PACKAGE INSERT TEMPLATE FOR CETIRIZINE TABLET/ ORAL DROPS/ ORAL SOLUTION

Brand or Product Name
[Product name] Tablet 10mg
[Product name] Oral drops 10mg/ml
[Product name] Oral solution 1mg/ml

Name and Strength of Active Substance(s)
Cetirizine hydrochloride ….mg equivalent to cetirizine 10mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc eg
Tablet - White, circular flat beveled edge tablets marked '100' on one side
Oral solution / oral drops - Clear, colourless solution]

Pharmacodynamics
Cetirizine hydrochloride, a human metabolite of hydroxyzine, is a potent antihistamine that selectively inhibits the effect of peripheral H(1)-receptors.

Cetirizine belongs to the piperazine class of antihistamines and is the major carboxylated metabolite of hydroxyzine. However, it is less lipophilic than hydroxyzine and thus less likely to distribute into the central nervous system (CNS) and produce sedation.
Generally, antihistamines contain 1 or 2 heterocyclic or aromatic rings attached to the side chain of histamine. Cetirizine has more polar or less lipophilic functional groups attached to the ethylamine side chain which has resulted in less CNS penetration, greater selectivity for the H1-receptor, and less anticholinergic side effects.
Cetirizine may also have a modulatory effect on inflammatory cells by inhibiting eosinophil migration or eosinophilotactic mediators. Additionally, cetirizine may also have inhibitory effects on other infiltrating inflammatory cells, such as neutrophils.

Cetirizine has shown to be safe for allergic patients with mild to moderate asthma and does not cause prolongation of QT interval.

Pharmacokinetics
Absorption
Cetirizine is rapidly absorbed from the gastrointestinal tract after oral doses and peak plasma concentrations occur within about an hour.
Food delays the time to peak plasma concentrations but does not decrease the amount of drug absorbed.
Bioavailability, oral: 70%.
The extent of bioavailability is similar when cetirizine is given as solutions, capsules or tablets.

Distribution
Cetirizine is highly bound to plasma proteins (93%).
Volume of distribution is 0.5 to 0.8 L/kg.
It does not appear to cross the blood-brain barrier to a significant extent.
It has been detected in breast milk.

Metabolism
Cetirizine is not extensively metabolized by the liver.

The inactive O-dealkylated metabolite has been identified in both the plasma and feces, but not in the urine.

Elimination
Cetirizine is excreted primarily in the urine (60%) mainly as unchanged drug and has an elimination half-life of about 10 hours.
Cetirizine is poorly cleared by hemodialysis.

Special populations
Children, infants and toddlers: 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.

Renal insufficiency
The elimination half-life of cetirizine may be prolonged
Dosing adjustment is necessary in patients with moderate or severe renal impairment.
Hemodialysis is unlikely to be of value in removing cetirizine from the plasma.

Elderly or hepatic insufficiency
The elimination half-life is prolonged by 50% in geriatrics and in patients with chronic liver disease as compared to normal healthy adults.
Dosing adjustment is only necessary in hepatically impaired patients if concomitant renal impairment is present.

Indication
Adults and children of 1 year and above: symptomatic treatment of seasonal allergic rhinitis, perennial allergic rhinitis and urticaria of allergic origin.

Recommended Dosage
The recommended dosage in children 1 to 2 years old is 2.5 mg twice daily (to be administered as 5 drops twice daily).

In children aged between 2 and 6 years old: 2.5 mg twice daily (5 drops bid or 2.5 ml oral solution bid)

Adults and children over 6 years old: 10 mg once daily [1 tablet, 20 drops, or 10 ml oral solution (2 full spoons)]. A 5 mg starting dose (1 half tablet, 10 drops, or 5 ml oral solution) may be proposed if this leads to satisfactory control of the symptoms.
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.

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.

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 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.

Mode of Administration
Oral. May be given without regard to meals.

Contraindications
- History of hypersensitivity to any of the constituents of the formulation, to hydroxyzine or to any piperazine derivatives.
- Cetirizine is contraindicated during lactation.
- Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

**Depending on the product formulation patients with rare hereditary problems of rare fructose intolerance, galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should be considered.*

Warnings and Precautions
Activities Requiring Mental Alertness: In clinical trials the occurrence of somnolence has been reported in some patients taking Cetirizine: due caution should therefore be exercised when driving a car or operating potentially dangerous machinery.

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

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.

The oral solution is not recommended in children aged less than 2 years.

The oral drops should not be used in children aged less than 1 year.

Concurrent use with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

Caution in elderly patients, patients with hepatic dysfunction and renal insufficiency is recommended.

Effects on the ability to drive and use machines
The occurrence of somnolence has been reported in some patients taking cetirizine. Hence, caution should be exercised when driving a car or operating potentially dangerous machinery.

Interactions with Other Medicaments
No evidence of adverse clinical interactions with cetirizine and azithromycin, erythromycin, ketoconazole, theophylline, and pseudoephedrine have been revealed.

Concurrent use of cetirizine and food will not reduce the extent of absorption of cetirizine but may decrease the rate of absorption by 1 hour.

Concurrent use of cetirizine and ritonavir may result in an increased exposure and half-life of cetirizine as well as reduced cetirizine clearance. Caution is advised if these agents are used concomitantly. Patients may need to be monitored for increased cetirizine side effects including drowsiness, fatigue, dry mouth, or cough.

Statement on Usage During 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. Cetirizine should not be administered to pregnant women during the first trimester.

Lactation
Cetirizine is contraindicated in lactating women since the active ingredient, cetirizine is excreted in breast milk.

Adverse Effects / Undesirable Effects
Cardiac disorders: Tachycardia (rare)

Blood and lymphatic Disorders: thrombocytopenia (Very rare)

Eye disorders: accommodation disorder, blurred vision, oculogyration (Very rare),

Gastro-intestinal disorders: diarrhea (Uncommon), xerostomia
Renal and urinary disorders: dysuria, enuresis (Very rare)

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

General disorders and administration site conditions: Asthenia, malaise (Uncommon), oedema (Rare), Fatigue

Immune system disorders: Hypersensitivity (Rare), anaphylactic shock (Very rare)

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

Psychiatric disorders: agitation (Uncommon), aggression, confusion, hallucination, insomnia (Rare), tic (Very rare)

Endocrine/Metabolic Effects: Weight gain (rare)

Neurologic Effects: Asthenia, somnolence, headache, Sedation, paraesthesia (Uncommon), convulsions (Rare), dysgeusia, syncope, tremor (Very rare), dyskinesia, dystonia (very rare), dizziness

Overdose and Treatment

Symptoms

Overdose symptoms include confusion, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention)

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.
Activated charcoal should be considered after extremely large ingestions or if more toxic coingestants are involved within 2 hours from the ingestion.
Cetirizine is not effectively removed by dialysis.

Storage Conditions

Store below ….°C

Dosage Forms and Packaging Available

[Packaging type & pack size]

Name and Address of Manufacturer

[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder

[Name & full address of marketing authorization holder]

Date of Revision of Package Insert

[day/month/year]