

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Zista, 10 mg, tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10 mg cetirizine hydrochloride.

Excipient with known effect: lactose monohydrate

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off white capsule shaped film coated tablets with breakline on one side and '10' embossed on the other side.

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

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.

Paediatric population

Children aged 6-12 years

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

Children aged 2-6 years

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

Special populations

Use in 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 (CL_{cr}) in mL/min is needed. The CL_{cr} (mL/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

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.

4.3 Contraindications

Cetirizine hydrochloride is contraindicated in:

- patients with a history of hypersensitivity to any of the constituents of the formulation, to hydroxyzine or to any piperazine derivatives
- patients with end stage renal impairment at 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.

Urinary retention

Caution should be taken in patients with predisposition factors of urinary retention (eg. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.

Patients at risk of convulsions

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

Rebound pruritus

Pruritus and/or urticaria 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.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic Interactions

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

Use in pregnancy (Category B2)

Caution should be exercised in pregnant women.

For cetirizine, very rare clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Use in lactation

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.

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, engaging in potentially hazardous activities or operating 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 antidepressants 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 H1-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 event (WHO-ART)	Cetirizine 10 mg (n= 3260)	Placebo (n = 3061)
Body as a whole – general disorders: Fatigue	1.63 %	0.95 %
Central and peripheral nervous system disorders: Dizziness Headache	1.10 % 7.42 %	0.98 % 8.07 %
Gastrointestinal system disorders: Abdominal pain Dry mouth Nausea	0.98 % 2.09 % 1.07 %	1.08 % 0.82 % 1.14 %
Psychiatric disorders: Somnolence	9.63 %	5.00 %
Respiratory system 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 drug reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled clinical or pharmacoclinical trials are:

Adverse drug reactions (WHO-ART)	Cetirizine (n=1656)	Placebo (n =1294)
Gastrointestinal 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 %
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Post-marketing experience

In addition to the adverse effects reported during clinical studies and listed above, isolated cases of the following adverse drug reactions 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.

Frequencies 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

Immune system disorders:

Rare: hypersensitivity

Very rare: anaphylactic shock

Metabolism and nutrition disorders:

Not known: increased appetite

Psychiatric disorders:

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tics

Not known: suicidal ideation

Nervous system disorders:

Uncommon: paraesthesia

Rare: convulsions

Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia

Not known: amnesia, memory impairment

Eye disorders:

Very rare: accommodation disorder, blurred vision, oculogyration

Cardiac disorders:

Rare: tachycardia

Gastrointestinal disorders:

Uncommon: diarrhoea

Hepatobiliary disorders:

Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, gamma-glutamyltransferase and bilirubin)

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash

Rare: urticaria

Very rare: angioneurotic oedema, drug eruption

Not known: acute generalized exanthematous pustulosis (AGEP)

Renal and urinary disorders:

Very rare: dysuria, enuresis

Not known: urinary retention

General disorders and administration site conditions:

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight increased

Description of selected adverse reactions:

After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported.

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 5 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, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence.

Cetirizine is not effectively removed by dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamine for systemic use, piperazine derivatives, ATC code: R06A E07

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H₁-receptors. In vitro receptor binding studies have shown no measurable affinity for other than H₁-receptors.

Ex vivo experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral H₁-receptors.

In addition to its anti-H₁ 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 urticaria 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.

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

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg. The terminal half-life is approximately 10 hours and the apparent volume of distribution is 0.50 l/kg.

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.

Plasma protein binding of cetirizine is 93±0.3%.

Cetirizine does not modify the protein binding of warfarin.

Cetirizine does not undergo extensive first pass metabolism. About two thirds of the dose are excreted unchanged in the urine.

The distribution of pharmacokinetic parameters as peak level and area under curve, is unimodal in human volunteer and no differences were observed in the kinetics of cetirizine between white and black adult males. The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased. The extent of bioavailability is similar when cetirizine is given as solutions, capsules or tablets.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, lactose monohydrate, pregelatinised starch, purified talc, Magnesium stearate. The film coating contains hypromellose, purified talc, titanium dioxide (E171), macrogol 6000.

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

PVC/Aluminium foil blister strips. Pack size of 10, 30 and 100 tablets.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MEDICINE SCHEDULE

Pharmacy Only Medicine

8. SPONSOR

Teva Pharma (New Zealand) Limited

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9. DATE OF FIRST APPROVAL

15 May 2014

10. DATE OF REVISION OF THE TEXT

5 June 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
4.4	Additional information on urinary retention and rebound pruritus.
4.8, 4.9	Additional safety information.