SUMMARY OF PRODUCT CHARACTERISTICS

ONCET TABLETS
(Cetirizine Diydrochloride Tablets 10 mg)

1. Summary of Products Characteristics

1. Name of Drug Product:

1.1 (Trade) Name of Product **:** Oncet Tablets

1.2 Strength **:** Each film coated contains:
Cetirizine Dihydrochloride BP 10 mg
Colour: Titanium dioxide
Excipients: q.s.

1.3 Pharmaceutical Form **:** Film Coated Tablets for Oral Use

2. Qualitative & Quantitative Composition:

Sr. No.	Ingredients
1	Cetirizine Dihydrochloride
2	Dibasic Calcium Phosphate (anhydrous)
3	Maize Starch
4	Lactose Monohydrate
5	Sodium Benzoate
6	Maize Starch
7	Magnesium Stearate
8	Maize Starch
9	Purified Water
10	Instacoat Sol IC-S-010 (White)
11	Isopropyl Alcohol
12	Dichloromethane

3. Pharmaceutical Form:

Film Coated Tablets for oral use

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4. Clinical Particulars:

4.1 Therapeutic indications

- Seasonal Allergic Rhinitis
- Perennial Allergic Rhinitis
- Chronic Urticaria
- Pruritus
- Allergic Conjunctivitis

4.2 Posology and method of administration:

The recommended initial dose of Oncet is 5 or 10 mg per day in adults and children above 12 years, depending on symptom severity. Most patients in clinical trials started at 10 mg. Oncet is given as a single daily dose, with or without food. The time of administration may be varied to suit individual patient needs.

In patients with decreased renal function (creatinine clearance 11-31 mL/min), patients on hemodialysis (creatinine clearance less than 7 mL/min), and in hepatically impaired patients, a dose of 5 mg once daily is recommended.

In children (2-12 years) Oncet in a dose of 5 - 10 mg has been tried.

4.3 Contraindications:

Cetirizine is contraindicated in those patients with a known hypersensitivity to it or hydroxyzine.

4.4 Special Warnings and Precaution for use:

Warnings:

The drug should not be given to children below 2 years of age, since adequate studies regarding the safety in this age group are not available.

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Precautions:

Activities Requiring Mental Alertness: In clinical trials, the occurrence of somnolence has been reported in some patients taking Cetirizine; due caution should therefore be exercised when driving a car or operating potentially dangerous machinery. Concurrent use of Oncet with alcohol or other CNS depressants should be avoided because additional reductions in alertness and additional impairment of CNS performance may occur.

Nursing Mothers: Cetirizine has been reported to be excreted in human breast milk; use of Oncet in nursing mothers is not recommended.

4.5 Interactions with other drugs, other forms of interactions:

There are no reports of hazardous interactions with other drugs to date. Concomitant administrations with alcohol or diazepam dose not impair psychomotor performance any more than the impairment of performance produced by alcohol alone. No clinically significant drug interactions have been found with Theophylline at a low dose, Azithromycin, Pseudoephedrine, Ketoconazole, or Erythromycin. There was a small decrease in the clearance of Cetirizine caused by a 400 mg dose of Theophylline; it is possible that larger Theophylline doses could have a greater effect.

4.6 Pregnancy & Lactation

Pregnancy: It is advised to avoid the use of antihistamines during pregnancy; however, there is no evidence of teratogenicity except for hydroxyzine where toxicity has been reported with high doses in animal studies. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor.

Lactation: Cetirizine has been reported to be excreted in human breast milk; use of Oncet in nursing mothers is not recommended.

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4.7 Effects on Ability to Drive and Use Machines:

Undesirable effects such as dizziness, drowsiness, fatigue, and visual disturbances are possible after taking NSAIDs. If affected, patients should not drive or operate machinery.

4.8 Side Effects and Special Precautions:

Most adverse reactions reported during therapy with Oncet are mild or moderate. The common side effects are somnolence, fatigue, dry mouth, pharyngitis, dizziness.

4.9 Overdosage:

Overdosage has been reported with Cetirizine. Should overdose occur, treatment should be symptomatic or supportive, taking into account any concomitantly ingested medications. There is no known specific antidote to Cetirizine. Cetirizine is not effectively removed by dialysis, and dialysis will be ineffective unless a dialyzable agent has been concomitantly ingested. The minimal lethal oral dose in rodents is approximately 100 times the maximum recommended clinical dose on a mg/m^2 basis, and the liver is the target organ of toxicity.

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5. Pharmacological properties:

5.1 Pharmacodynamics properties*:*

Cetirizine, a human metabolite of hydroxyzine, is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H_1 receptors.

5.2 Pharmacokinetic properties:

Absorption: Cetirizine was rapidly absorbed with a time to maximum concentration (Tmax) of approximately 1 hour following oral administration of syrup in adults. Cetirizine pharmacokinetics was linear for oral doses ranging from 5 to 60 mg.

Distribution: The mean plasma protein binding of cetirizine is 93%, independent of concentration in the range of 25-1000 ng/mL, which includes the therapeutic plasma levels observed.

Metabolism: A mass balance study in 6 healthy male volunteers indicated that 70% of the administered radioactivity was recovered in the urine and 10% in the feces. Approximately 50% of the radioactivity was identified in the urine as unchanged drug. Most of the rapid increase in peak plasma radioactivity was associated with parent drug, suggesting a low degree of first-pass metabolism. Cetirizine is metabolized to a limited extent by oxidative O-dealkylation to a metabolite with negligible antihistaminic activity.

Elimination: The mean elimination half-life in 146 healthy volunteers across multiple pharmacokinetic studies were 8.3 hours and the apparent total body clearance for cetirizine was approximately 53 mL/min.

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5.3 Preclinical Safety Data:

1) Experimental Pharmacology, Olsén L, Bondesson U, Broström H, Tjälve H, Ingvast-Larsson C. Vet J. 2008 Aug; 177(2):242-9.

Cetirizine in horses: pharmacokinetics and pharmacodynamics following repeated oral administration.

The pharmacokinetics of the histamine H(1)-antagonist cetirizine and its effect on histamine-induced cutaneous wheal formation were studied in six healthy horses following repeated oral administration. After three consecutive administrations of cetirizine (0.2 mg/kg body weight, bw) every 12h, the trough plasma concentration of cetirizine was 16+/-4 ng/mL (mean+/-SD) and the wheal formation was inhibited by 45+/-23%. After four additional administrations of cetirizine (0.4 mg/kg bw) every 12 h, the trough plasma concentration was 48+/-15 ng/mL and the wheal formation was inhibited by 68+/-11%. The terminal half-life was about 5.8 h. A pharmacokinetic/pharmacodynamic link model showed that the maximal inhibition of wheal formation was about 95% and the EC(50) about 18 ng/mL. It is concluded that cetirizine in doses of 0.2-0.4 mg/kg bw administered at 12 h intervals exhibits favourable pharmacokinetic and pharmacodynamic properties without causing visible side effects, and the drug may therefore be a useful antihistamine in equine medicine.

2) Bizikova P, Papich MG, Olivry T. Vet Dermatol. 2008 Dec; 19(6):348-57.

Hydroxyzine and cetirizine pharmacokinetics and pharmacodynamics after oral and intravenous administration of hydroxyzine to healthy dogs.

Pharmacokinetic parameters of hydroxyzine and its active metabolite cetirizine were determined after oral and intravenous administration of 2 mg kg(-1) of hydroxyzine to six healthy dogs. Plasma drug levels were determined with high-pressure liquid chromatography. Pharmacodynamic studies evaluated the suppressive effect on histamine and anticanine IgE-mediated cutaneous wheal formation. Pharmacokinetic and pharmacodynamic correlations were determined with computer modelling. The mean systemic availability of oral hydroxyzine was 72%. Hydroxyzine was rapidly converted to cetirizine regardless of the route of administration. The mean area-under-the-curve was eight and ten times higher for cetirizine than hydroxyzine after intravenous and oral dosing, respectively. After oral administration of hydroxyzine, the mean peak concentration of cetirizine was approximately 2.2 microg mL(-1) and that of hydroxyzine 0.16 microg mL(-1). The terminal half-life for cetirizine varied between 10 and 11 h after intravenous and oral administration of hydroxyzine. A sigmoidal relationship was fit to the data comparing cetirizine plasma concentration to wheal suppression. Maximum inhibition (82% and 69% for histamine and anticanine IgE-mediated skin reactions, respectively) was observed during the first 8 h, which correlated with a plasma concentration of cetirizine greater than 1.5 microg mL(-1). Pharmacological modelling suggested that increasing either hydroxyzine dosages or frequencies of administration would not result in histamine inhibition superior to that obtained with twice daily hydroxyzine at 2 mg kg(-1). In conclusion, there was rapid conversion of hydroxyzine to cetirizine. The reduction of wheal formation appeared almost entirely due to cetirizine. Pharmacodynamic modelling predicted that maximal antihistamine effect would occur with twice daily oral administration of hydroxyzine at 2 mg kg(-1).

3) Jin HR, Okamoto Y, Matsuzaki Z, Endo S, Ito E. Am J Rhinol. 2002 Jan-Feb; 16(1):43-8.

Cetirizine decreases interleukin-4, interleukin-5, and interferon-gamma gene expressions in nasal-associated lymphoid tissue of sensitized mice.

Although the action of cetirizine dihydrochloride (cetirizine), a potent histamine H1 receptor antagonist, has been well known, its effect on the cytokine profiles in the nasal immune inductive site has not been elucidated yet. We studied the effect of cetirizine on the cytokine profiles in the nasal-associated lymphoid tissue (NALT), which is a principal mucosal lymphoid tissue of the respiratory tract in rodents. Two different doses of cetirizine were given intraorally for 5 days before the nasal challenge of ovalbumin in sensitized mice. The sensitized group was given normal saline instead of cetirizine, and the nonsensitized group had no sensitization or medication. The cytokine gene expressions in the NALT taken from the mice were investigated with real-time quantitative reverse-transcription polymerase chain reaction. The effect of cetirizine on the allergic symptom score, histamine threshold, and the eosinophil count in the nasal septal mucosa were examined also. Compared with the normal mice, the sensitized mice showed significantly increased levels of interleukin (IL)-4 and IL-5 gene expression although the increase of interferon (INF)-gamma gene expression was not significant. In the cetirizine groups, the levels of expression of IL-4, IL-5, and INF-gamma in the NALT were significantly decreased compared with the sensitized group. The cetirizine groups also showed decreased allergic symptom score, histamine threshold, and eosinophil count in the nasal septal mucosa compared with the sensitized group. In conclusion, cetirizine reduced the levels of expression of IL-4, IL-5, and INF-gamma in the NALT of ovalbumin-sensitized mice. Cetirizine also reduced the acute allergic symptom, histamine sensitivity, and eosinophil count in the nasal septal mucosa.

4) Al Suleimani YM, Dong Y, Walker MJ. Pulm Pharmacol Ther. 2008; 21(2):340-8.

Differential responses to various classes of drugs in a model of allergic rhinitis in guinea pigs.

Different drugs from various pharmacological classes were compared for their ability to protect against the nasal effects of acute allergen challenge in a guinea pig model. In the model, sneezing and nose rubbing were recorded after an initial allergen challenge in guinea pigs previously sensitized to egg albumin. Four days later the same guinea pigs were re-challenged a second time when anesthetised. In these anaesthetized animals, nasal airway pressure, pulmonary inflation pressure and cellular infiltration into nasal lavage fluid were measured. The drug tested were autacoid antagonists (mepyramine--3mg/kg, cetirizine - 3mg/kg and montelukast--10mg/kg), L-NAME (10 or 20mg/kg), heparin (20mg/kg) and dexamethasone (20mg/kg) given either intraperitoneally or intravenously; all were given shortly before challenge. Sneezing induced by allergen challenge was statistically significantly reduced by mepyramine, cetirizine and dexamethasone whereas only cetirizine reduced nose rubbing. Changes in nasal airway pressure due to allergen exposure were reduced by cetirizine, montelukast, L-NAME, and heparin, but not by mepyramine, nor dexamethasone. In the presence of L-NAME, nasal airway pressure actually changed in the opposite direction. Cellular infiltration, as assessed by cytometry in nasal lavage fluid 60min after acute allergen challenge, was reduced by montelukast and heparin but not by antihistamines, L-NAME nor dexamethasone. This pattern of effects of the drugs, given by doses and routes previously described in the literature as being effective was not completely consistent with expected responses. The lack of effect of dexamethasone probably reflects the fact that it was given acutely whereas in the clinic chronic administration is used. The two antihistamines were not identical in their actions, presumably reflecting the fact that cetirizine has therapeutic actions not entirely confined to blockade of H1 receptors. Montelukast has not been reported to have major effects on sneezing and itching in the

clinic but reduces nasal obstruction (lower nasal airway pressure or nasal patency). Montelukast's effects on cellular infiltration indicate the possible involvement of leukotrienes. Heparin has actions on inflammatory cell infiltration. This could explain its profile of reducing both cellular infiltration, and increased nasal airway pressure.

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6. Pharmaceutical Particulars

6.1 List of Excipients

Sr. No.	Item	Specification
1	Dibasic Calcium Phosphate (anhydrous)	BP
2	Maize Starch	BP
3	Lactose Monohydrate	BP
4	Sodium Benzoate	BP
5	Magnesium Stearate	BP
6	Purified Water	BP
7	Instacoat Sol IC-S-010 (White)*	In-House
8	Isopropyl Alcohol	BP
9	Dichloromethane	BP

* Instacoat Sol White IC-S-010 contains Titanium Dioxide

6.2 Incompatibilities:

Not Applicable

6.3 Shelf-Life:

36 months from the date of manufacture.

6.4 Special Precautions for Storage:

Store at a temperature not exceeding 30^0C in a dry place.

6.5 Nature and contents of container:

Blister pack of 10 Tablets

6.6 Special Precaution for Disposal

None

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7 Marketing Authorization Holder

Medley Pharmaceutical Ltd,

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8 Marketing Authorization Numbers: -

07095/07938/REN/2021

9 Date of first Authorization :

24.05.2017
Date of renewal; Feb 4, 2022

10 Date of revision of the text:

Not Applicable