Cetirizine dihydrochloride

Virlix®

Oral Preparations

PRODUCT DESCRIPTION

Cetirizine dihydrochloride (Virlix®) tablet: White oblong film coated tablet, with breakline and Y-Y logo, each containing 10mg Cetirizine dihydrochloride.
Cetirizine dihydrochloride (Virlix®) 10mg/mL Oral Drops, Solution: A clear, colorless liquid, with slightly sweet taste and a bitter flavor containing 10mg Cetirizine dihydrochloride per mL.
Cetirizine dihydrochloride (Virlix®) 1mg/mL Oral Solution: A clear and colourless liquid with a slightly sweet taste and a banana-flavour, containing 1mg Cetirizine dihydrochloride per mL.

PHARMACOLOGIC PROPERTIES

Pharmacodynamic properties
Mechanism of Action and Pharmacodynamic effects
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 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.
Pharmacokinetics
Absorption
No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. The steady - state peak plasma concentration is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.
The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) and area under curve (AUC) is unimodal in human volunteers. 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.
Distribution
The apparent volume of distribution is 0.50 l/kg. Plasma protein binding of cetirizine is 93 ± 0.3 %. Cetirizine does not modify the protein binding of warfarin.
Metabolism and Elimination
Cetirizine does not undergo extensive first pass metabolism. About two-thirds of the dose is excreted unchanged in urine. The terminal half-life is approximately 10 hours.
Cetirizine exhibits linear kinetics over the range 5 to 60 mg.
Special patient populations
Children
The half-life of cetirizine was about 6 hours in children of 6-12 years and 5 hours in children 2-6 years
Elderly
Following a single 10 mg oral dose, the 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.
NON-CLINICAL INFORMATION
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.

INDICATIONS

For the relief of:

- nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- symptoms of urticaria.

DOSAGE AND ADMINISTRATION

The tablets need to be swallowed with a glass of liquid.
The drops have to be diluted in liquid, while the solution can be swallowed as such.

Route of Administration

For oral use.

Adults

10mg (20 drops or 10 ml of oral solution or 1 tablet) once daily.
A 5 mg starting dose (10 drops or 5 ml of oral solution or half of the tablet) may be proposed if this leads to satisfactory control of the symptoms.

Children

Children aged from 2 to 6 years
2.5 mg (5 drops or 2.5 ml of oral solution) twice daily.
Children aged from 6 to 12 years
5 mg (10 drops or 5 ml of oral solution or half of the tablet) twice daily.
Children over 12 years of age
10 mg (20 drops or 10 ml of oral solution or 1 tablet) once daily.

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:

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

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, his age and his body weight.

Hepatic impairment

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

Patients with hepatic impairment and renal impairment

Dose adjustment is recommended *(see Renal Impairment above)*.

CONTRAINDICATIONS

Cetirizine is contraindicated in:

- hypersensitivity to any of the constituents of this formulation, to hydroxyzine or to any piperazine derivatives,
- patients with severe renal impairment at less than 10 ml/min creatinine clearance.

WARNINGS AND PRECAUTIONS

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.

Patients at risk of convulsions

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

Children

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. It is recommended to use a paediatric formulation of cetirizine.
Please be aware that in some markets, film-coated tablet may not be indicated in children below 12 years.

Allergy skin tests

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

Food
The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.
Excipients
Lactose
Film-coated tablets, 10mg
This product contains lactose. Patients with rare hereditary problems of galactose intolerance, (the Lapp lactase deficiency or glucose-galactose malabsorption) should not take this medicine.
Sorbitol
Oral solution, 1mg/mL
This product contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.
Sucrose
Oral solution, 1 mg/ml
This product contains sucrose. Patients with rare hereditary problems of fructose intolerance, glucosegalactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
Parabens
Oral solution, 1mg/ml
Oral drops, solution, 10 mg/ml
This product contains methylparahydroxybenzoate or propylparahydroxybenzoate, which may cause allergic reactions (possibly delayed).
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.

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

PREGNANCY AND LACTATION
Fertility
There are no relevant data available.
Pregnancy
Caution should be exercised when prescribing to 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 when prescribing cetirizine to lactating women.
Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration.

ADVERSE 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 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 Data
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).

Blood and lymphatic system 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: tic
Not known: suicidal ideation
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
Ear and labyrinth disorders
Not known: vertigo
Cardiac disorders
Rare: tachycardia
Gastrointestinal disorders
Uncommon: diarrhoea
Hepatobiliary disorders
Rare: hepatic function abnormal (transaminases increased, blood bilirubin increased, blood alkaline phosphatase increased, Gamma-glutamyl transferase increased)
Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioedema, drug eruption
Renal and urinary disorders
Very rare: dysuria, enuresis
Not known: urinary retention (*see Section Warnings and Precautions*)
General disorders and administration site conditions
Uncommon: asthenia, malaise
Rare: oedema
Investigations
Rare: weight increased.

OVERDOSAGE AND TREATMENT

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.

STORAGE CONDITION

Store at temperatures not exceeding 25ºC.

AVAILABILITY

* Cetirizine (Virlix®) 10mg tablets: 10 tablets per blister (Box of 50's).
** Cetirizine (Virlix®) 10mg/mL Drops, Solution: Bottles of 10mL.
*** Cetirizine (Virlix®) 1mg/mL Oral Solution: Bottles of 30mL.

CAUTION

Keep all medicines out of reach of children.

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