AUSTRALIAN PRODUCT INFORMATION

ALZENE®

(cetirizine hydrochloride) tablets

1 NAME OF THE MEDICINE

Cetirizine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ALZENE tablet contains 10 mg of cetirizine hydrochloride as the active ingredient.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

ALZENE 10 mg tablets: white, capsule-shaped, film-coated tablet, approximately 8.5 mm by 4 mm, marked "CZ" breakline "10" on one side and 'G' on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

In adults and children aged 6 years and over, cetirizine is indicated for the relief of symptoms associated with:

- Seasonal allergic rhinitis (hayfever). Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing and redness of the eyes.
- Perennial allergic rhinitis. Symptoms treated effectively include sneezing, rhinorrhoea, post-nasal discharge, nasal pruritus, ocular pruritus and tearing.
- The uncomplicated skin manifestations of chronic idiopathic urticaria. 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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Adults and children over 12 years of age.

The recommended initial dose of cetirizine is 10 mg (one tablet) daily, 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.

Children 6 to 12 years of age.

The recommended daily dose is 5 mg (half a tablet), given twice daily 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. (See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in the Elderly).

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. (See Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in the Elderly).

4.3 CONTRAINDICATIONS

- Known hypersensitivity to cetirizine, or to its parent compound, hydroxyzine
- Known hypersensitivity to any of the excipients in ALZENE tablets
- Patients with severe renal impairment (less than 10 mL/min creatinine clearance)

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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.

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. (See Section 4.2 – DOSE AND METHOD OF ADMINISTRATION).

Paediatric Use

No data available.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No data available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B2

Reproduction studies in mice, rats and rabbits failed to show evidence of teratogenicity using doses up to 96 mg, 225 mg, and 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.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 per day. It pools all the American and European clinical studies (including open studies with access to rescue drug) conducted up to 1997 in urticaria, perennial and seasonal rhinitis. The sedation rate is equal to 14.3% (7.6% under placebo). 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.

Ear, nose and throat. 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.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms.

Overdoses of 150 mg to 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 and 18 month old child resulted in restlessness followed by drowsiness with no other abnormalities. All patients available to follow up recovered without sequelae.

Treatment.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Cetirizine hydrochloride is an orally active, H_1-receptor antagonist.

Mechanism of Action

Cetirizine, a human metabolite of hydroxyzine, is an anti-allergic 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 antiserotoninergic 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.

Clinical Trials

No data available.

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 significantly 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Cetirizine is rapidly absorbed after oral administration. In adults, peak plasma levels reported after a10 mg dose of ALZENE ranged from 205 to 427 nanogram/mL (mean 329 nanogram/mL), occuring at about 1 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%.

Distribution

The apparent volume of distribution is 0.45 L/kg, suggestive of significant extravascular distribution. The plasma elimination half-life in adults is approximately 7 hours (range 5 to 10 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.

Metabolism

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.

Excretion

In children, as with adults, cetirizine is eliminated mostly in the urine. Children over 6 yr of age show peak plasma levels and times to peak similar to adults, with slightly more rapid elimination (half life about 6 to9 hours). Younger children have more rapid clearance with half life approximately 5 hours.

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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cetirizine was devoid of mutagenic activity in a series of *in vitro* and *in vivo* assays.

Carcinogenicity

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.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets also contain lactose, pregelatinised maize starch, povidone, magnesium stearate, Opadry White Y-1-7000 E171 (ARTG PI No. 2731).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: PVC/PVDC/Al blister pack.

Pack sizes: blister packs of 10, 30, 50, 70, 90 and 100 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 116582 - ALZENE cetirizine hydrochloride 10 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

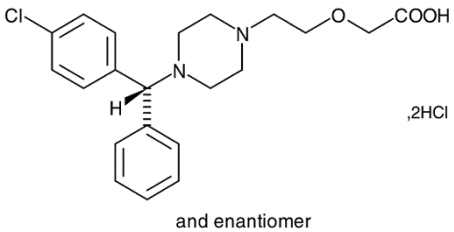
6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Cetirizine hydrochloride is a white to almost white, crystalline powder and is water soluble (160 g/100 mL).

Chemical name: (*RS*)-2-[2-[4-[(4-chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid hydrochloride.

Structural formula:



and enantiomer

Molecular formula: $C_{21}H_{25}ClN_2O_3.2HCl$ Molecular weight: 461.8

CAS Number

83881-52-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

S2 (Pharmacy Medicine)

8 SPONSOR

Alphapharm Pty Ltd trading as Viatris

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Millers Point NSW 2000

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9 DATE OF FIRST APPROVAL

15/02/2005

10 DATE OF REVISION

11/09/2024

Summary Table of Changes

Section Changed	Summary of New Information
All	Minor editorial changes
2, 6.1	Minor editorial change to update to excipient details
6.5	Added AUST R details
8	Updated Sponsor details

ALZENE® is a Viatris company trade mark

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