Product Information

Zyrtec

NAME OF THE DRUG
Cetirizine hydrochloride

DESCRIPTION
Cetirizine hydrochloride is an orally active, $H_1$-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:

![Chemical Structure](image)

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, white to off-white oro-dispersible 10 mg tablets (Fastmelts), oral solution 1mg/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 $H_1$-receptors. Cetirizine is distinguished from other antihistamines by the presence of a carboxylic acid function. This difference may be partly responsible for the selectivity of cetirizine seen in pharmacological models and its distinctive pharmacokinetic properties in man. Thus, while the activity of cetirizine as an antihistamine is comparable to other agents, in vivo animal models have shown negligible anticholinergic or antiserotonergic activity.

In vitro receptor binding studies have shown no measurable affinity for receptors other than $H_1$-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 $H_1$-receptors. Studies in normal volunteers using objective measurements, such as sleep latency time, mental alertness and simulated driving performance, showed that cetirizine at doses up to 20 mg induced minimal CNS-depressant 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 to 20 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 slows absorption (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 recommended range of 5 to 20 mg.

The bioavailability of cetirizine hydrochloride is similar from the different dosage forms of Zyrtec. Administration of a single dose of Zyrtec film coated tablets 10 mg or Zyrtec Fastmelts 10 mg resulted in comparable values for AUC, C_{max} and elimination half-life. The mean time taken to reach the peak serum cetirizine concentration (t_{max}) was 1.01 hour for the Fastmelts and 0.67 hour for 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; 7 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 60% 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. 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), or to the parent compound of cetirizine, hydroxyzine, or in patients with severe renal impairment (less than 10 mL/min creatinine clearance).

PRECAUTIONS

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.

Patients with Epilepsy: CNS stimulation may occur with antihistamines, especially in children. Therefore caution is recommended when treating patients suffering from epilepsy.

Carcinogenesis and mutagenesis: 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.

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. The extent of excretion in human milk is unknown. Use of cetirizine in breastfeeding mothers is not recommended.

Use in Children: Cetirizine is not recommended for use in children under 12 months of age.

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 starting dose of 5 mg/day is recommended.

ADVERSE REACTIONS

The more commonly observed untoward events 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 all the 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.
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.
**Post Marketing Experience:** The following additional rare, but potentially severe adverse events have been reported: anaphylaxis, cholestasis, glomerulonephritis, haemolytic anaemia, hepatitis, orofacial dyskinesia, severe hypotension, stillbirth, thrombocytopenia, aggressive reaction and convulsions.

**DOSAGE AND ADMINISTRATION**

Zyrtec Fastmelts are not suitable for children under 12 years of age or those requiring a dose lower than 10 mg. One Zyrtec Fastmelt tablet should be placed on the tongue and allowed to dissolve. Do not chew or place tablet under the tongue.

**Children:**

6 years of age and over: The recommended daily dose is 10 mg, given as 5 mg twice daily with or without food.

1-6 years of age: 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:

<table>
<thead>
<tr>
<th>Body weight kg</th>
<th>Up to 14</th>
<th>14-18</th>
<th>18-22</th>
<th>22-26</th>
<th>26-30</th>
<th>Over 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>mL of Oral Solution</td>
<td>2.0</td>
<td>2.5</td>
<td>3.0</td>
<td>3.5</td>
<td>4.0</td>
<td>5.0</td>
</tr>
<tr>
<td>No. drops of Oral Drops</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

**Adults:** The recommended initial dose of cetirizine is 10 mg, given as a single dose, with or without food. The time of administration may be varied to suit individual patient needs. If sufficient response is not obtained, the dose may be increased as necessary to the maximum recommended daily dose of 20 mg.

**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.

**OVERDOSAGE**

Overdoses of 150 mg – 300 mg cetirizine have been reported in adults. Symptoms included somnolence and pruritus with no abnormal cardiac function. One subject suffered urinary retention requiring catheterisation after a 150 mg dose. Overdose in children has also been reported. A single report of 180 mg in an 18 month old child resulted in restlessness followed by drowsiness with no other abnormalities. All patients available to follow up recovered without sequelae. Should it 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.
PRESENTATION

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

Zyrtec® Fastmelts (oro-dispersible tablets): white to off-white, plain round tablets, containing 10 mg cetirizine hydrochloride.

Zyrtec® oral solution: 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, titanium dioxide, macrogol 400 and talc.

Zyrtec® Fastmelts (oro-dispersible tablets) contain betadex, microcrystalline cellulose, lemon flavour, acesulfame potassium, colloidal anhydrous silica and magnesium stearate.

Zyrtec® oral solution 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 solution and drops: Shelf life 3 years
Fastmelts: Shelf life 3 years
Tablets, solution & drops Store below 30°C.

NAME AND ADDRESS OF SPONSOR

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Date of TGA Approval: 7 March 2006.