

 COOPER <small>PHARMA</small>	SOCIETE MAROCAINE DE COOPERATION PHARMACEUTIQUE
CETIRIZINE DIHYDROCHLORIDE 10 MG, TABLETS	
Module 1: Administrative Information and Product Information	1.6 Product Information

1.6.1 Prescribing Information (Summary of Product Characteristics)

Please find here attached the SmPC of Cetirizine dihydrochloride 10 mg coated tablets

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALER-Z[®] 10 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 10 mg Cetirizine dihydrochloride.

Excipients with known effect: one film-coated tablet contains 100.2 mg Lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White coloured, coated, circular, biconvex with 'CZ' embossed on one side and deep score on the other, in packs of 7, 14 and 28, blister packed in PVC / ALU

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine dihydrochloride 10 mg film-coated tablets are indicated in adults and paediatric patients 6 years and above:

- For the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- For the relief of symptoms of chronic idiopathic urticaria.

Medical advice is recommended for chronic idiopathic urticaria

4.2 Posology and method of administration

Adults and adolescents over 12 years of age: 1 tablet (10 mg) once daily.

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: there are no data to document the efficacy/safety ratio patients with renal impairment. Since cetirizine is mainly excreted via renal route (see section 5.2), in cases where no alternative treatment can be used, the dosing intervals must be individualized according to renal function. Refer to the following table and adjust the dose as indicated. To use the 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:

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

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

Patients with hepatic impairment:

No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with moderate to severe renal impairment above).

Paediatric population

The tablet formulation should not be used in children under 6 years of age as it does not allow the necessary dose adjustments.

Children aged 6 to 12 years: 5 mg twice daily (a half tablet twice daily).

Adolescents above 12 years: 10 mg once daily (1 tablet).

In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance, age and body weight of the patient.

Method of administration:

The tablets should be swallowed with a drink.

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, to hydroxyzine or to any piperazine derivatives.
- Patients with severe renal impairment with a creatinine clearance below 10 ml/min.

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 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.

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

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

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

Paediatric population

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.

4.5 Interaction 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.

In sensitive patients, the concurrent use of alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance, although cetirizine does not potentiate the effect of alcohol (0.5 g/L in the blood). There was no evidence of interaction of cetirizine with alcohol at blood alcohol levels below 0.5 g/L in the blood.

4.6 Fertility, pregnancy and lactation:

- *Pregnancy*

For cetirizine prospectively collected data on pregnancy outcomes do not suggest potential for maternal or foetal/embryonic toxicity above background rates.

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.

- *Breast feeding*

Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

- *Fertility*

Limited data is available on human fertility but no safety concern has been identified.

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 these 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

- Overview

Clinical studies have shown that cetirizine at the recommended dosage has minor undesirable 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 treatment with cetirizine dihydrochloride.

- Listing of ADRs

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)
General disorders and administration site conditions		
Fatigue	1.63 %	0.95 %
Nervous system disorders		
Dizziness	1.10 %	0.98 %
Headache	7.42 %	8.07 %
Gastro-intestinal 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, thoracic and mediastinal 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.

- Paediatric population

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 disorders Diarrhoea	1.0 %	0.6 %
Psychiatric disorders Somnolence	1.8 %	1.4 %
Respiratory, thoracic and mediastinal disorders Rhinitis	1.4 %	1.1 %
General disorders and administration site conditions Fatigue	1.0 %	0.3 %

- 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 ($\geq 1/10$); 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

- **Ear and labyrinth disorders**

Not known: vertigo

- **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

Not known: urinary retention

- **General disorders and administration site conditions**

Uncommon: asthenia, malaise

Rare: oedema

- **Investigations**

Rare: weight increased

- ***Reporting of suspected adverse reactions***

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

- ***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.

- *Management*

There is no known specific antidote to cetirizine.

Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug.

Cetirizine is not effectively removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

- *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.

- *Pharmacodynamic effects*

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 eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

- *Clinical efficacy and safety*

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, but the correlation with efficacy is not established.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and concomitant mild to moderate asthma, cetirizine 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine to allergic patients with mild to moderate asthma.

In a placebo-controlled study, cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of QT interval.

At the recommended dosage, cetirizine has demonstrated that it improves the quality of life of patients with perennial and seasonal allergic rhinitis.

- *Paediatric population*

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

- *Absorption*

The steady - state peak plasma concentrations 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.

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 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.

- *Biotransformation*

Cetirizine does not undergo extensive first pass metabolism.

- *Elimination*

The terminal half-life is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. About two third of the dose are excreted unchanged in urine.

- *Linearity/Non-linearity*

Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Renal impairment: The pharmacokinetics of the drug was similar in patients with mild impairment (creatinine clearance higher than 40 ml/min) and healthy volunteers.

Patients with moderate renal impairment had a 3-fold increase in half-life and 50 % decrease in clearance compared to healthy volunteers.

Patients on hemodialysis (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 (see section 4.2).

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 patients with hepatic impairment if concomitant renal impairment is present.

Older people: 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 younger subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Paediatric population: 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

5.3 Preclinical safety data

Preclinical data from conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and embryofoetal reproductive and developmental functions did not reveal any particular risk to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose
- Starch
- Silica colloidal anhydrous
- Talc
- Microcrystalline cellulose
- Magnesium stearate
- Opadry white (Code N° 31F58914)
- Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister comprising of PVC/Aluminium foil with 7, 14 and 28 tablets.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

COOPER PHARMA
41, Rue Mohamed DIOURI,
20 110 Casablanca, Morocco.

8. MARKETING AUTHORISATION NUMBER

- **Pack of 7 tablets:** 135/12DMP/21/NCI
- **Pack of 14 tablets:** 136/12DMP/21/NCI
- **Pack of 28 tablets:** 137/12DMP/21/NCI

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

- **Date of first authorisation:** 30/04/2012

10. DATE OF REVISION OF THE TEXT

16/11/2016