New Zealand Data Sheet

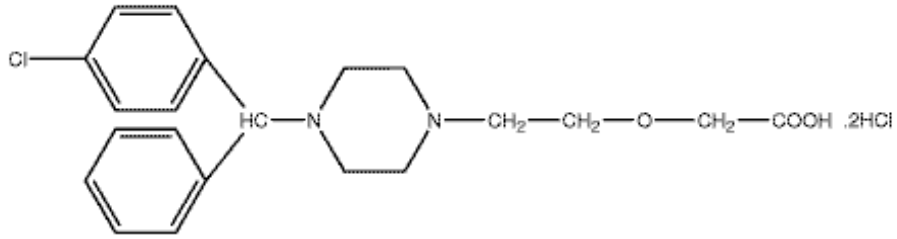
1 PRODUCT NAME

Cetirizine Hydrochloride (BP) 10mg Film Coated Tablets
Cetirizine Hydrochloride (BP) 1 mg/mL Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Cetirizine Hydrochloride 10 mg
Cetirizine Hydrochloride 1 mg/mL

CAS: 83881-51-0



Cetirizine hydrochloride

The molecular weight is 461.8
Cetirizine hydrochloride is an orally active, H1-receptor antagonist.

Chemical name: 2-(2-(4-(4-chlorophenyl) phenylmethyl)-1-piperazinyl) ethoxy) acetic acid hydrochloride.
Cetirizine hydrochloride is a white, crystalline powder and is water-soluble (160 g/100 mL).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets: White to off-white capsule-shaped tablet, debossed on one face embossed with "Y" on each side of the break line and blank on the other face.

Oral solution: Clear, colourless liquid with a slight sweet taste and banana flavour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the relief of:

- Nasal and ocular symptoms of seasonal and perennial allergic rhinitis
- Symptoms of urticaria and insect bites

4.2 Dose and method of administration

The tablets need to be swallowed with a glass of liquid. The solution can be swallowed as such.

For oral use

Adults

10mg once daily (1 tablet or 10mL oral solution).

A 5mg starting dose (1 half tablet or 5mL oral solution) may be proposed if this leads to satisfactory control of the symptoms.

If sufficient response is not obtained, the dose may be increased to the maximum recommended dose of 20mg

Children

Children aged from 2 to 6 years:

2.5mL oral solution twice daily.

Children aged from 6 to 12 years

10mg once daily (1 tablet) or 10mL oral solution

A 5mg starting dose (1 half tablet or 5mL oral solution) may be proposed if this leads to satisfactory control of the symptoms.

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	Contra-indicated

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 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.

Increased risk of urinary retention

Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention (see section 4.8 Undesirable effects)

Patients at risk of convulsions

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

Skin reactions

Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation (see section 4.8 Undesirable effects). 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

The use of the film-coated tablet and capsule formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use the oral solution of cetirizine in children under 6 years.

Due to the amount of some excipients in the formulation, the oral solution is not recommended in children aged less than 2 years.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic Interactions

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, antypirine, 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 Pregnancy and lactation

Fertility

Limited data is available on human fertility but no safety concern has been identified. Animal data show no safety concern for human reproduction.

***Pregnancy* (Category B2)**

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.

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 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 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 reactions: **(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 %
Gastro-intestinal 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 reactions at rates of 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
Metabolism and nutrition disorders	Increased appetite	Not known
Psychiatric disorders	Agitation Aggression, confusion, depression, hallucination, insomnia Tic Suicidal ideation, nightmare	Uncommon Rare Very rare Not known
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
Ear and labyrinth disorders	Vertigo	Not known
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 Hepatitis	Rare Not known
Skin and subcutaneous tissue disorders	Pruritus, rash Urticaria Angioedema, fixed drug eruption Acute generalized exanthematous pustulosis (AGEP)	Uncommon Rare Very rare Not known
Musculoskeletal and connective tissue disorders	Arthralgia	Not known
Renal and urinary disorders	Dysuria, enuresis Urinary retention (See Section 4.4 Special warnings and precautions for use)	Very rare Not known
General disorders and administration site conditions	Asthenia, malaise Oedema	Uncommon Rare
Investigations	Weight gain	Rare

Skin reactions occurring after discontinuation of cetirizine
After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported (see Section 4.4 Special warnings and precautions for use).

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 to 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.

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: Antihistamines for systematic use, piperazine derivatives.
ATC code: R06AE07

Mechanism of action
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.

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

Cetirizine exhibits linear kinetics over the range 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 third of the dose are excreted unchanged in 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.

Special patient population

Children

The half-life of cetirizine was about 6 hours in children of 6-12 years and 5 hours in children 2-6 years. In infants and toddlers aged 6 to 24 months, it is reduced to 3.1 hours.

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 increase 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 normals. 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 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

Tablet core:
Microcrystalline cellulose
Lactose monohydrate
Colloidal anhydrous silica
Magnesium stearate

Tablet Coating:
Hypromellose (E464)
Macrogol 4000
Titanium dioxide (E171)
Polydextrose

Oral solution
Glycerol

Propylene glycol
Liquid Sorbitol (non-crystallising) (E420)
Methyl Parahydroxybenzoate (E218)
Propyl Parahydroxybenzoate (E216)
Sodium acetate
Acetic acid
Saccharin sodium
Banana flavour
Purified water

Lactose
Cetirizine hydrochloride, 10 mg, film-coated tablets contains lactose. Patients with rare hereditary problems of galactose intolerance, (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

Fructose
Patients with rare hereditary problems of fructose intolerance should not take Cetirizine dihydrochloride 1mg/mL oral solution.

Sorbitol
The product contains sorbitol. Patients with rare hereditary problems of galactose intolerance, (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.

Parabens
The product contains methylparahydroxybenzoate (methyl paraben) or propylparahydroxybenzoate (propyl paraben), which may cause allergic reactions (possibly delayed).

6.2 Incompatibilities
Not applicable

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Store at or below 30°C.

6.5 Nature and contents of container

Tablets
Transparent or white opaque PVC/PVdC – aluminium blister packs containing 10 or 30 film-coated tablets.

Oral Solution
75 mL or 150 mL amber glass bottle with child-resistant polypropylene screw cap incorporating a tamper evident seal.

Measuring device: 5 mL plastic PP measuring spoon graduated at 2.5 mL

Instructions for Use/Handling:
Not applicable.

6.6 Special precautions for disposal
No special requirements.

7 MEDICINE SCHEDULE
Pharmacy Only Medicine.

8 SPONSOR
GlaxoSmithKline Consumer Healthcare
Level 11 Zurich House
21 Queen Street
Auckland 1010, New Zealand
FREECALL NZ: 0800 540 144

9 DATE OF FIRST APPROVAL
Cetirizine Hydrochloride (BP) 10mg Film Coated Tablets 25 February 1993
Cetirizine Hydrochloride (BP) 1 mg/mL Oral Solution 17 October 1997

10 DATE OF REVISION OF THE TEXT
29 May 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Transferred to new data sheet template
Section 4.4 Special warnings and precautions for use	Addition of a statement for Increased risk of urinary retention.
Section 4.4 Special warnings and precautions for use	Addition of a statement for Skin reactions.
Section 4.6 Pregnancy and lactation	Updated fertility statement.
Section Post marketing experience	Addition of safety data of Unknown type.