

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALLERSET® 10 mg Film Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

Each film-coated tablet contains 10 mg cetirizine dihydrochloride.

Excipients:

Lactose monohydrate (65.3 mg)

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Film-coated tablets.

White or practically white biconvex, round film-coated tablets with sn/10 logo on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine is indicated in adults and children over 6 years of age for the symptomatic treatment of allergic rhinitis, chronic idiopathic urticaria and itching.

4.2 Posology and method of administration

Posology/frequency and duration of administration

Adults and children over 6 years of age: 5 mg (½ tablet) or 10 mg (1 tablet) once daily based on the intensity of the symptoms.

Method of administration:

ALLERSET® 10 mg Film Tablet is for oral use. Swallow with a glass of water.

Additional 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 this 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:

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

Dosing Adjustments for 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 and patients undergoing dialysis	10	Contraindicated

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 and his body weight.

Hepatic impairment:

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

Dose adjustment is recommended in patients with hepatic impairment and renal impairment (see section “renal impairment”).

Pediatric population:

See section “Posology/Frequency and duration of administration”.

Geriatric population:

Data suggest that the dose doesn't need to be reduced in elderly subjects whose renal function is normal.

4.3 Contraindications

ALLERSET® 10 mg Film Tablets are contraindicated in

- Patients with a history of hypersensitivity to the active ingredient or any of the excipients of ALLERSET®, to hydroxyine or to any piperazine derivatives.
- Patients with severe renal impairment at less than 10ml/min creatine clearance
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.

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

The use of ALLERSET® 10 mg Film Tablet is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. ALLERSET® Syrup 1 mg/ml or ALLERSET® Oral Drops 10 mg/ml may be used in this population.

4.5 Interactions with other medicinal products and other forms of interaction

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

No evidence of adverse pharmacodynamics interactions has been found in studies with cimetidine, glipizide, diazepam, antipyrine, and pseudoephedrine administered concurrently with cetirizine.

There were no adverse clinical interactions with azithromycin, erythromycin, ketoconazole, theophylline and pseudoephedrine administered concurrently with cetirizine. In particular, no clinically significant ECG changes have ever been observed following concomitant use of cetirizine with macrolides or ketoconazole.

In a multiple dose study with ritonavir (600 mg twice daily) and cetirizine (10 mg daily), exposure to cetirizine was increased by about 40%, and when ritonavir was administered with cetirizine, the distribution of ritonavir was slightly changed (-11%).

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.

Antihistamines inhibit allergy skin tests and therefore a 3-day wash-out period is required before conducting such tests.

4.6 Pregnancy and lactation

General recommendation

Pregnancy category is: B

Women with childbearing potential / Contraception

Women with childbearing potential can be treated with cetirizine. Simultaneous use of cetirizine and oral contraceptives is not expected to reduce the effectiveness of contraception.

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/foetal development, parturition or postnatal development.

It should be given to pregnant women only if absolutely necessary and caution should be exercised.

Lactation

Cetirizine is excreted in human milk at concentrations representing 25% to 90% of those measured in plasma, depending on sampling time after administration. Therefore, the use of cetirizine in lactating women is not recommended.

Fertility Animal studies do not indicate any effect of cetirizine on fertility.

Reproduction / Fertility

Studies on animals showed that cetirizine has no effect on fertility.

4.7 Effects on ability to drive and use machines

Objective measurements of driving ability, sleep latency and simulated assembly line performance (Computer-generated and accurate measurement of all variables in the sleep state, used to measure the sedative effect of the drug, representing performance in the real work environment) 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 have shown that cetirizine at the recommended dosage has minor undesirable effects on the central nervous system, including somnolence, fatigue, dizziness and headache. In some cases, paradoxical central nervous system 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.

From this pooling, the following adverse events were reported for cetirizine 10 mg in the placebocontrolled trials at rates of 1.0 % or greater:

Adverse event (WHO-ART)	Cetirizine 10 mg (n= 3260)
Body as a whole – general disorders	
Fatigue	1.63 %
Central and peripheral nervous system disorders	
Dizziness	1.10 %
Headache	7.42 %
Gastro-intestinal system disorders	
Abdominal pain	0.98 %
Dry mouth	2.09 %
Nausea	1.07 %
Psychiatric disorders	

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 drug reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in placebo-controlled clinical or pharmacoclinical trials are:

Adverse drug 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 %

Undesirable effects are described according to MedDRA System Organ Class and by estimated frequency (marked adverse events are reported only in placebo controlled clinical trials, while those unmarked are based on post-marketing experience).

Frequency estimates: Very common ($\geq 1/10$); Common ($\geq 1/100$, $< 1/10$); Uncommon ($\geq 1/1,000$, $< 1/100$); Rare ($\geq 1/10,000$, $< 1/1,000$); 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

Psychiatric disorders:

Common: somnolence

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tics

Nervous system disorders:

Uncommon: paraesthesia

Rare: convulsions, movement disorders

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

Eye disorders:

Very rare: blurred vision, accommodation disorder, oculogyration

Cardiac disorders:

Rare: tachycardia

Gastrointestinal disorders:

Uncommon: diarrhoea

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: angioedema, fixed drug eruption

Renal and urinary disorders:

Very rare: dysuria, enuresis

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 very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to Turkish Pharmacovigilance Center (TUFAM) (www.titck.gov.tr e-mail: tufam@titck.gov.tr; tel: 0 800 314 00 08; fax: 0 312 218 35 99).

4.9 Overdose

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 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.

There is no known specific antidote to cetirizine. Symptomatic or supportive treatment is recommended in case of overdose. Gastric lavage should be considered following ingestion of a short occurrence. Cetirizine is not effectively removed by dialysis.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivative, ATC Code: R06AE07

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.

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.

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 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 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.

5.2 Pharmacokinetic properties

General properties

The distribution of pharmacokinetic parameters such as peak concentration and AUC is unimodal in humans and no difference is observed in the kinetics of cetirizine in white and black adult male subjects

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:

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

Linearity:

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

Special populations

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 Impairment:

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 impairment:

Patients with chronic liver disease (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, toxicity to reproduction, genotoxicity or carcinogenicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Corn starch
Lactose monohydrate
Polyvinylpyrrolidone
Magnesium stearate
Eudragit E
Polyethylene glycol 6000
Titanium dioxide
Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

36 months.

6.4 Special Precautions for Storage

Store at room temperature below 25°C in its container, and keep out of reach and sight of children.

6.5 Nature and Contents of Container

Presented in 3 different blister packs containing 10, 20 and 30 film-coated tablets.

6.6 Special Precautions for Disposal and Other Handling

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)

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9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: -

Date of renewal: -

10. DATE OF REVISION OF THE TEXT

11.03.2020