1. NAME OF THE MEDICINAL PRODUCT

Cetirizine dihydrochloride, 10 mg, film-coated tablet

Cetirizine dihydrochloride, 1 mg/ml, oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cetirizine dihydrochloride, 10 mg, film-coated tablet

Each film-coated tablet contains 10 mg of cetirizine dihydrochloride.

Cetirizine dihydrochloride, 1 mg/ml, oral solution

Each 1 ml contains 1 mg of cetirizine dihydrochloride.

Excipients

For the full list of excipients, see section 6.1.

None of the excipients used in this formulation has been identified or reported to cause side effects.

3. PHARMACEUTICAL FORM

Cetirizine dihydrochloride, 10 mg, film-coated tablet

White, oblong, film-coated tablet, with a bisect line and Y-Y logo.

Cetirizine dihydrochloride, 1 mg/ml, oral solution

Clear and colourless liquid with a slightly sweet taste and a 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.

4.2. Posology and method of 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

10 mg (20 drops or 10 ml of oral solution or 1 tablet or 1 capsule) 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 or 1 capsule) 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

Since cetirizine is mainly excreted via renal route, in cases no alternative treatment can be used, the dosing intervals must be individualised according to renal function.

Group	Estimated Glomerular Filtration Rate (eGFR) (ml/min)	Dosage and frequency
Normal renal function	≥90	10 mg once daily
Mild decrease renal function	60 – < 90	10 mg once daily
Moderately decreased renal function	30 – < 60	5 mg once daily
Severely decreased renal function	15 - < 30 not requiring dialysis treatment	5 mg once every 2 days
End-stage renal disease	<15 requiring dialysis treatment	Contraindicated

Refer to the following table and adjust the dose as indicated.

Dosing adjustments for adult patients with impaired renal function

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.

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)*.

4.3. Contraindications

Cetirizine is contraindicated in:

- hypersensitivity to any of the constituents of this formulation, to hydroxyzine or to any piperazine derivatives,
- patients with end-stage renal disease with eGFR (Estimated Glomerular Filtration Rate) below 15 ml/min.

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 (*see Section Interactions*).

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 Adverse Reactions*).

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 Adverse Reactions*). In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

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 tablets may be indicated in children 12 years and above.]*

The use of the hard capsules formulation is not recommended in children aged less than 12 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of cetirizine.

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.

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. Neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).

Alcohol and other CNS depressants

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 blood levels) (*see Section Warnings and Precautions*).

4.6. Fertility, 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

Caution should be exercised when prescribing to pregnant women.

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/foetal development, parturition or postnatal development.

Lactation

Cetirizine passes into breast milk. A risk of side effects in breastfed infants cannot be excluded. 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.

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. However, patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery.

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.

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 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 the treatment with cetirizine.

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 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 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 system 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 Data

Adverse drug reactions (ADRs) are listed below by MedDRA system organ class and by frequency.

Frequencies are defined as:

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: tics

Not known: suicidal ideation, nightmare

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, oculogyric crisis

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)
Not known: hepatitis

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash
Rare: urticaria
Very rare: angioedema, fixed drug eruption
Not known: acute generalized exanthematous pustulosis (AGEP)

Musculoskeletal and connective tissue disorders
Not known: arthralgia, myalgia

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.

Skin reactions occuring after discontinuation of cetirizine

After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported *(see Section Warnings and Precautions)*.

Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) **https://pv.pharmacyboardkenya.org**.

4.9. Overdosage

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 haemodialysis.

Management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group

Antihistamines for systemic use, piperazine derivatives

ATC Code

R06AE07

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, but the correlation with efficacy is not established. 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 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.

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 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.

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 and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. 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 younger 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 healthy volunteers. Patients with moderate renal impairment had a 3-fold increase in half-life and 70% decrease in clearance compared to healthy 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

Tablets: *Microcrystalline cellulose*

Lactose monohydrate

Colloidal anhydrous silica

Magnesium stearate

Opadry Y-1-7000

Oral Solution:

Sorbitol

Glycerol

Propylene glycol

Saccharin sodium

Banana flavour

Methyl parahydroxybenzoate

Propyl parahydroxybenzoate

Sodium acetate

Glacial acetic acid

6.2. Incompatibilities

There are no relevant data available.

6.3. Shelf-Life

Tablets: *60 Months*

Oral Solution: *36 Months*

6.4. Special precautions for storage

Store Below 30℃

6.5. Nature and contents of container

Tablets: are *primary packed in PVC/aluminium blister*

Oral Solution: *Cetirizine Dihydrochloride 1 mg/ml Oral Solution is packed in amber glass bottle. The bottles are closed with a child resistant cap and supplied with a graduated spoon*

6.6. Special precautions for disposal and other handling

There are no special requirements for use or handling of this product.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

H96/496

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF TEXT:

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