# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

HITRIZIN 10 mg Film Coated Tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
**Active substance:**
Cetirizine dihydrochloride 10 mg

**Excipients:**
Lactose monohydrate 79 mg (from cow milk)
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film Coated Tablet
White, film-coated, slightly convex, oblong tablets embossed “HTZ” on one side and scored on the other.
The score is to help to break the tablet into two halves.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

In adults and children aged 6 years and over:
HITRIZIN is indicated for the treatment of nasal and ocular symptoms of allergic rhinitis, and treatment of symptoms of urticaria.

### 4.2 Posology and method of administration

**Posology/frequency and duration of administration:**
In children between 6-12 years:
Twice daily 5 mg (twice daily 1/2 tablet)

In adults and adolescents over 12 years of age:
Once daily 10 mg (1 tablet)

**Method of administration:**
HITRIZIN is for oral use; it must be swallowed with a glass of water.

**Additional information on special populations**

**Renal impairment**
The dosing intervals are individualized according to renal function. Dose is adjusted as indicated by referring to the following table. To use this 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:

$$\text{CLcr (mL/ min)} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \text{ (x 0.85 – for women)}$$

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 - Patients undergoing dialysis | <10 | Contra-indicated |

**Hepatic impairment:**
No dose adjustment is needed in patients with solely hepatic impairment.
In patients with hepatic impairment and renal impairment, dose adjustment is recommended (see "Renal impairment").

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

HITRIZIN tablet should not be used in children below 6 years of age as this pharmaceutical form is unsuitable for the necessary dosage adjustments.

In pediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the patient's renal clearance, age and body weight.

**Geriatric population:**
Data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

**4.3 Contraindications**
It is contraindicated in

- Hypersensitivity to the active substance of HITRIZIN, to any of the excipients, to hydroxyzine or to any piperazine derivatives.
- Patients with severe renal impairment at less than 10 mL/min creatinine clearance.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption.

HITRIZIN tablet should not be used in children below 6 years of age as this pharmaceutical form is unsuitable for the necessary dosage adjustments. A pediatric form of cetirizine is recommended.

**4.4 Special warning 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 advised in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.

Allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

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

HITRIZIN contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

Pruritus and/or urticaria may occur when cetirizine is stopped, even if those symptoms were not present before treatment initiation. In some cases, the symptoms may be intense and may require treatment to be restarted. The symptoms should resolve when the treatment is restarted.

**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. Actually, neither pharmacodynamic nor significant pharmacokinetic interaction was reported in drug-drug interactions studies performed, notably with pseudoephedrine or theophylline (400 mg/day).
The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.
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 (for a blood alcohol level of 0.5 g/L).

**Additional information on special populations**
No clinical interaction studies have been conducted with special populations.

**Pediatric populations**
No clinical interaction studies have been conducted with pediatric populations.

**4.6 Fertility, pregnancy and lactation**

**General Recommendation**
Pregnancy category is “B”.

**Women of child-bearing potential/ Contraception**
Women of child-bearing potential can be treated with cetirizine. Concomitant use of cetirizine and oral contraceptives is not expected to decrease efficacy of contraception.

**Pregnancy**
For cetirizine prospectively collected data on pregnancy outcomes do not suggest potential for maternal or fetal/embryonic toxicity above background rates.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should nevertheless be exercised when prescribing to pregnant women.

It should be applied to pregnant women only when absolutely necessary, and caution should be exercised when administering.

**Breast-feeding**
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.

**Fertility**
Data on fertility in humans are limited, but no problem with safety has been identified. Data from animals did not show a safety problem related to fertility in humans.

**4.7 Effects on ability to drive and use machines**
At the recommended dose of 10 mg; based on objective measurements of driving ability, sleep latency and simulated assembly line performance (measurement test used to measure sedative effect of the drug, representing the actual performance in work environment, applied with computer and sensitive to all the variables in state of sleep), patients working in potentially hazardous activities or operating machinery should not exceed the recommended dose and should consider their response to the medicinal product.

In sensitive patients, concurrent use of cetirizine with alcohol or other CNS depressants may cause additional reductions in alertness and impairment of performance.

However patients who experience somnolence should refrain from driving, engaging in potentially hazardous activities or operating machinery. They should not exceed the recommended dose and should take their response to the medicinal product into account.

**4.8 Undesirable effects**
Clinical studies
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 treatment with the drug.
Double-blind, controlled, clinical or pharmacoclinical 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*** | 1.10% | 0.98% |

| | | |
|---|---|---|
| Dizziness<br>Headache | 7.42% | 8.07% |
| ***Gastro-intestinal disorders***<br>Abdominal pain<br>Dry mouth<br>Nausea | <br>0.98%<br>2.09%<br>1.07% | <br>1.08%<br>0.82%<br>1.14% |
| ***Psychiatric disorders***<br>Somnolence | 9.63% | 5.00% |
| ***Respiratory, thoracic and mediastinal disorders***<br>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.

Pediatric 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 disorders***<br>Diarrhea | 1.0% | 0.6% |
| ***Psychiatric disorders***<br>Somnolence | 1.8% | 1. 4% |
| ***Respiratory, thoracic and mediastinal disorders***<br>Rhinitis | 1.4% | 1.1% |
| ***General disorders and administration site conditions***<br>Fatigue | 1.0% | 0.3% |

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

Undesirable effects are described according to MedDRA System Organ Class and frequencies are defined as follows:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <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

**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, nightmares

**Nervous system disorders**
*Uncommon*: paresthesia
*Rare*: convulsions,
*Very rare*: dysgeusia, dyskinesia, dystonia, syncope, tremor
*Not known*: amnesia, memory impairment

**Eye disorders**
*Very rare*: blurred vision, accommodation disorder, oculogyration

**Ear and labyrinth disorders**
*Not known*: vertigo

**Cardiac disorders**
*Rare*: tachycardia

**Gastro-intestinal disorders**
*Uncommon:* diarrhea

**Hepatobiliary disorders**
*Rare*: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)
*Unknown*: hepatitis

**Skin and subcutaneous tissue disorders**
*Uncommon*: pruritus, rash
*Rare*: urticaria
*Very rare*: angioneurotic edema, fixed drug eruption
*Unknown*: acute generalized exanthematous pustulosis

**Musculoskeletal and connective tissue disorders**
*Unknown*: arthralgia

**Renal and urinary disorders**
*Very rare*: dysuria, enuresis
*Not known*: urinary retention

**General disorders and administration site conditions**
*Uncommon*: asthenia, malaise
*Rare*: edema

**Investigations**
*Rare*: weight increased

Description of selected adverse reactions

After discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported.

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**
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, diarrhea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.
There is no known specific antidote to cetirizine. Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered following ingestion of a short occurrence. Cetirizine is not effectively removed by hemodialysis.

## 5. PHARMACOLOGICAL PROPERTIES

**5.1 Pharmacodynamic properties**
**Pharmacotherapeutic group**: Systemic antihistaminics, piperazine derivatives
**ATC code:** R06AE07

Mechanism of action:
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 of Cetirizine for other than 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 eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

Clinical efficacy and safety
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 6-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 7 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.

Pediatric population
In a 35-day study in children aged 5 to 12, no tolerance to the antihistamine 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**

**General properties**

The distribution of pharmacokinetic parameters such as peak plasma concentration and area under curve (AUC) is similar.

Absorption:

The steady - state peak plasma concentration is approximately 300 ng/mL and is achieved within 1 ± 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 0.5 L/kg. Plasma protein binding of cetirizine is 93 ± 0.3%. Cetirizine does not modify 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. Accumulation was not observed with daily 10 mg dose of cetirizine for 10 days. 2/3 of the dose are excreted unchanged in urine.

Linearity/Non-linearity

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

**Characteristics in patients**

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 healthy volunteers. Cetirizine was poorly cleared by hemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment (see section 4.2).

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 the healthy volunteers. Dosing adjustment is only necessary in hepatically impaired patients if concomitant renal impairment is present.

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 younger 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 aged 6 to 24 months, it is reduced to 3.1 hours.

**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**
Maize starch
Sodium starch glycolate
Lactose monohydrate
Colloidal silicon dioxide
Magnesium stearate

Opadry OY-38951 white:
Hydroxypropyl methyl cellulose
Titanium dioxide
Polyethylene glycol
Talc

**6.2 Incompatibilities**
Not applicable.

**6.3 Shelf life**
36 months

**6.4 Special precautions for storage**
Keep at room temperature below 25°C. Protect from light.

**6.5 Nature and contents of container**
Blisters of 10 tablets coated with transparent PVC/PVDC foil on one side while coated with printed aluminum foil on the other.
Each cardboard box contains 10 or 20 tablets.

**6.6 Special precautions for disposal and other handling**
Any unused material should be disposed according to local disposal regulations.

## 7. MARKETING AUTHORIZATION HOLDER

DEVA Holding A.Ş.
Halkalı Merkez Mah. Basın Ekspres Cad. No.:1
34303 Küçükçekmece – ISTANBUL/TÜRKİYE
Phone: +90 212 692 92 92
Fax: +90 212 697 00 24
E-mail: deva@devaholding.com.tr

## 8. MARKETING AUTHORIZATION NUMBER

180/98

## 9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization : 21.01.1997
Date of last renewal :

## 10. REVISION DATE OF TEXT