Cetirizine

Core Safety Profile

4.2 Posology and method of administration

Elderly subjects: data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

Patients with moderate to severe renal impairment: the dosing intervals must be individualized 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:

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

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 pediatric 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 his body weight.

Patients with hepatic impairment: no dose adjustment is needed in patients with solely hepatic impairment.

Patients with hepatic impairment and renal impairment: adjustment of the dose is recommended (see Patients with renal impairment above).

4.3 Contra-indications

History of hypersensitivity to any of the constituents of the formulation, to hydroxyzine or to any piperazine derivatives.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take cetirizine film-coated tablet.

Patients with rare hereditary problems of fructose intolerance should not take cetirizine 1 mg/ml oral solution**.**

4.4 Special warnings and precautions for use

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.

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

Methyl parahydroxybenzoate and propyl parahydroxybenzoate included in the 10 mg/ml oral drops and in the 1 mg/ml oral solution may cause allergic reactions (possibly delayed).

The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation.

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Due to the pharmacokinetic, pharmacodynamic and tolerance profile of cetirizine, no interactions are expected with this antihistamine. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

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

4.6 Pregnancy and lactation

Pregnancy
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/fetal development, parturition or postnatal development. Caution should be exercised when prescribing to pregnant women.

Lactation
Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

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 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.

a) Clinical trials
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	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 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 %

b) Post-marketing experience

In addition to the adverse reactions reported during clinical studies and listed above, the following undesirable effects 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥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

• Psychiatric disorders:
Uncommon: agitation
Rare: aggression, confusion, depression, hallucination, insomnia
Very rare: tics

• Nervous system disorders:
Uncommon: paraesthesia
Rare: convulsions
Very rare: dysgeusia, dyskinesia, dystonia, syncope, tremor
Not known: amnesia, memory impairment

• Eye disorders:
Very rare: accommodation disorder, blurred vision, oculogyration

• Cardiac disorders:
Rare: tachycardia

• Gastro-intestinal disorders:
Uncommon: diarrhea

• Hepatobiliary disorders:
Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)

• Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioneurotic oedema, fixed drug eruption

• Renal and urinary disorders:
Very rare: dysuria, enuresis

• General disorders and administration site conditions:
Uncommon: asthenia, malaise
Rare: oedema

• Investigations:
Rare: weight increased

4.9 Overdose

a) Symptoms
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.

b) Management
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.