SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

HITRIZIN 1 mg/ml syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Active ingredient:

Cetirizine dihydrochloride ..... 1 mg

Excipients:

Sorbitol (70%) ..... 150 mg
Methylparaben ..... 1 mg
Propylparaben ..... 0.08 mg
Sodium saccharin ..... 1.5 mg
Sodium acetate trihydrate ..... 2 mg

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Syrup

A nearly colorless to pale yellow clear solution with a characteristic (raspberry) odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

HITRIZIN is indicated for adults and children aged 2 years and above:

For the treatment of nasal and ocular symptoms of allergic rhinitis and symptoms of chronic idiopathic urticaria.

4.2 Posology and method of administration

Posology/frequency and duration of administration:

- Children aged 2-6 years:

2.5 mg twice daily (2.5 ml of syrup twice daily (half a spoon twice a day)).

- Children aged 6-12 years:

5 mg twice daily (5 ml of syrup twice daily (one full spoon twice a day)).

- Adolescents aged 12 years and older and adults:

10 mg once daily (10 ml of syrup once daily (two full spoons once a day)).

Method of administration:

HITRIZIN is for oral use.

Additional information for special populations:
Kidney impairment:
Dose ranges are adjusted according to the patient's kidney function. The dose is adjusted as shown in the table below. To use this table, the patient's creatinine clearance [(CLcr), ml/min] must be calculated.

The CLcr (ml/min) value is calculated from the serum creatinine level (mg/dl) using the following formula.

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

Dose Adjustment in Adult Patients with Kidney Impairment:

Group	**Creatinine Clearance (ml/min)**	**Dose and Dosing Frequency**
Normal	≥ 80	Once daily 10 mg
Mild	50 - 79	Once daily 10 mg
Moderate	30 - 49	Once daily 5 mg
Severe	< 30	Once every two days 5 mg
In end-stage kidney failure and patients on dialysis	< 10	Contraindicated

Liver Impairment:
No dose adjustment is necessary for patients with liver impairment only.

Dose adjustment is recommended for patients with both liver and kidney impairment (see "Kidney Impairment" section).

Pediatric Population:
See the "Posology/Dosage and Duration of Treatment" section.

In pediatric patients with kidney impairment, the dose should be individualized taking into account the patient's renal clearance, age, and body weight.

Geriatric Population:
Data indicate that no dose reduction is necessary in elderly patients with normal kidney function.

4.3 Contraindications

- In patients with a history of hypersensitivity to the active substance of HITRIZIN or any of the excipients, hydroxyzine, or any piperazine derivatives,
- It is contraindicated in patients with severe kidney impairment with creatinine clearance below 10 ml/min.
- It is contraindicated in patients with rare hereditary disorders such as fructose intolerance.

Use of HITRIZIN is not recommended in children under 2 years of age.

4.4 Special warnings and precautions for use

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

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

Caution is advised in epileptic patients and in those at risk of convulsions.

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

This medicinal product contains 1.5 mg of sodium saccharin and 2 mg of sodium acetate trihydrate per ml. This should be taken into account for patients on a controlled sodium diet.

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

Even if intense pruritus and/or urticaria were not present before starting treatment, such symptoms may appear when cetirizine treatment is discontinued. In some cases, these symptoms may be severe and restarting treatment may be necessary. Symptoms should resolve once treatment is restarted.

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. In fact, drug–drug interaction studies conducted with pseudoephedrine or theophylline (400 mg/day) have not reported any pharmacodynamic or significant 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 reduced 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 recommendations
Pregnancy category: "B"

Women of childbearing potential/Birth control (Contraception):
Women of childbearing potential may be treated with cetirizine. Concomitant use of cetirizine and oral contraceptives is not expected to reduce contraceptive efficacy.

Pregnancy:
Prospective data collected on Setirizin during pregnancy do not indicate any potential for maternal or embryonic/fetal toxicity above the rates determined in the past.

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 if clearly necessary, and caution is advised when giving.

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, cetirizine passes into breast milk at levels ranging from 25% to 90% of those measured in plasma; therefore, its use is not recommended in breastfeeding women.

Reproductive ability/Fertility:
Human data on fertility are limited, but no safety concerns have been identified. Animal data do not indicate any safety concerns regarding fertility 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 latency, and performance on a simulated assembly line task (A computerized test used to measure the sedative effect of the drug, representing performance in a real work environment, and sensitive to all variables during sleep.) indicate that patients engaged in potentially hazardous activities or operating machinery should not exceed the recommended dose and should consider their individual response to the medicinal product. In such sensitive patients, concurrent use of cetirizine with alcohol or other central nervous system depressants may lead to reduced alertness and impaired performance. Patients with a history of somnolence should avoid driving, operating machinery, or engaging in potentially hazardous activities. These patients should not exceed the recommended dose and should take into account their individual response to the medicinal product.

4.8 Undesirable effects

Clinical Studies

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

Although cetirizine is a selective peripheral H_1-receptor antagonist and is relatively free of anticholinergic activity, isolated cases of difficulty in urination, accommodation disorders in the eye, and dry mouth have been reported.

There have been reports of liver function abnormalities accompanied by elevated liver enzymes and elevated bilirubin levels. These conditions generally resolved upon discontinuation of the drug.

More than 3,200 patients have been exposed to cetirizine in controlled, double-blind, quantitative safety data clinical or pharmacokinetic studies comparing cetirizine at the recommended dose (10 mg daily) with placebo or other antihistamines. The following adverse reactions are those observed in placebo-controlled studies at a rate of 1% or higher with 10 mg of cetirizine, based on these pooled data:

:

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	% 1.1	% 0.98

Headache	% 7.42	% 8.07
Gastrointestinal disorders: Abdominal pain Dry mouth Nausea	 % 0.98 % 2.09 % 1.07	 %1.08 % 0.82 % 1.14
Psychiatric disorders: Somnolence	 % 9.63	 % 5
Respiratory, thoracic and mediastinal disorders: Pharyngitis	 % 1.29	 % 1.34

In clinical trials, somnolence, which was reported statistically more frequently than with placebo, was mostly mild to moderate in severity. Objective tests used in other studies have shown 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 1% or more of children (aged 6 months to 12 years) receiving cetirizine are listed below:

Adverse Reactions (WHO-ART)	Cetirizine (n=1656)	Placebo (n=1294)
Gastrointestinal disorders: Diarrhea	 % 1	 % 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	 % 0.3

Post-Marketing Experience
In addition to the adverse reactions reported in clinical trials and listed above, the following undesirable effects have been reported during post-marketing experience.

Adverse effects are classified according to the MedDRA System Organ Class and frequency categories as defined below:

Very common (≥ 1/10); Common (≥ 1/100 ila < 1/10); Uncommon (≥ 1/1000 ila < 1/100*)*; Rare (≥ 1/10000 ila <1/1000); Very rare (< 1/10000), Unknown (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:
Uncommon: Agitation
Rare: Aggression, confusion, depression, hallucination, insomnia
Very rare: Tick
Unknown: Suicidal ideation, nightmares

Nervous system disorders:
Uncommon: Paresthesia
Rare: Convulsions
Very rare: Taste disorder, syncope, tremor, dystonia, dyskinesia
Unknown: Amnesia, memory impairment

Eye disorders:
Very rare: Blurred vision, accommodation disorder, oculogyration

Ear and labyrinth disorders:
Unknown: Vertigo

Cardiac disorders:
Rare: Tachycardia

Gastrointestinal disorders:
Uncommon: Diarrhea

Hepatobiliary disorders:

Rare:	Liver function impairment (increased transaminases, alkaline phosphatase, γ-GT, and bilirubin)
Unknown:	Hepatitis

Skin and subcutaneous tissue disorders:

Uncommon:	Itching, rash
Rare:	Urticaria
Very rare:	Angioneurotic edema, fixed drug eruption
Unknown:	Acute generalized exanthematous pustulosis

Musculoskeletal, connective tissue and bone disorders:

Unknown:	Arthralgia

Renal and urinary disorders:

Very rare:	Dysuria, enuresis
Unknown:	Urinary retention

General disorders and administration site conditions:

Uncommon:	Asthenia, malaise
Rare:	Edema

Investigations:

Rare:	Weight increase

Explanations regarding selected adverse drug reactions:
Intense itching and/or urticaria have been reported after discontinuation of cetirizine treatment.

Reporting of suspected adverse reactions
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 and Treatment
Following an overdose of cetirizine, symptoms primarily related to central nervous system effects or those resembling anticholinergic effects may be observed.

Adverse events reported with ingestion of at least five times the recommended daily dose include confusion, diarrhea, dizziness, fatigue, headache, malaise, mydriasis, itching, marked

restlessness with incessant movement, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.
There is no known specific antidote for cetirizine. In case of overdose, symptomatic or supportive treatment is recommended. Gastric lavage may be considered if the drug was recently ingested. Cetirizine is not effectively removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antihistamines, piperazine derivatives
ATC code: R06AE07

Mechanism of Action:
Cetirizine, a metabolite of hydroxyzine in humans, is a potent and selective peripheral H_1-receptor antagonist.

In vitro receptor binding studies have shown that cetirizine has no measurable affinity for receptors other than H_1 receptors.

Pharmacodynamic Effects:
When administered once or twice daily at a dose of 10 mg, cetirizine not only exhibits anti-H_1 effects but also demonstrates anti-allergic activity by inhibiting late-phase eosinophil accumulation in the skin and conjunctiva of atopic patients exposed to allergens.

Clinical Efficacy and Safety:
Studies in healthy volunteers have shown that cetirizine, at doses of 5 and 10 mg, strongly inhibits the erythema and wheal reactions induced by intradermally administered histamine at very high concentrations, although a correlation with clinical efficacy has not been established.
In a placebo-controlled, 6-week study involving 186 patients with allergic rhinitis accompanied by mild to moderate asthma, once-daily administration of 10 mg cetirizine improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of cetirizine use in allergic patients with mild to moderate asthma.

In a placebo-controlled study, administration of a high dose of 60 mg cetirizine 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 quality of life in patients with seasonal and perennial allergic rhinitis.

Pediatric Population:

In a 35-day study conducted in children (aged 5 to 12 years), no tolerance developed against the antihistaminic effects of cetirizine (suppression of erythema and wheal). After repeated administration, normal skin reactivity to histamine returned within 3 days following discontinuation of cetirizine treatment.

5.2 Pharmacokinetic properties

General properties

The distribution of pharmacokinetic parameters such as peak concentration and AUC is similar.

Absorption:

The steady-state maximum plasma concentration is approximately 300 ng/ml, reached within 1 ± 0.5 hours.

When taken with food, cetirizine's absorption rate decreases, but the extent of absorption remains unchanged. The bioavailability of cetirizine is similar whether administered as a solution, capsule, or tablet.

Distribution:

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

Biotransformation:

Cetirizine does not undergo extensive first-pass metabolism.

Elimination:

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

Linearity/Non-linearity:

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

Characteristics in Patients

Kidney Impairment:

Pharmacokinetics in patients with mild kidney impairment (creatinine clearance above 40 ml/min) are similar to those in healthy volunteers. In patients with moderate kidney impairment, the half-life is increased threefold, and clearance is reduced by 70% compared to healthy volunteers.

In hemodialysis patients (creatinine clearance below 7 ml/min) given a single oral 10 mg dose of cetirizine, half-life is increased threefold and clearance decreased by 70% compared to

normal volunteers. Cetirizine is only minimally removed by hemodialysis. Dose adjustment is necessary in patients with moderate to severe kidney impairment (see Section 4.2).

Liver Impairment:
In chronic liver disease patients (hepatocellular, cholestatic, and biliary cirrhosis) given single doses of 10 or 20 mg cetirizine, the half-life is increased by 50%, and clearance is reduced by 40% compared to healthy volunteers. Dose adjustment is only required if hepatic impairment is accompanied by renal impairment.

Geriatric Population:
In sixteen elderly volunteers given a single 10 mg oral dose of cetirizine, half-life was increased by 50% and clearance decreased by 40% compared to younger volunteers. This reduction in clearance appears related to decreased renal function in elderly volunteers.

Pediatric Population:
The half-life of cetirizine is approximately 6 hours in children aged 6-12 years, 5 hours in children aged 2-6 years, and decreases to 3.1 hours in infants aged 6-24 months.

5.3 Preclinical safety data
Non-clinical data, based on conventional studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and reproductive toxicity, do not indicate any special hazard for humans.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Propylene glycol
Glycerin
Sorbitol (70%)
Sodium saccharin
Methylparaben
Propylparaben
Sodium acetate trihydrate
Acetic acid (33% v/v)
Raspberry flavor
Deionized water
6.2 Incompatibilities
There is no known incompatibility.

6.3 Shelf life
60 months

6.4 Special precautions for storage
Store at room temperature below 25°C.

6.5 Nature and Contents of the Packaging
Amber-colored glass bottles containing 150 ml and 200 ml of syrup, closed with an HDPE plastic cap.

Each carton box contains one bottle of syrup 75 ml, 150 ml, or 200 ml and one 5 ml spoon marked at 2.5 ml.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product
Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORIZATION HOLDER
Deva Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad.
No:1 34303 Küçükçekmece-İSTANBUL/TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24

8. MARKETING AUTHORISATION NUMBER
180/99

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 21.01.1997
Date of latest renewal:

10. DATE OF REVISION OF THE SPC