

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALLERSET® oral drop 10 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Each 1 ml (20 drops) of solution contains 10.0 mg of cetirizine dihydrochloride.

Excipients:

Methyl paraben (E218) (1.35 mg) and propyl paraben (E216) (0.15 mg)

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Oral drop
Clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults and children aged 2 years and over:

For the treatment of nasal and ocular symptoms of allergic rhinitis, symptoms of idiopathic urticaria, and symptomatic treatment of pruritus.

4.2 Posology and method of administration

Posology/Frequency and duration of administration:

Children aged between 2 and 6 years: Once daily 2.5 mg (5 drops). The daily dose may be increased up to 5 mg in this age group and once daily 5 mg (10 drops) or twice daily (every 12 hours) 2.5 mg (5 drops) may be given.

Children aged between 6 and 12 years: Depending on the severity of symptoms once daily 5 mg (10 drops) or 10 mg (20 drops) may be given.

In adults and children over 12 years of age: Depending on the severity of symptoms, once daily 5 mg (one spoonful) (5 mg/5 ml syrup) or 10 mg (two spoonful) (10 mg/10 ml syrup) of cetirizine may be administered.

Method of administration:

ALLERSET® Oral Drop is for oral use.

ALLERSET® Oral Drop should be taken diluting in some liquid.

Information on special populations

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 the 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:

$$\text{CLcr (ml/min)} = \frac{[140 - \text{age (y)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0,85\text{-for women})$$

Dosing adjustment 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, their age and body weight.

Hepatic failure:

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

Dose adjustment is recommended in patients with hepatic and renal impairment (see Patients with renal impairment)

Pediatric population: See "Posology/frequency and duration of administration"

Geriatric population: Data do not suggest that the dose needs to be reduced in elderly subjects.

4.3. Contraindications

Contraindicated in:

- Patients with a history of hypersensitivity to the active ingredient of ALLERSET® or any of the constituents of the formulation and to hydroxyzine or to any piperazine derivatives
- Patients with severe renal impairment with a creatine 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.
- Since cetirizine may increase the risk of urinary retention, precaution is required in patients with propensity for urinary retention (e.g. spinal cord lesions, prostatic hyperplasia).
- Precaution is required in epileptic patients and in individuals with a risk of conclusions.
- ALLERSET® Oral Drop is not recommended for children under 2 years of age.

4.5. Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction studies with cetirizine were conducted with pseudoephedrine, antipyrine, ketoconazole, erythromycin and azithromycin and no pharmacokinetic interactions were observed. In a multiple dose study of theophylline (400 mg once daily) and cetirizine, a small (16%) decrease in the clearance of cetirizine was observed, while the disposition of theophylline was not altered by concomitant cetirizine administration.

Concomitant administration of cetirizine with cimetidine, glypizide, diazepam, antipyrine, and pseudoephedrine did not reveal any evidence suggesting adverse pharmacodynamics interactions.

Also, concomitant administration of cetirizine and azithromycin, erythromycin, ketoconazole, teophylline, and pseudoephedrine did not cause any adverse clinical interactions. In particular, concomitant use of cetirizine with macrolides or ketoconazole did not result in any clinically significant ECG changes.

In a multiple dose study of ritonavir (600 mg twice daily) and cetirizine (10 mg daily), the extent of exposure to cetirizine was increased by about 40% while the disposition of ritonavir was slightly altered (-11%) further to concomitant cetirizine administration.

Concomitant food intake did not result in a decrease in the extent of absorption, although a decrease in the rate of absorption was noted.

Antihistamines can interfere with cutaneous tests for allergies and an appropriate 3-day wash-out period is recommended before conducting such tests.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: "B"

Women of childbearing potential/Contraception

Women of childbearing potential may be treated with cetirizine. Concomitant use of cetirizine and oral contraceptives is not expected to result in decreased contraceptive efficacy.

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 post-natal development.

Cetirizine should be prescribed to pregnant women only when it is absolutely necessary, and caution should be exercised if prescribed.

Breastfeeding

Cetirizine is excreted in human milk at concentrations representing 0.25 to 0.90 of those measured in plasma, depending on sampling time after administration. Therefore, prescribing cetirizine to lactating women is not recommended.

Ability to reproduce/Fertility

Animal studies have shown no effect of cetirizine on fertility.

4.7. Effects on ability to drive and use machines

Objective measurements of driving ability, sleep latency and simulated assembly line performance (a computer based measurement used for assessing the sedative effects of medications and representing the real-life workplace performance that is sensitive to all parameters during sleep) 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 medicine into account.

In these sensitive patients, concurrent use with alcohol or other central nervous system 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 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 hydrochloride.

Although somnolence has occurred statistically more commonly than in placebo in clinical trials, it 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.

Undesirable effects are described according to MedDRA System Organ Class and by estimated frequency based on post-marketing experience (Marked adverse effects have been reported in placebo controlled studies only, while unmarked adverse effects are based on the 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 system disorders:

Very rare: thrombocytopenia



Immune system disorders:

Rare: hypersensitivity

Very rare: anaphylactic shock

Metabolism and nutrition disorders:

Unknown: increased appetite

Psychiatric disorders:

Common: Somnolence^{a,b}

Uncommon: agitation

Rare: aggression, confusion, depression, hallucinations, insomnia

Very rare: tics

Nervous system disorders:

Common: Dizziness^a, headache^a

Uncommon: paresthesia

Rare: convulsions

Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia

Not known: amnesia, memory impairment

Eye disorders:

Very rare: blurred vision, accommodation disorder, oculogyration

Ear and labyrinth disorders:

Unknown: vertigo

Cardiac disorders:

Rare: tachycardia

Respiratory, thoracic, and mediastinal disorders:

Common: pharyngitis^a, rhinitis^b

Gastrointestinal disorders:

Common: Abdominal pain^a, dry mouth^a, nausea^a, diarrhea^b

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders:

Uncommon: skin rash, pruritus

Rare: urticaria

Very rare: fixed drug eruption, angioneurotic oedema

Renal and urinary disorders:

Very rare: dysuria, enuresis

Unknown: urinary retention



General disorders and administration site conditions:

Common: fatigue ^{a,b}

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight gain

^a Double blind controlled clinical or pharmaco-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 events were commonly reported for cetirizine 10 mg in the placebo-controlled trials.

^b Adverse drug reactions commonly reported in children aged from 6 months to 12 years, included in placebo-controlled trials

Reporting of suspected adverse effects

Post-marketing reporting of suspected drug adverse effects is of major significance. Reporting allows continuous monitoring of the risk/benefit ratio for a particular drug. Health care professionals are required to report any adverse reactions to TÜFAM (Turkish Pharmacovigilance Center) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel : 0 800 314 00 08; faks: 0 312 218 35 99)

4.9. Overdose and treatment

Symptoms observed after an overdose of cetirizine are mainly associated with central nervous system effects or with effects that could suggest an anticholinergic effect.

Adverse effects reported after an intake of at least 5 times the recommended daily dose include confusion, diarrhea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

There is no known specific antidote to cetirizine. If overdose occurs, symptomatic or supportive treatment is recommended. Gastric lavage should be considered following ingestion of a short occurrence. Cetirizine cannot be effectively removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES**5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Piperazine derivatives, ACT code. R06AE07

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H₁-receptors.

Mechanism of action: *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H₁-receptors. Ex vivo experiments in mice have shown that systemically administered cetirizine does not significantly occupy the cerebral 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 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 urticarial 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.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis and concomitant mild to moderate asthma, cetirizine 10mg once daily improved rhinitis symptoms and did not later 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 60mg 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.

5.2 Pharmacokinetic properties

General Properties

In humans, the distribution of pharmacokinetic parameters such as the peak concentration and AUC are similar and no differences in cetirizine kinetics were observed between black and white adult males.

Absorption:

The steady-state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.

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 $93 \pm 0.3\%$. Cetirizine does not modify the protein binding of warfarin.

Biotransformation:

Cetirizine does not undergo extensive first pass metabolism.

Elimination

Plasma elimination half-life of cetirizine is approximately 10 hours. After dosing with 10 mg of cetirizine for 10 days, no evidence of drug accumulation was observed. Two-thirds of the dose is excreted unchanged in the urine.

Linearity/Non-Linearity:

Cetirizine has linear kinetics between a dose range of 5 to 60 mg.

Patient Characteristics

Geriatric population:

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 normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Pediatric 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.

Renal failure:

The pharmacokinetics of the drug were 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 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 failure:

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

Glycerin
Propylene glycol
Sodium saccharine
Methyl paraben (E218)
Propyl paraben (E216)



Sodium acetate
Acetic acid
Deionized water

6.2. Incompabilities

None

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Keep it in its original packing in room temperature under 25°C

6.5 Nature and contents of container

Allerset Oral Drop is provided in cartoon boxes containing 20 ml honey-colored glass bottles, with plastic pilfer proof caps, plastic dropper.

6.6. Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product

Unused or waste drug material should be disposed according to the "Regulations for the Control of Medical Waste" and "Regulations for the Control of Packing and Packing Waste"

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

179/45

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first license: 09 09 1996
Date of license renewal: 09.04.2010

10. DATE OF REVISION OF THE SmPC

