

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ALLERSET® 1 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

1 ml of syrup contains 1 mg of cetirizine dihydrochloride.

Excipients:

1 ml of syrup contains sorbitol (E420) (0.6 g), methyl parahydroxybenzoate (E218) (1.35 mg), propyl parahydroxybenzoate (E216) (0.15 mg), sodium saccharine (1 mg) and sodium acetate (4.2 mg).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup.

Colorless, almost clear solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In adults and children 2 years and above;

Cetirizine is indicated for the relief of nasal and ocular symptoms of allergic rhinitis, for the symptomatic treatment of idiopathic urticaria and itching.

4.2. Posology and method of administration

Posology / frequency and time of administration

Children aged between 2-6 years:

2.5 mg twice daily (equivalent to 2.5 ml of syrup twice daily, corresponding to half a spoonful per dose).

Children aged between 6-12 years:

5 mg twice daily (equivalent to 5 ml of syrup twice daily, corresponding to one full spoonful per dose).

Adults and children over 12 years of age:

10 mg once daily (equivalent to 10 ml of syrup once daily, corresponding to two full spoonfuls per dose).

Method of application:

ALLERSET® syrup is for oral use.

Additional information on special populations

Renal failure:

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, patient's creatinine clearance [(CLcr), ml/min] must be calculated.

The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) value using the following formula:

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

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 and patients undergoing dialysis	< 10	Contraindicated

Hepatic failure:

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

In pediatric patients with renal impairment, the dose should be individualized based on the patient's renal clearance, age, and body weight.

Geriatric population:

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

4.3. Contraindications

- In patients with a history of hypersensitivity to the active ingredient or any of the excipients of ALLERSET®, to hydroxyzine or to any piperazine derivatives,
- In patients with severe renal impairment at less than 10ml/min creatinine clearance
- In patients with rare hereditary problems of fructose intolerance.

The use of ALLERSET® is not recommended in children under 2 years of age.

4.4. Special warnings and precautions for use

Cetirizine has not shown clinically significant interactions with alcohol (for a blood alcohol level of 0.5 g/L) at therapeutic doses; however, caution is recommended when taken with alcohol.

As cetirizine may increase the risk of urinary retention, it should be used with caution in patients with predisposing factors for urinary retention (e.g., spinal cord lesion, prostatic hyperplasia).

Antihistamines may inhibit responses to allergy skin tests; therefore, a washout period of 3 days is recommended prior to conducting such tests.

The syrup contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, which may cause allergic reactions (possibly delayed).

This medicinal product contains 1 mg of sodium saccharin and 4.20 mg of sodium acetate per ml, which should be taken into consideration in patients on a controlled sodium diet.

The syrup also contains sorbitol. Patients with rare hereditary problems of fructose intolerance should not take this medicine.

Symptoms such as intense itching and/or urticaria may occur after discontinuation of cetirizine, even if these symptoms were not present before starting treatment.

In some cases, these symptoms can be severe and may require reinitiation of treatment. Upon restarting treatment, the symptoms are expected to resolve.

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

Due to the pharmacokinetic and pharmacodynamic tolerance profile of cetirizine, no interactions are expected with this antihistamine.

Indeed, drug–drug interaction studies with pseudoephedrine or theophylline (400 mg/day) have not reported any significant pharmacodynamic or clinically relevant pharmacokinetic interactions.

When taken with food, the extent of absorption is not reduced, although the rate of absorption is decreased.

Cetirizine does not potentiate the effects of alcohol (for a blood alcohol level of 0.5 g/L); however, in sensitive patients, concurrent use of cetirizine with alcohol or other central nervous system depressants may lead to a reduction in alertness and impaired performance.

Additional information on special populations

No clinical interaction studies have been conducted in special populations.

Pediatric population

No clinical interaction studies have been conducted in the pediatric population.

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: “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

Prospective data collected on cetirizine use in pregnancy do not indicate an increased risk of maternal or embryonic/fetal toxicity above the background rate.

Animal studies have not shown any direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development.

Cetirizine should only be administered to pregnant women when clearly necessary, and caution should be exercised during its use.

Lactation

Cetirizine is excreted into breast milk. The risk of adverse effects in breastfed infants cannot be excluded.

Depending on the timing of sampling after administration, 25% to 90% of the plasma concentrations of cetirizine may be transferred to breast milk.

Therefore, the use of cetirizine is not recommended in breastfeeding women.

Fertility

Human fertility data is limited, but no safety concerns have been identified.

Data from animal studies have not shown any reproductive safety concerns in humans.

4.7. Effects on ability to drive and use machines

At the recommended dose of 10 mg, objective measurements of driving ability, sleep onset, and simulated assembly line performance (a computer-based test used to measure the sedative effects of the drug, representing real work environment performance, and sensitive to all variables related to sleepiness) show that patients working in potentially hazardous activities and operating machinery should not exceed the recommended dose and must consider their response to the medicinal product. In these sensitive patients, concomitant use of cetirizine with alcohol and other central nervous system depressants may lead to decreased alertness and impaired performance. Patients with a history of somnolence should avoid driving, working in potentially hazardous activities, and operating machinery. These patients should not exceed the recommended dose and must consider their response to the medicinal product.

4.8. Undesirable effects

Clinical studies have shown that at the recommended dose, cetirizine causes minor adverse effects such as somnolence, fatigue, dizziness, and headache on the central nervous system. In some cases, paradoxical central nervous system stimulation has been reported.

Although cetirizine is a selective peripheral H₁-receptor antagonist and relatively independent of anticholinergic activity, individual cases have reported difficulty urinating, accommodation disorders in the eyes, and dry mouth.

Examples of liver dysfunction with elevated liver enzymes accompanied by increased bilirubin levels have been reported. This condition usually resolves when the drug is discontinued.

In controlled, double-blind, quantitative safety studies comparing cetirizine (10 mg daily) with placebo or other antihistamines, more than 3,200 patients were exposed to cetirizine. The following adverse reactions, observed in placebo-controlled studies from this pooled data, were reported at a rate of 1% or more with 10 mg cetirizine:

Advers reaction (WHO-ART)	Cetirizine 10 mg (n=3260)	Placebo (n=3061)
General disorders and conditions related to the application site		
Fatigue	1.63%	0.95%
Nervous System Disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastrointestinal diseases		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	1.14%
Psychiatric disorders		
Somnolence	9.63%	5%
Respiratory, thoracic, and mediastinal disorders		
Pharyngitis	1.29%	1.34%

In clinical studies, somnolence was statistically more frequent compared to placebo, with the majority of cases being mild to moderate in severity. Objective tests used in other studies showed that, at the recommended daily dose, daily activities were not affected in healthy young volunteers.

Pediatric Population

In placebo-controlled clinical trials, the adverse events reported in children (6 months to 12 years) for cetirizine at a rate of 1% or more are listed below:

Advers reaction (WHO-ART)	Cetirizine 10 mg (n=3260)	Placebo (n=3061)
Gastrointestinal diseases		
Diarrhea	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 in clinical trials and listed above, the following undesirable effects have been reported in post-marketing experience.

The undesirable effects are classified according to the MedDRA System Organ Class and the frequency groups are defined as follows:

- Very common ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1000$ to $< 1/100$)
- Rare ($\geq 1/10000$ to $< 1/1000$)
- Very rare ($< 1/10000$)
- Unknown (cannot be estimated from 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, hallucinations, insomnia

Very Rare: Tics

Unknown: Suicidal thoughts, nightmares

Nervous system disorders:

Uncommon: Paresthesia

Rare: Seizures

Very Rare: Dysgeusia, syncope, tremor, dystonia, dyskinesia

Unknown: Amnesia, memory impairment

Eye disorders:

Very rare: blurred vision, accommodation disorder, oculogyration

Ear and Labyrinth Disorders:

Not known: vertigo

Cardiac disorders:

Rare: tachycardia

Gastrointestinal disorders

Common: abdominal pain^a, dry mouth^a, nausea^a, diarrhoea^b

Hepatobiliary Disorders:

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

Not known: Hepatitis

Skin and subcutaneous tissue disorders:

Uncommon: Skin rash, pruritus

Rare: Urticaria

Very rare: angioedema, fixed drug eruption

Not known: Acute generalized exanthematous pustulosis

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

Explanations related to selected adverse drug reactions

Intense itching and/or urticaria have been reported after discontinuation of treatment with cetirizine.

Reporting of suspected adverse reactions

Talk to your doctor, pharmacist or nurse if you experience any side effects listed or not listed in this leaflet. Also reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Symptoms observed following the intake of an overdose of cetirizine primarily include effects on the central nervous system or symptoms resembling anticholinergic effects.

After taking at least five times the recommended daily dose, adverse events such as confusion, diarrhea, dizziness, fatigue, headache, lethargy, mydriasis, itching, noticeable excessive restlessness with continuous movement, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention have been reported.

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 PROPERTIES**5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: Purine derivatives,
ATC code: R06AE07

Mechanism of action:

Cetirizine, which is the metabolite of human hydroxylase, is a potent and selective peripheral H₁-receptor antagonist.

In vitro receptor binding studies have shown no measurable affinity for receptors other than H₁-receptors. Ex vivo experiments in the mouse have shown that systemically administered cetirizine does not significantly occupy cerebral H(1) receptors.

Pharmacodynamics:

When cetirizine is administered at a dose of 10 mg once or twice a day, it demonstrates not only its anti-H₁ effect but also anti-allergic activity by inhibiting the late-phase accumulation of eosinophils in the skin and conjunctiva of atopic patients exposed to allergens.

Clinical Efficacy and Safety

In studies conducted on healthy volunteers, cetirizine at doses of 5 and 10 mg was found to strongly inhibit erythema and wheal reactions induced by histamine applied at very high concentrations in the skin.

However, no correlation between efficacy and these reactions was established. In a placebo-controlled, 6-week study involving 186 patients with allergic rhinitis accompanied by mild-to-moderate asthma, 10 mg of cetirizine administered once daily significantly improved rhinitis symptoms without affecting pulmonary function. This study supports the safety of cetirizine in patients with mild-to-moderate asthma and allergic rhinitis.

In a placebo-controlled study, cetirizine administered at a high dose of 60 mg daily for 7 days did not cause a statistically significant prolongation of the QT interval. Cetirizine at the recommended dose has been shown to improve the quality of life in patients with seasonal and perennial allergic rhinitis.

Pediatric Population

In a 35-day study conducted in children (ages 5 to 12), no tolerance development was observed against the antihistaminic effects of cetirizine (inhibition of erythema and wheal formation). After repeated administration, once cetirizine treatment was discontinued, the skin's normal reactivity to histamine resumed within 3 days.

5.3. Pharmacokinetic properties

General properties

The distribution of pharmacokinetic parameters such as peak concentration and AUC (Area Under the Curve) is similar.

Absorption:

The steady-state maximum plasma concentration is approximately 300 ng/ml, and it is reached within 1 ± 0.5 hours. When cetirizine is taken with food, there is a decrease in absorption rate, but the total absorption remains unchanged. The bioavailability of cetirizine is similar when administered in solution, capsule, or tablet form.

Distribution:

The apparent volume of distribution of cetirizine is 0.5 l/kg. Cetirizine binds to plasma proteins at a rate of $93 \pm 0.3\%$. Cetirizine does not alter the binding of warfarin to proteins.

Biotransformation

Cetirizine does not undergo extensive first pass metabolism.

Elimination:

The plasma half-life of cetirizine is approximately 10 hours. No accumulation was observed after 10 days of daily 10 mg doses of cetirizine. Two-thirds of the dose is excreted unchanged in the urine.

Linearity / Non-linearity:

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

Characteristic Features in Patients:

Renal Impairment:

In patients with mild renal impairment (creatinine clearance >40 ml/min), the pharmacokinetics of cetirizine are similar to those in healthy volunteers. In patients with moderate renal impairment, the half-life is increased threefold and clearance is reduced by 70%, compared to healthy volunteers. In patients undergoing hemodialysis (creatinine clearance <7 ml/min), after a single oral dose of 10 mg cetirizine, the half-life is three times longer, and clearance is reduced by 70%. Cetirizine is only minimally removed by hemodialysis. Dose adjustments are necessary in patients with moderate to severe renal impairment (see Section 4.2).

Hepatic Impairment:

In patients with chronic liver disease (hepatocellular, cholestatic, and biliary cirrhosis) who were given a single dose of 10 or 20 mg cetirizine, the half-life was increased by 50%, and clearance was reduced by 40%, compared to healthy volunteers. Dose adjustment is necessary only if liver impairment is accompanied by renal impairment.

Geriatric Population:

In sixteen elderly volunteers, following a single dose of 10 mg oral cetirizine, the half-life was 50% longer, and clearance was reduced by 40%, compared to younger volunteers. This decrease in cetirizine clearance in elderly volunteers appears to be related to a decline in renal function.

Pediatric Population:

The half-life of cetirizine is approximately 6 hours in children aged 6-12 years and 5 hours in children aged 2-6 years. In infants aged 6-24 months, the half-life is reduced to 3.1 hours.

Preclinical Safety Data:

Non-clinical data, including safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity, do not indicate any specific risks for humans.

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Non-clinical data, including safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity, do not indicate any specific risks for humans.

PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sorbitol Solution (E420)

Glycerol

Propylene glycol

Saccharin sodium

Banana flavour

Sodium acetate

Acetic acid

Methyl parahydroxybenzoate (E218)

Propyl parahydroxybenzoate (E216)

Deionized water

6.2. . Incompatibilities

Not applicable.

6.3. Shelf Life

36 months

6.4. Special precautions for storage

Store at room temperature below 25°C.

6.5. Nature and contents of container

Cardboard box containing 200 ml amber glass bottle with plastic pilver proof cap, 5 ml plastic graduated measuring spoon and the patient leaflet.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with the “Regulation on Medical Waste” and “Regulation on the Control of Packaging and Packaging Waste”.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST LICENSE/RENEWAL OF THE LICENSE

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]