatinine clearance is reduced.

Renal impairment

Cetirizine clearance is reduced in patients with renal impairment. In patients with renal insufficiency, dosage should be reduced to half the usual recommended dose. Zyrtec is contraindicated in patients with severe renal impairment (less than 10 mL/min creatinine clearance) (see under CONTRAINDICATIONS)

OVERDOSAGE

Symptoms observed after an overdose of cetirizine are mainly associated with CNS 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.

Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless an agent which is removed by dialysis has been concomitantly ingested

For further information, advice may be sought from the Poisons Information Centre (telephone 13 11 26).

PRESENTATION AND STORAGE CONDITIONS

Zyrtec® tablets: white, film-coated, oblong tablets, scored on one face and embossed Y-Y, containing 10 mg cetirizine hydrochloride.

Zyrtec® oral liquid: is a clear, colourless, banana flavoured liquid containing 1 mg/mL cetirizine hydrochloride.

Zyrtec® oral drops: is a clear, colourless liquid with a slightly bitter-sweet taste which contains 10 mg/mL (2.5 mg/ 5 drops) cetirizine hydrochloride.

Zyrtec® tablets contain microcrystalline cellulose, lactose, colloidal anhydrous silica, magnesium stearate, and Opadry white Y-1-7000.

Zyrtec® oral liquid contains sorbitol, glycerol, propylene glycol, saccharin sodium, methyl hydroxybenzoate, propyl hydroxybenzoate, banana flavour, sodium acetate, acetic acid and purified water.

Zyrtec® oral drops contain glycerol, propylene glycol, saccharin sodium, methyl hydroxybenzoate and propyl hydroxybenzoate, sodium acetate, acetic acid and purified water.

Tablets:	Shelf life 4 years
Oral liquid and drops:	Shelf life 3 years
Tablets, liquid & drops:	Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Johnson & Johnson Pacific Pty Ltd
45 Jones Street
Ultimo, NSW, 2007
Australia

POISON SCHEDULE OF THE MEDICINE

S2

Date of first inclusion in the Australian Register of Therapeutic Goods: 28th August 1997

Date of most recent amendment: 3rd April 2014