SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ROLINOZ 10 mg Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Each film-coated tablets contains 10 mg Cetirizine dihydrochloride.

Excipients:

Lactose monohydrate	35.00 mg
Sodium starch glycolate	2.40 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

White, oblong, two sided notched film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine; in adults and children aged 6 years and older:

It is indicated in the treatment of nasal and ocular symptoms of allergic rhinitis, symptoms of chronic idiopathic urticarial and in the symptomatic treatment of itching.

4.2 Posology and method of administration

Posology and frequency/time of administration:

In adults and children aged 6 years and older: 5 mg (1/2 tablet) or 10 mg (1 tablet) is administered once a day depending on the severity of symptoms.

Method of administration:

ROLINOZ Tablets is for oral use, should be swallowed with one glass of water.

Additional information for special population:

Renal Failure:

Dose intervals are adjusted in accordance with the renal function of the individual. Dose is adjusted by using the table as shown below. The creatinine clearance [CL_{cr} (mL/min)] should be calculated in order to use this table.

The CL_{cr} (mL/min) value is calculated from serum creatinine (mg/dl) value according to the formula below.

$$CL_{cr} = \frac{[140 - age(years)] \, x \, weight \, (kg)}{72 \, x \, serum \, creatinine \, (mg \, / \, dl)} \, (x \, 0.85 \, for \, women)$$

Dosing adjustments for patients with impaired renal function

Group	Creatinine clearance (mL/minute)	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
In patients at end-stage renal failure and undergoing dialysis	<10	Contra-indicated

In pediatric patients with renal failure, the dose should be individualized on the basis taking into account the renal clearance of the patient and body weight.

Hepatic Failure:

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

Dose adjustment is recommended in patients with hepatic and renal failure (see "renal failure" section).

Peadiatric population:

See "Posology and method of administration" section.

Geriatric population:

Data have been shown that reduction in dose is not necessary in geriatric patients with normal renal function.

4.3 Contraindications

It is contraindicated in patients with

- Hypersensitivity history to the active substance of ROLINOZ or to any of the excipients, to hydroxyzine or to any piperazine derivatives.
- severe renal failure that the creatinine clearance is less than 10 mL/min
- rare hereditary problems such as galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption.

4.4 Special warnings and precautions for use

At therapeutic doses, cetirizine have been demonstrated no clinically significant interactions with alcohol (for a blood alcohol level of 0.5 g/L), nevertheless, precaution is recommended if alcohol is taken concomitantly.

Caution should be taken in patients with predisposition factors of urinary retention (e.g. spinal cord lesion, prostatic hyperplasia) as cetirizine may increase the risk of urinary retention.

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

The use of the ROLINOZ 10 mg Film-coated Tablet is not recommended in children aged less than 6 years since this formulation does not allow appropriate dose adaptation.

ROLINOZ contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption problem should not use this drug.

ROLINOZ contains sodium less than 1 mmol (23 mg) in each tablet; no sodium-induced side effect at this dose is expected.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction studies of Cetirizine with pseudoephedrine, antipyrine, cymetidine, ketoconazole, erythromycin and azithromycin have been performed and no pharmacokinetic interaction has been observed. In a multiple dose study performed with Cetirizine and Theophylline (400 mg once a day), a small decrement (16%) in Cetirizine clearance has been observed, however, the distribution of Theophylline administered concomitantly with Cetirizine has not changed.

In studies performed with cymetidine glipizide, diazepam, antipyrine and pseudoephedrine administered concurrently with Cetirizine, no proof related to adverse Pharmacodynamics interactions has been detected.

In studies performed with azithromycin, erythromycin, ketoconazole, theophylline and pseudoephedrine administered concurrently with Cetirizine, no adverse clinical interaction has been detected. Especially, no clinically significant ECG change has been observed as a result of concomitant administration of cetirizine with macrolides or ketoconazole.

In a multiple dose study performed with Ritonavir (600 mg twice a day) and Cetirizine (10 mg Daily), exposure to Cetirizine was increased by 40% approximately and Ritonavir distribution slightly changed (-11%), when administered with Cetirizine.

When it was taken with foods, the absorption amount did not decreased, however, there was a reduction in the absorption rate.

Antihistamines inhibits allergic tests, therefore a cleaning period for 3 days before administration of these tests is recommended.

4.6 Pregnancy and lactation

General recommendation:

Pregnancy category: "B"

Women of childbearing potential / Birth Control (Contraception):

Women with childbearing potential can be treated with Cetirizine. It is not expected that the concomitant use of Cetirizine and oral contraceptives to decrease contraception efficacy.

Pregnancy

Clinical data on the exposure of Cetirizine in pregnancy is very few.

Studies conducted on animals do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

It should only be administered in pregnant women if necessary and caution should be exercised when it is given.

Lactation period:

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

Reproduction ability/Fertility

Studies conducted on animals has shown that Cetrizine has no effect on fertility.

4.7 Effects on ability to drive and use machines

Objective measurements of driving ability, sleep latency and assembly line performance (measurement test of drug used in measurement of sedative effect, representing the performance of the real business environment, performed with computer and sensitive to all somnolence variables) have not demonstrated any clinically significant 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 type of sensitive patients, concurrent use with alcohol or other central nervous system depressants may cause reductions in alertness and impairment of performance.

4.8 Undesirable effects

Clinical studies have shown that cetirizine at the recommended dosage has minor adverse 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 H_1-receptors and is relatively free of anticholinergic activity, difficulty in urination, 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. This case stops mostly upon discontinuation of the drug.

In clinical studies, somnolence, which is more common than placebo statistically, is mild to moderate in most cases. In objective tests used in other studies have demonstrated that daily activities has not been affected at the recommended dose daily in healthy young volunteers. Undesirable effects are described according to MedDRA System Organ Class and the frequencies are defined as follows (The marked ones of these adverse effects has been informed only in placebo-controlled clinical studies, the unmarked ones belong to the post marketing experience.):

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:

Common: Somnolence[a,b]

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tics

Not known: suicidal ideation

Nervous system disorders:

Common: Dizziness[a], headache[a]

Uncommon: paraesthesia

Rare: convulsions, movement disorders

Very rare: Taste disorder, 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

Respiratory, chest disorders and mediastinal diseases

Common: pharyngitis[a], rhinitis[b]

Gastro-intestinal disorders:

Common: Stomach-ache[a], dry-mouth[a], nausea[a], diarrhea[b]

Hepatobiliary diseases:

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

Skin and subcutaneous tissue disorders:

Uncommon: pruritus, rash

Rare: urticaria

Very rare: angioneurotic oedema, fixed drug eruption

Renal and urinary disorders:

Very rare: dysuria, enuresis

Not known: urinary retention

General disorders and administration site conditions:

Common: Weakness[a, b]

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight increased

[a]More than 3200 patients were exposed to Cetirizine in a clinical and pharmacoclinic studies with controlled, double blinded qualitative safety data in which Cetirizine is compared with placebo at the recommended dose (10 mg daily) or other antihistamines. These are adverse events seen commonly with 10 mg Cetirizine from these gathered data in placebo controlled studies.

[b] In placebo controlled studies, they are commonly known adverse events for Cetirizine in children (6 months - 12 years old).

4.9 Overdose and treatment

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, diarrhoea, dizziness, fatigue, headache, malaise, mydriasis, pruritus, a state of severe restlessness which is notable with continuous motion, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

There is no known specific antidote to Cetirizine. When overdose occurs, symptomatic or supportive treatment is recommended. Gastric lavage should be considered if the drug is taken short time ago. Cetirizine cannot be effectively removed by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1-receptors.

Mechanism of action: *In vitro* receptor binding studies have shown no measurable affinity for receptors other than H_1-receptors of Cetirizine. *Ex vivo* experiments on rats have demonstrated that Cetirizine administered systematically has not significantly occupied cerebral H_1 receptors.

Pharmacodynamic effects:
In addition to its anti-H_1 effect, Cetirizine inhibits the late phase accumulation of inflammation cells as to be specially eosinophils in in the skin and conjunctiva of atopic patients submitted to allergen exposure when it is administered at a dose of 10 mg once or twice daily by also displaying anti-allergic activities.

At 30 mg daily dose, it inhibits the flow of eosinophils to bronco- alveolar liquid at the late phase bronchial construction in asthma patients exposed to specific allergen inhalation. In addition, Cetirizine inhibits the late phase inflammatory reaction stimulated by the intradermal administration of kallikrein in chronic urticaria patients. Moreover, it decreases the expression of adhesion molecules such as ICAM-I and VCAM-I which are indicators of allergic inflammation.

In studies performed in healthy volunteers, it has been observed that Cetirizine, at doses of 5 and 10 mg strongly inhibits the redness and bulging induced by histamine administered at very high concentrations into the skin. The effect following a single dose 10 mg Cetirizine starts in 20 minutes of 50% of the subjects and in 1 hour in 95%. This effects lasts for at least 24 hours following a single dose. In a 35-day study in children (aged 5 to 12), no tolerance to the antihistaminic effect (suppression of redness and bulging) of Cetirizine was found. When a treatment with cetirizine is stopped after repeated administrations, the normal reactivity of skin to histamine starts within 3 days again.

In a six-week, placebo-controlled study of 186 patients with allergic rhinitis that mild to moderate asthma accompanies, Cetirizine administered 10 mg once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administration of Cetirizine in 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 characteristics

In human, the distribution of pharmacokinetic parameters such as peak concentration and AUC are similar and no differences in Cetirizine kinetics have been observed in caucasian or black adults.

Absorption:

The steady - state maximum plasma concentrations is approximately 300 ng/mL and is achieved to this concentration within 1.0 ± 0.5 h.

The absorption amount does not change, although there is a decrement in absorption rate, when it is taken with foods. When Cetirizine is given in solution, capsule or tablet form, its bioavailability is similar.

Distribution:

The apparent distribution volume of Cetirizine is 0.5 L/kg. Cetirizine binds to plasma proteins in a ratio of 93% ± 0.3%. Cetirizine does not change the protein binding of warfarin.

Biotransformation:

Cetirizine does not undergo extensive first pass metabolism.

Elimination:

The plasma half-life of is Cetirizine approximately 10 hours. No accumulation is observed for Cetirizine with daily doses of 10 mg for 10 days. 2/3 of dose stays unchanged.

Linearity/Non-linear situation:

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

Characteristic Properties in Patients

Geriatric population:

Following a single 10 mg oral Cetirizine 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.

Peadiatric 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.

Renal failure:

The pharmacokinetics of the drug is similar in patients with mild renal failure (creatinine clearance higher than 40 mL/min) and healthy volunteers. The half-life increased 3-fold and clearance decreased by 70 % in patients with moderate renal failure compared to healthy volunteers. The half-life increased 3-fold and clearance decreased by 70% in hemodialysis. patients (creatinine clearance lower than 7 mL/min) given a single oral 10 mg dose of cetirizine compared to healthy volunteers. Cetirizine is cleared poorly by hemodialysis. Dosing adjustment is necessary in patients with moderate or severe renal impairment (see section 4.2).

Hepatic failure:

The half-life increased by 50% and clearance decreased by 40 % in patients with chronic liver diseases (hepatocellular, cholestatic, and biliary cirrhosis) given single dose of 10 or 20 mg of cetirizine compared to healthy subjects. Dosing adjustment is only necessary if renal failure accompanies liver failure.

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

Microcrystalline cellulose

Lactose monohydrate

Silica colloidal anhydrous

Sodium starch glycolate (Type A)

Magnesium stearate

Opadry® II 85F18422 White

- Polyvinyl alcohol
- Titanium dioxide (E 171)
- Polyethylene glycol 3350 (Macrogol 400)
- Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C at room temperature.

6.5 Nature and contents of container

Alu-PVC blister packaging;

Boxes containing 10 tablets in blister

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

World Medicine İlaç San. ve Tic. A.Ş.
Bağcılar/İstanbul/TURKEY

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization:
Renewal of the authorization:

10. DATE OF REVISION OF THE TEXT