

RAZENE

Cetirizine Hydrochloride 10 mg Tablets

Presentation

White, capsule shaped, coated tablets marked **CZ** breakline **10** on one side and **G** on the reverse. Each tablet contains 10 mg cetirizine hydrochloride.

Uses

Actions

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.

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 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, 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.

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 intra-subject 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

Cetirizine is indicated for the relief of symptoms associated with seasonal allergic rhinitis (hay fever) and perennial allergic rhinitis. Symptoms treated effectively include sneezing, rhinorrhea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.

Cetirizine is also indicated for the treatment of:

- allergic conjunctivitis;
- insect bites and
- the uncomplicated skin manifestations of chronic idiopathic urticaria. It significantly reduces the occurrence, severity and duration of hives and markedly reduces pruritus.

Dosage and Administration

ADULTS

The recommended initial dose of cetirizine is 5 to 10 mg depending on symptom severity, given as a single daily 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 to the maximum recommended daily dose of 20 mg.

Recommended starting dose for patients with renal impairment is 5 mg.

USE IN ELDERLY

Reduce the dose in cases of renal insufficiency only when total cetirizine clearance is reduced, but only proportionally to the decrease in creatinine clearance.

CHILDREN AGED 6-12 YEARS

Same dose as for adults given as a single or divided dose.

CHILDREN AGED 1-6 YEARS

The recommended dose of cetirizine is 5 mg (half a tablet) once daily.

Contraindications

Cetirizine hydrochloride is contraindicated in patients with a known hypersensitivity to any of the ingredients in the formulation (see under FURTHER INFORMATION), or to the parent compound of cetirizine, hydroxyzine, or in patients with severe renal impairment (less than 10 mL/min creatinine clearance).

Warnings and 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 foetal 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 foetus.

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 Effects

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 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 cetirizine 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 = 2487)	Placebo (n = 1577)
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.

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.

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.

Pharmaceutical Precautions

Store below 25°C. Protect from light.

Medicine Classification

Pharmacy Only Medicine.

Package Quantities

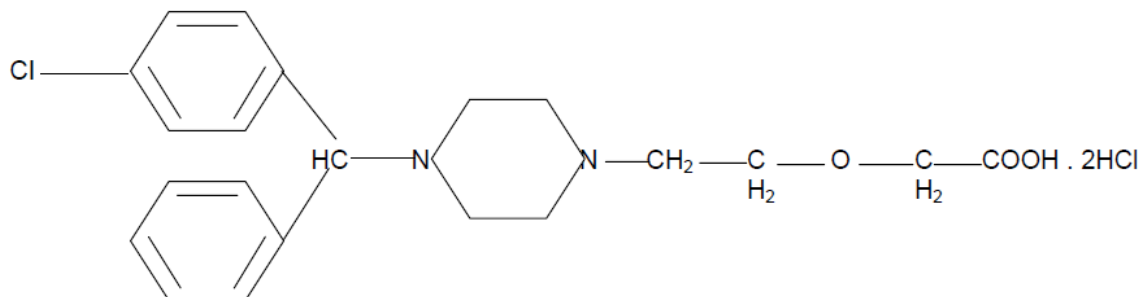
Blister packs containing 10, 30, 50, 90 or 100 tablets.

Bottles containing 30, 100 or 250 tablets.

Not all pack sizes may be marketed.

Further Information

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).

Excipients

Each Razene tablet also contains lactose, pregelatinised maize starch, povidone, magnesium stearate, talc, opadry white, hydroxypropylmethyl cellulose, titanium dioxide and polyethylene glycol.

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