Summary of Product Characteristics

1. Name of the Medicinal Product
DIO-1

2. Quality and Quantitative Composition
Qualitative Declaration
Cetirizine Hydrochloride

Quantitative Declaration
Each film coated tablet contains:
Cetirizine Hydrochloride USP…10 mg
Excipients……q.s.
Colour: Titanium Dioxide USP

Excipients with known effect: One film coated tablet contains 61.50 mg Lactose Monohydrate.

For a full list of Excipients, see section 6.1.

3. Pharmaceutical Form
Film coated tablets
Description: White, round, biconvex film-coated tablets with plain on both sides.

4. Clinical Particulars
4.1Therapeutic indications
Cetirizine hydrochloride 10 mg film-coated tablets are indicated in adults and paediatric patients 6 year and above:
- for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- for the relief of symptoms of chronic idiopathic urticaria.

4.2 Posology and method of administration
Posology
10 mg once daily (1 tablet).

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

Renal impairment
There are no data to document the efficacy/safety ratio in patients with renal impairment. Since cetirizine is mainly excreted via renal route (see section 5.2), in cases no alternative treatment can be used, 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, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is needed. The CL_{cr} (mL/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

$$CL_{cr} = \frac{[140 - age(years)]\, x\, weight\,(kg)}{72\, x\, serum\, creatinine\,(mg/dl)} (x0.85\ for\ women)$$

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	Contraindicated

Hepatic impairment
No dose adjustment is needed in patients with solely hepatic impairment. In patients with hepatic impairment and renal impairment, adjustment of the dose is recommended (see Patients with moderate to severe renal impairment above).

Paediatric Population
The tablet formulation should not be used in children under 6 years of age as it does not allow the necessary dose adjustments

Children aged 6 to 12 years: 5 mg twice daily (a half tablet twice daily).

Adolescents above12 years: 10 mg once daily (1 tablet).
In paediatric patients suffering from renal impairment, the dose will have to be adjusted on an individual basis taking into account the renal clearance, age and body weight of the patient.

Method of administration
The tablets need to be swallowed with a glass of liquid.

4.3 Contraindications
Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, to hydroxyzine or to any piperazine derivatives.
Patients with severe renal impairment with a creatinine clearance below 10 ml/min.

4.4 Special warnings 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 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 at risk of convulsions.
Response to allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take cetirizine film-coated tablets.

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.

Paediatric population
The use of the film-coated tablet formulation is not recommended in children aged less than 6 years since this formulation does not allow for appropriate dose adaptation. It is recommended to use a paediatric formulation of cetirizine.

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 (0.5 g/L blood levels).

4.6 Fertility, pregnancy and lactation
Pregnancy
For cetirizine prospectively collected data on pregnancy outcomes do not suggest potential for maternal or foetal/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 be exercised when prescribing to pregnant women.

Breast-feeding
Cetirizine is excreted in human milk at concentrations representing 25% to 90% those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

Fertility
Limited data is available on human fertility but no safety concern has been identified.
Animal data show no safety concern for human reproduction.

4.7 Effects on ability to drive and use machines
Objective measurements of driving ability, sleep latency and assembly line performance have not demonstrated any clinically relevant effects at the recommended dose of 10 mg.
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
• *Overview*

Clinical studies have shown that cetirizine at the recommended dosage has minor undesirable 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 Cetirizine hydrochloride.

• *Listing of ADRs*
Double blind controlled clinical 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 Dizziness Headache	 1.10 % 7.42 %	 0.98 % 8.07 %
Gastro-intestinal disorders Abdominal pain Dry mouth Nausea	 0.98 % 2.09 % 1.07 %	 1.08 % 0.82 % 1.14 %
Psychiatric disorders Somnolence	 9.63 %	 5.00 %
Respiratory thoracic and mediastinal disorders 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.

<u>Paediatric population</u>
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 Diarrhoea	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 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 by estimated frequency based on 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:*
Not known: increased appetite
• *Psychiatric disorders:*
Uncommon: agitation
Rare: aggression, confusion, depression, hallucination, insomnia
Very rare: tics
Not known: suicidal ideation, nightmare
• *Nervous system disorders:*
Uncommon: paraesthesia
Rare: convulsions
Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia
Not known: amnesia, memory impairment
• *Eye disorders:*
Very rare: accommodation disorder, blurred vision, oculogyration
• *Ear and labyrinth disorders:*
Not known: vertigo

• *Cardiac disorders:*
Rare: tachycardia
• *Gastro-intestinal disorders:*
Uncommon: diarrhoea
• *Hepatobiliary disorders:*
Rare: hepatic function abnormal (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
Not known: acute generalized exanthematous pustulosis
• *Musculoskeletal and connective tissue disorders*
Not known: arthralgia
• *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

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

4.9 Overdose
Symptoms
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, restlessness, sedation, somnolence, stupor, tachycardia, tremor, and urinary retention.

Management
There is no known specific antidote to cetirizine.
Should overdose occur, symptomatic or supportive treatment is recommended. Gastric lavage may be considered shortly after ingestion of the drug.

Cetirizine is not effectively removed by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antihistamine for systemic use, piperazine derivatives, ATC code: R06A E07.

Mechanism of action
Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H_1-receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than H_1-receptors.

Pharmacodynamics effects
In addition to its anti-H_1 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 six-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 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.

Paediatric population
In a 35-day study in children aged 5 to 12, no tolerance to the antihistaminic 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
Absorption
The steady - state peak plasma concentrations is approximately 300 ng/mL and is achieved within 1.0 ± 0.5 h. The distribution of pharmacokinetic parameters such as peak plasma concentration (C_{max}) and area under curve (AUC), is unimodal.

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 0.50 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 terminal half-life is approximately 10 hours and no accumulation is observed for cetirizine following daily doses of 10 mg for 10 days. About two third of the dose are excreted unchanged in urine.

Linearity/Non-linearity
Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Renal impairment
The pharmacokinetics of the drug was 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 normal. Cetirizine was poorly cleared by haemodialysis. 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 healthy subjects.

Dosing adjustment is only necessary in patients with hepatic impairment if concomitant renal impairment is present.

Elderly: Following a single 10 mg oral dose, half-life increased by about 50% and clearance decreased by 40% in 16 elderly subjects compared to younger subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Paediatric 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 and toddlers 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
Dibasic Calcium Phosphate
Lactose Monohydrate
Croscarmellose Sodium
Colloidal Silicone dioxide
Magnesium Stearate
Instacoat Aqua III White

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
36 Months

6.4 Special precautions for storage
Do not store above 30°C, Protected from light and moisture.

6.5 Nature and contents of container
Cetirizine Hydrochloride Tablets USP 10 mg is packed in ALU-ALU blister of 10 tablets. Such blisters are packed in a carton with an insert.

7. Marketing Authorization Holder

Unison Pharmaceuticals Pvt. Limited,
“Unison House”, Near Prernatirth Derasar,
Near Ratnadeep-II, Satellite, Jodhpur,
Ahmedabad-380015, Gujarat, India.

Manufacturer Name
Unison Pharmaceuticals Pvt. Limited
C/6, Steel Town, Opp. Nova Petro,
Moraiya, Ta-Sanand, Dist. Ahmedabad- 382 213,
Gujarat, India.

8. Marketing Authorization Number(s)
TAN 22 HM 0178

9. Date of first Authorization/renewal of the Authorization
04/05/2022

10. Date of Revision of the Text