SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ROLINOZ 10 mg/mL Oral Drops

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Cetirizine dihydrochloride	10 mg/ml

Excipients:

Methyl parahydroxybenzoate	1.35 mg/mL
Propyl parahydroxybenzoate	0.15 mg/mL
Propylene glycol	350 mg/mL

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral drops.

Colorless clear liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine is indicated in adults, children, infants 2 year and above;

It is indicated for the treatment of nasal and ocular symptoms of allergic rhinitis, the treatment of symptoms of chronic idiopathic urticaria, and the symptomatic treatment of pruritus.

4.2 Posology and method of administration

Posology/frequency of administration and period

Children aged from 2 to 6 years: 2.5 mg (5 drops) is administered once a day. In this age group, the daily dose can be increased to 5 mg. It can be administered 5 mg (10 drops) once a day or 2.5 mg (5 drops) twice a day (every 12 hours).

Children aged from 6 to 12 years: Depending on the severity of the symptoms, 5 mg (10 drops) or 10 mg (20 drops) is administered once a day, or it can be administered by dividing the daily dose into two.

Children aged 12 years above and adults: Depending on the severity of the symptoms, 5 mg (10 drops) or 10 mg (20 drops) are administered once a day.

Route of administration:

ROLINOZ is for oral use.

ROLINOZ should be taken by diluting in some amount of liquid.

Additional information about special populations:

Renal impairment:

Dosage intervals are adjusted according to the renal function of the person. Adjust the dose as shown using the table below. To use this table, the patient's creatinine clearance [(CLcr), ml/min] should be calculated.

CLcr (ml/min) value; It is calculated over serum creatinine value (mg/dl) according to the formula below.

$$\text{CLcr (mL/min.)} = \frac{[\,140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \quad (\times 0.85 \text{ - in women})$$

Dosing adjustments for adult patients with Kidney Dysfunction:

Group	**Creatinine clearance (ml/min)**	**Posology and frequency**
Normal	≥80	10 mg once a day
Light	50-79	10 mg once a day
Mild	30-49	5 mg once a day
Severe	<30	Once every 2 days, 5 mg once
In patients with end-stage renal impairment and on dialysis	< 10	Contraindicated

Hepatic impairment:

Any dose adjustment is not required only in patients with hepatic impairment.

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

Pediatric population: See section ‘Posology/frequency of administration and period’.

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

Geriatric population:

Data suggest that dose reduction is not required in the elderly with normal renal function.

4.3 Contraindications

It is contraindicated

- in patients with a history of hypersensitivity to the active substance of ROLINOZ or any of the excipients, hydroxyzine or any of its piperazine derivatives,
- in patients with severe renal impairment with creatinine clearance below 10 ml/min.

ROLINOZ should not be used in children under 2 years of age.

4.4. Special warnings and precautions for use

Cetirizine showed no clinically relevant interactions with alcohol (for alcohol level of 0.5 g/l in blood) at therapeutic doses, but caution is recommended when co-administered with alcohol.

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

Since ROLINOZ contains methyl parahydroxybenzoate and propyl parahydroxybenzoate, it may cause allergic reactions (possibly delayed).

ROLINOZ may cause alcohol-like symptoms due to the propylene glycol it contains.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interaction studies were conducted with cetirizine and pseudoephedrine, antipyrine, cimetidine, ketoconazole, erythromycin, and azithromycin; no pharmacokinetic interactions were 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.

In studies with cimetidine, glipizide, diazepam, antipyrine, and pseudoephedrine co-administered with cetirizine, no evidence of adverse pharmacodynamic interactions detected.

Studies with azithromycin, erythromycin, ketoconazole, theophylline and pseudoephedrine co-administered with cetirizine did not reveal any adverse clinical interactions. In particular, no clinically significant ECG changes have ever been observed as a result of co-administration of cetirizine with macrolides or ketoconazole.

In a multiple dose study with ritonavir (600 mg twice a day) and cetirizine (10 mg a day), exposure to cetirizine was increased by approximately 40%, with the distribution of ritonavir slightly altered (-11%) when co-administered with cetirizine.
The amount of absorption was not decreased when taken with food, but there was a decrease in the rate of absorption.

Antihistamines inhibit allergy skin tests; therefore a 3-day washout period is recommended prior to performing these tests.

Cetirizine does not potentiate the effects of alcohol (for a blood alcohol level of 0.5 g/l), but in susceptible patients, simultaneous use of cetirizine with alcohol or other central nervous system depressants may lead to decreased alertness and impaired performance.

4.6 Pregnancy and lactation:

General recommendation:

Pregnancy category: "B"

Women of childbearing potential / birth control (contraception):

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

Pregnancy Period:

Prospectively collected data on pregnancy for cetirizine do not indicate a potential for maternal or embryonal/fetal toxicity beyond historically established rates.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

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

Lactation Period:

After administration, cetirizine is excreted into breast milk at a rate of 25%-90% relative to that measured in plasma, depending on sampling time points; therefore, it is not recommended for use in lactating women.

Reproductive ability / fertility

Data on fertility in humans are limited, however no safety issues have been identified. Data from animals have not shown a reproductive safety issue in humans.

4.7 Effects on ability to drive and use machines

At the recommended 10 mg dose, objective measures of driving ability, falling asleep, and simulated assembly line performance (a computerized test used to measure the sedative effect of the drug, representing performance in a real work environment, and sensitive to all variables in sleep) and patients using machinery should not exceed the recommended dose and should take into account their response to the medicinal product. In such susceptible patients, concomitant use of cetirizine with alcohol and other central system depressants may lead to decreased alertness and impaired performance. Patients with a history of somnolence should avoid driving, engaging in potentially hazardous activities, and operating machinery. These patients should not exceed the recommended dose and should take into account their response to the medicinal product.

4.8 Undesirable effects

Clinical studies have demonstrated that cetirizine at the recommended dose exhibits minor adverse effects on the central nervous system such as somnolence, fatigue, drowsiness and headache. Paradoxical central nervous system stimulation has been reported in some cases.

Although cetirizine is a selective peripheral H1-receptor antagonist and relatively independent of anticholinergic activity, individual cases of urination difficulty, ocular adjustment disorders, and dry mouth have been reported.

Examples of liver function abnormalities with elevated liver enzymes accompanied by increased bilirubin have been reported. This usually ends when the drug is discontinued.

Somnolence, which was statistically more common in clinical trials than placebo, was mild to moderate in the majority of cases. Objective tests used in other studies have shown that daily activities are not affected in healthy young volunteers at the recommended daily dose. Undesirable effects are defined according to MedDRA System Organ Class and frequency grouping as follows (These adverse effects with labels have been reported only in placebo-controlled clinical studies, those without labels are from post-marketing experience);

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:

Unknown: increased appetite

Psychiatric disorders:

Common: somnoloance[a,b]

Uncommon: agitation

Rare: aggression, confusion, depression, hallucinations, insomnia

Very rare: tics

Unknown: suicidal ideation

Nervous system disorders:

Common: dizziness[a], headache[a]

Uncommon: paraesthesia

Rare: convulsions, movement disorders

Very rare: taste perversion, dyskinesia, dystonia, syncope, tremor

Unknown: amnesia, memory impairment

Eye disorders:

Very rare: blurred vision, accommodation disorder, oculogyration

Ear and internal ear disorders:

Unknown: vertigo

Cardiac disorders:

Rare: tachycardia

Respiratory, thoracic disorders and mediastinal diseases:

Common: pharyngitis[a], rhinitis[b]

Gastro-intestinal disorders:

Uncommon: abdominal pain[a], dry mouth[b], nausea[a], diarrhoea[b]

Hepatobiliary disorders:

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

Skin and subcutaneous tissue disorders:

Uncommon: pruritis, rash

Rare: urticaria

Very rare: angioneurotic oedema, fixed drug eruption

Renal and urinary disorders:

Very rare: dysuria, enuresis

Unknown: urinary retention

General disorders and administration site conditions:

Common: asthenia[a,b]

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight gain

[a] More than 3,200 patients were exposed to cetirizine in controlled, double-blind, clinical or pharmacoclinical studies with quantitative safety data comparing cetirizine to placebo or other antihistamines at the recommended dose (10 mg daily). From these pooled data, adverse events were commonly seen with cetirizine 10 mg in placebo-controlled studies.

[b] Adverse events commonly reported for cetirizine in children (6 months to 12 years) in placebo-controlled studies.

4.9 Overdose and treatment

The symptoms observed following an overdose of cetirizine are mainly accompanied by central nervous system effects or effects that seem to be anticholinergic effects.

Adverse events such as confusion, diarrhoea, dizziness, malaise, headache, malaise, mydriasis, pruritus, irritability with relentless movement, sedation, somnolence, stupor,

tachycardia, tremor, and urinary retention at doses at least 5 times the recommended daily dose has been reported.

There is no known specific antidote for cetirizine. When overdose occurs, symptomatic or supportive treatment is recommended. Gastric lavage may be considered if the drug has been taken recently. Cetirizine cannot be effectively removed by hemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Systemic antihistamines, piperazine derivatives
ATC Code: R06A E07

Cetirizine, the human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H1-receptors.

Mechanism of Action: In vitro receptor binding studies have shown that cetirizine has no measurable affinity for receptors other than H_1 receptors. Ex vivo experiments in mice have shown that systemically administered cetirizine does not significantly occupy cerebral H_1 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 inflammatory cells, notably eosinophils, in the skin and conjunctiva of atopic subjects submitted to antigen challenge, and the dose of 30 mg/day inhibits the influx of eosinophils in the bronchoalveolar lavage fluid during a late-phase bronchial constriction induced by allergen inhalation in asthmatic subjects. Moreover, cetirizine inhibits the late-phase inflammatory reaction induced in chronic urticarial patients by intradermal administration of kallikrein. It also down-regulates the expression of adhesion molecules, such as ICAM-1 and VCAM-1, which are markers of allergic inflammation.

Clinical efficacy and safety: Studies in healthy volunteers have shown that cetirizine potently inhibits histamine-induced redness and blistering reactions administered intradermally at very high concentrations at doses of 5 and 10 mg. After a single dose of 10 mg of cetirizine, the

effect begins within 20 minutes in 50% of subjects and within 1 hour in 95%. This effect lasts for at least 24 hours after a single dose.

In a placebo-controlled, 6-week study of 186 patients with allergic rhinitis accompanied by mild-to-moderate asthma, cetirizine 10 mg administered once daily improved rhinitis symptoms and did not alter pulmonary function. This study supports the safety of administering cetirizine in allergic patients with mild to moderate asthma.

In a placebo-controlled study, cetirizine given at a high dose of 60 mg daily for 7 days did not cause statistically significant prolongation of the QT interval.

Cetirizine has been shown to improve quality of life in patients with seasonal and perennial allergic rhinitis at the recommended dose.

Pediatric population: In a 35-day study in children (5 to 12 years), no tolerance was observed to the antihistamine effect (suppression of redness and swelling) of cetirizine. When treatment with cetirizine is discontinued after repeated applications, normal skin reactivity to histamine resumes within 3 days.

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 and is achieved within 1.0 ± 0.5 h. When cetirizine is taken with food, although the rate of absorption is reduced, the amount of absorption does not change. The bioavailability of cetirizine is similar when administered in solution, capsule or tablet form.

Distribution:

The apparent volume of distribution of cetirizine is 0.50 l/kg. Cetirizine is 93% ± 0.3% bound to plasma proteins. Cetirizine does not alter the protein binding of warfarin.

Biotransformation:

Cetirizine does not undergo extensive first pass metabolism.

Elimination:

The terminal half-life is approximately 10 hours. No accumulation has been observed for cetirizine following daily doses of 10 mg for 10 days. 2/3 of the dose are excreted unchanged in urine.

Linearity/Non-linearity:

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

Characteristics features in patients

Renal Impairment:

The pharmacokinetics of the drug are similar in patients with mild renal impairment (creatinine clearance greater than 40 ml/min) and healthy volunteers. In patients with moderate renal impairment, the half-life was increased by 3 times compared to healthy volunteers, the clearance was reduced by 70%. In hemodialysis patients (creatinine clearance less than 7 ml/min) given a single, oral, 10 mg dose of cetirizine, the half-life was increased by 3 times and clearance decreased by 70% compared to normal volunteers.

Cetirizine is slightly removed by hemodialysis. Dose adjustment is required 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) given a single dose of 10 or 20 mg of cetirizine, the half-life was increased by 50% and clearance decreased by 40% compared to healthy subjects. Dose adjustment is only necessary if Hepatic impairment is accompanied by renal impairment.

Geriatric population:

Following administration of a single 10 mg oral dose of cetirizine in 16 elderly subjects, the half-life was increased by 50% and clearance decreased by 40% compared to normal subjects. In elderly volunteers, this decrease in cetirizine clearance appears to be associated with decreased 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 babies aged 6-24 months, this period 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 and toxicity to reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol
Propylene glycol
Sodium Saccharine
Methyl parahydroxybenzoate
Propyl parahydroxybenzoate
Sodium acetate trihydrate
Glacial acetic acid
Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at the room temperature below 30^{o}C.

6.5 Nature and contents of container

ROLINOZ is presented in in amber colored type III glass bottles with 20 ml nominal capacity with 18 mm mouth diameter and closed with a screwed dropper cap and in a cardboard box with patient information leaflet.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be destroyed according to "Medical Material Control Regulation" and "Packaging and Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First authorization date:
Authorization renewal date:

10. DATE OF REVISION OF THE TEXT