NEW ZEALAND DATA SHEET

RAZENE

1. Product Name

Razene, 10 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 10 mg of cetirizine hydrochloride.

Razene tablets contain lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

White, capsule shaped, film coated tablets marked CZ break line 10 on one side and G on the reverse.

The tablet can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic 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.

4.2 Dose and method of administration

Dose

Adults

The recommended initial dose of cetirizine is 5 to 10 mg depending on symptom severity, given as a single daily dose with a glass of liquid. 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.

Special populations

Elderly

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

Renal impairment

The dosing intervals must be individualised according to renal function. Refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is needed. The CLcr (mL/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - age(years)]\, x\, weight\,(kg)}{72\, x\, serum\, creatinine\,(mg\,/\,dl)} (x\, 0.85\ for\ women)$$

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine clearance (mL/min)	Dosage and frequency
Normal	≥ 80	10 mg once daily
Mild	50-79	10 mg once daily
Moderate	30-49	5 mg once daily
Severe	<30	5 mg once every 2 days
End-stage renal disease – patients undergoing dialysis	<10	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 of the patient and body weight.

Hepatic impairment

No dose adjustment is needed in patients with solely hepatic impairment.

Children aged 6-12 years

10 mg once daily.

A 5 mg starting dose (half a tablet) may be proposed if this leads to satisfactory control of the symptoms.

Children aged 2-6 years

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

4.3 Contraindications

Hypersensitivity to cetirizine hydrochloride or to any of the excipients listed in section 6.1.

Hypersensitivity to the parent compound of cetirizine, hydroxyzine or to any piperazine derivatives.

Patients with end stage renal impairment (less than 10 mL/min creatinine clearance).

4.4 Special warnings and precautions for use

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.

Patients at risk of convulsions

Caution in epileptic patients and patients at risk of convulsions is recommended.

Rebound pruritus

Pruritus and/or urticarial may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

Use in children

Cetirizine is not recommended for use in children under 2 years of age.

4.5 Interaction with other medicines and other forms of interaction

Lack of interaction

- Pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, cimetidine, ketoconazole, erythromycin, and azithromycin; no pharmacokinetic interactions were observed.

- In a multiple dose study of theophylline (400 mg once a day) and cetirizine, there was a small (16%) decrease in clearance of cetirizine, while the disposition of theophylline was not altered by concomitant cetirizine administration.

- Studies with cetirizine and cimetidine, glipizide, diazepam, and pseudoephedrine have revealed no evidence of adverse pharmacodynamic interactions.

- Studies with cetirizine and azithromycin, erythromycin, ketoconazole, theophylline, antipyrine, and pseudoephedrine have revealed no evidence of adverse clinical interactions.

- In particular, concomitant administration of cetirizine with macrolides or ketoconazole has never resulted in clinically relevant ECG changes.

Ritonavir

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.

Food

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased by 1 hour.

Allergy skin test

Allergy skin tests are inhibited by antihistamines and a wash-out period of 3 days is recommended before performing them.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2. Caution should be exercised in pregnant women.

For cetirizine, very rare clinical data on exposed pregnancies are available.

Breast-feeding

Caution should be exercised in lactating women.

Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration.

Fertility

No data available. For pre-clinical fertility data refer to section 5.3.

4.7 Effects on ability to drive and use machines

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.

Patients intending to drive, engage in potentially hazardous activities or operate machinery should not exceed the recommended dose and should take their response to the medicinal product into account.

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

4.8 Undesirable effects

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_1-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 drug.

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:

Adverse reactions: (WHO-ART)	**Cetirizine (n=3260)**	**Placebo (n=3061)**
Body as a whole- general disorders:		
Fatigue	1.63%	0.95%
Central and peripheral nervous systems disorders:		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastro-intestinal system disorders:		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
Psychiatric disorders:		
Somnolence	9.63%	5.00%
Respiratory disorders:		
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.

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

Adverse reactions (WHO-ART)	**Cetirizine (n=1656)**	**Placebo (n=1294)**
Gastro-intestinal system disorders: Diarrhoea	1.0%	0.6%
Psychiatric disorders: Somnolence	1.8%	1.4%
Respiratory system disorders: Rhinitis	1.4%	1.1%
Body as a whole- general disorders: Fatigue	1.0%	0.3%

Post marketing experience

Adverse reactions are ranked under headings of frequency using the following convention:
Very common ≥ 1/10
Common ≥ 1/100 to <1/10
Uncommon ≥ 1/1000 to <1/100
Rare ≥ 1/10000 to <1/1000
Very Rare <1/10000
Not known (cannot be estimated from the available data).

Body system	**Undesirable effect**	**Frequency**
Blood and lymphatic system disorders	Thrombocytopenia	Very rare
Immune system disorders	Hypersensitivity Anaphylactic shock	Rare Very rare
Psychiatric disorders	Agitation Aggression, confusion, depression, hallucination, insomnia Tic	Uncommon Rare Very rare
Nervous system disorder	Paraesthesia Convulsions Dysgeusia, dyskinesia, dystonia, syncope, tremor Amnesia, memory impairment	Uncommon Rare Very rare Not known
Eye disorder	Accommodation disorder, blurred vision, oculogyration	Very rare
Cardiac disorder	Tachycardia	Rare
Gastrointestinal disorders	Diarrhoea	Uncommon

Hepatobilary disorder	Hepatic function abnormal, transaminases increased, blood bilirubin increased, blood alkaline phosphatase increased, Gamma-glutamyltransferase increased	Rare
Skin and subcutaneous tissue disorders	Pruritis, rash Urticaria Angioedema, drug eruption	Uncommon Rare Very rare
Renal and urinary disorders	Dysuria, enuresis	Very rare
General disorders and administration site conditions	Asthenia, malaise Oedema	Uncommon Rare
Investigations	Weight gain	Rare

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

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 five 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, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. 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 advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihistamines for systemic use, ATC code: R06AE07

Mechanism of action

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1-receptors. *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H_1-receptors.

Ex vivo experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H_1-receptors.

In addition to its anti-H_1 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 urticarial 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.

Onset and duration of action

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. 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 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.

5.2 Pharmacokinetic properties

Absorption

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased. No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. The steady state maximum plasma concentration is approximately 300 ng/mL and is achieved within 1.0 ± 0.5 h.

Distribution

Plasma protein binding is 93 ± 0.3%. The apparent volume of distribution is 0.50 L/kg. The distribution of pharmacokinetic parameters as peak level and area under curve, is unimodal in human volunteers and no differences were observed in the kinetics of cetirizine between white and black adult males.

Biotransformation

Cetirizine does not undergo extensive first pass metabolism.

Elimination

The terminal half-life is approximately 10 hours. About two third of the dose are excreted unchanged in urine.

Linearity/non-linearity

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Special populations

Children

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

Elderly

Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects compared to the normal 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 normal volunteers. Moderately renally impaired patients had a 3-fold incease in half-life and 70% decrease in clearance compared to normal 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 normal. 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.

5.3 Preclinical safety data

Non-clinical data reveals no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction.

Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

6. Pharmaceutical Particulars

6.1 List of excipients

Each Razene tablet also contains lactose, pregelatinised maize starch, povidone and magnesium stearate.

The film coat contains hydroxypropylmethyl cellulose, titanium dioxide and macrogol.

Razene tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

This medicine is gluten free.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Clear blister: 3 years.

Bottle, or green blister: 2 years.

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

Al/PVC/PVdC blister packs containing 10, 30, 50, 90 or 100 film coated tablets.

PP bottle with LDPE cap containing 30, 100 or 250 film coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal

Not applicable.

7. Medicines Schedule

Pharmacy Only Medicine.

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 09-579-2792

9. Date of First Approval

4 October 2001

10. Date of Revision of the Text

24 April 2018	Revise to SmPC format.
	Section 4.4 – Added information regarding rebound pruritus.