For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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ZYNCET

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1. Generic Name

Cetirizine Tablets I.P.

2. Qualitative and quantitative composition

Each film coated tablet contains:

Cetirizine Hydrochloride I.P. ……10 mg

Excipients……q.s.

Colour: Titanium Dioxide I.P.

The excipients used are Lactose Monohydrate, Starch, Povidone, Magnesium Stearate, Eudragit E-100, Polyethylene Glycol 6000, Titanium Dioxide, Talc, Methylene Chloride, and Acetone & Isopropyl Alcohol.

3. Dosage form and strength

Dosage form: Film Coated

Strength: 10 mg

4. Clinical particulars

4.1. Therapeutic indication

It is indicated for Seasonal rhinitis and conjunctivitis, perannual allergic rhinitis, pruritis and urticaria.

4.2. Posology and method of administration

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

Adults and adolescents over 12 years of age: 10 mg once daily (1 tablet).

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

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

Patients with moderate to severe 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, 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:

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

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

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

Patients with hepatic impairment: no dose adjustment is needed in patients with solely hepatic impairment.

Patients with hepatic impairment and renal impairment: dose adjustment is recommended (see Patients with moderate to severe renal impairment above).

4.3. Contraindications

History of hypersensitivity to any of the constituents of the formulation, to hydroxyzine or to any piperazine derivatives.

Patients with severe renal impairment at less than 10 ml/min creatinine clearance.

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

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 tablet.

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.

4.5. Drugs interactions

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.

4.6.Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric Patients etc.)

Pregnancy

For cetirizine very rare clinical data on exposed pregnancies are available. 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% of those measured in plasma, depending on sampling time after administration. Therefore, caution should be exercised when prescribing cetirizine to lactating women.

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.

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

4.8. Undesirable effects

Reported 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 H1-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 dihydrochloride.

Clinical trials

Reported 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 events 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)
Body as a whole – general disorders Fatigue	1.63 %	0.95 %

Central and peripheral nervous system disorders Dizziness Headache	1.10 % 7.42 %	0.98 % 8.07 %
Gastro-intestinal system 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 system 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.

Adverse reactions at rates of 1 % or greater in children aged from 6 months to 12 years, included in reported placebo-controlled clinical trials are:

Adverse reactions (WHO-ART)	Cetirizine (n=1656)	Placebo (n =1294)
Gastro-intestinal system disorders Diarrhoea	1.0 %	0.6 %
Psychiatric disorders Somnolence	1.8 %	1.4 %
Respiratory system disorders Rhinitis	1.4 %	1.1 %
Body as a whole – general disorders 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

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, -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:

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight increased.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9.Overdose

Symptoms

Reported 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 should be considered following ingestion of a short occurrence.

Cetirizine is not effectively removed by dialysis.

5. Pharmacological properties

5.1 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.

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

5.2 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

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Reported 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 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.

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.

5.3 Pharmacokinetic properties

The steady - state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h. No accumulation is observed for cetirizine following daily doses of 10 mg for 10 days.

The distribution of pharmacokinetic parameters such as peak plasma concentration (Cmax) and area under curve (AUC), is unimodal in human volunteers. 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.

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.

Cetirizine does not undergo extensive first pass metabolism. About two third of the dose are excreted unchanged in urine. The terminal half-life is approximately 10 hours.

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

Special populations

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 the normal subjects. The decrease in cetirizine clearance in these elderly volunteers appeared to be related to their decreased renal function.

Children, infants and toddlers: 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

Renally impaired patients: 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 normal.

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

Hepatically impaired patients: 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 hepatically impaired patients if concomitant renal impairment is present.

6. Nonclinical properties

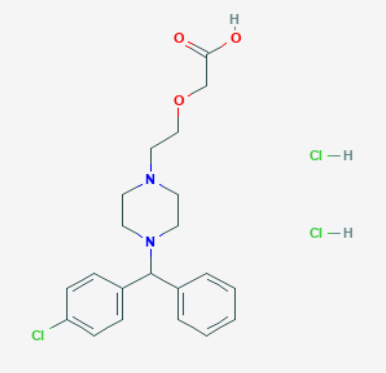
6.1 Animal Toxicology or Pharmacology

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.

7. Description

Cetirizine Hydrochloride

Cetirizine Hydrochloride is 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride having molecular weight of 461.8 and molecular formula of $C_{21}H_{25}ClN_2O_3.2HCl$ with the chemical structure as below:



Cetirizine Hydrochloride is white to almost white powder which is freely soluble in water; practically insoluble in acetone and in dichloromethane.

Cetirizine Tablets are oblong, biconvex, white, film coated tablets with score on one side. The excipients used are Lactose Monohydrate, Starch, Povidone, Magnesium Stearate, Eudragit E-100, Polyethylene Glycol 6000, Titanium Dioxide, Talc, Methylene Chloride, and Acetone & Isopropyl Alcohol.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

ZYNCET is available in Blister strip of 10 Tablets.

8.4 Storage and handing instructions

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

9. Patient Counselling Information

PATIENT INFORMATION LEAFLET

Read this leaflet carefully before you start taking this Zyncet.

• This Zyncet is available without a prescription, however you still need to use ZYNCET 10mg Tablets carefully to get the best results from them.

• Keep this leaflet. You may need to read it again.

• Ask your pharmacist if you need more information or advice.

• You must contact your doctor if your symptoms change, worsen or do not improve.

IN THIS LEAFLET:

9.1 What this Zyncet is for

Zyncet 10mg Tablets contain cetirizine hydrochloride, which belongs to a group of drugs called antihistamines. These Zyncets help to relieve the symptoms of some allergies.

This Zyncet is used to relieve:

Seasonal rhinitis and conjunctivitis, perannual allergic rhinitis, pruritis and urticaria.

9.2 Before you take the Zyncet

This Zyncet can be taken by adults, and children aged 6 years and over. Some people should not take this Zyncet or should talk to their pharmacist or doctor first.

Do not take if you:

• Are allergic (hypersensitive) to cetirizine hydrochloride or any of the other ingredients in the Zyncet.

• Have serious kidney problems Talk to your doctor or pharmacist before taking this Zyncet if you:

• Have epilepsy or are at risk of convulsions.

• Have predisposition factor of urinary retention (e.g. spinal cord lesion or prostatic hyperplasia) as cetirizine increases the risk of urinary retention.

Taking this Zyncet with food and drink

• Avoid alcoholic drink while you are taking this Zyncet.

Pregnancy and breast-feeding

• Do not take if you are pregnant or breast-feeding.

Driving and using machines

• Tests have shown that this Zyncet does not cause drowsiness in the vast majority of people using it. Therefore, it will not normally affect your ability to drive or operate machinery. However, there may be very rare exceptions and if you experience dizziness, Nausea or drowsiness, do not drive or operate machinery.

Important information about some of the ingredients in your Zyncet

• This product contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this Zyncet.

Allergy Testing

• If you are due to have an allergy test, ask your doctor if you should stop taking ZYNCET 10mg Tablets for several days before testing. This Zyncet may affect your allergy test results.

Taking other Zyncets

• ZYNCET 10mg Tablets are not expected to interact with other Zyncets you may be taking. However, if you are unsure talk to your pharmacist or doctor.

9.3 How to take the Zyncet?

AGE	**DOSE**
Adults and children aged 12 years and above	Take 1 tablet once a day
Children aged 6 to 12 years	Take half a tablet twice a day
DO NOT GIVE to children under the age of 6 years	
DO NOT EXCEED THE RECOMMENDED DOSE	

If symptoms worsen or do not improve, talk to your doctor or pharmacist. If you take too many tablets: Talk to a doctor straight away, or go to your nearest hospital casualty department. Take the carton and this leaflet with you.

If you forget to take your Zyncet: If you forget to take a tablet, take one as soon as you remember, unless it is nearly time to take the next one, in which case skip the missed dose. Never take two doses together to make up for a missed dose.

9.4 Possible side effects

Like all Zyncets, ZYNCET 10mg Tablets can sometimes have side effects although not everybody gets them. If you experience any of the following, stop taking this Zyncet and seek immediate medical help:

• Sudden signs of allergy such as rash, itching or hives on the skin, swelling of the face, lips, tongue or other parts of the body, shortness of breath, wheezing or trouble breathing

• Bruising or bleeding more easily than normal

• Convulsions (fits)

• In some very rare cases people have thought about committing suicide and if you feel this way then stop taking this Zyncet and see your doctor

If you experience any of the following, stop taking this Zyncet and talk to your doctor:

• Confusion

• Hallucinations

• Abnormal liver function tests

• Rapid heartbeat

• Loss of consciousness

Other effects which may occur include:

Common (affecting 1 in 100 to 1 in 10 people):

• Headache or dizziness

• Drowsiness or tiredness

• Restlessness

• Dry mouth, sore throat

• Upset stomach, diarrhoea, nausea

• Runny nose

Uncommon (affecting 1 in 1000 to 1 in 100 people):

• Agitation

• Weakness

• Malaise

• Pins & needles

• Itching

• Rash

• Abdominal pain

Rarely (affecting 1 in 10,000 to 1 in 1000 people):

• Aggression, depression

• Weight gain

• Swelling

• Muscle spasm

• Insomnia

• Hives

Very Rarely (affecting less than 1 in 10,000 people):

• Taste disorder

• Blurred vision, eye movement disorder

• Difficult, painful or involuntary urination

• Tremors, tics

Not known side effects

• Increased appetite

• Vertigo (sensation of spinning or whirling motion)

• Urinary retention (Difficulty passing water)

Some cases of memory loss and/or impairment have also been reported.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting. By reporting side effects, you can help provide more information on the safety of this Zyncet

9.5 STORING THE ZYNCET

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

9.6 FURTHER INFORMATION

What is in this Zyncet?

The active ingredient is: Cetirizine hydrochloride, 10mg per tablet.

The excipients used are Lactose Monohydrate, Starch, Povidone, Magnesium Stearate, Eudragit E-100, Polyethylene Glycol 6000, Titanium Dioxide, Talc, Methylene Chloride, and Acetone & Isopropyl Alcohol. Colour: Titanium Dioxide I.P.

ZYNCET is available in Blister strip of 10 Tablets.10. Details of manufacturer

Torrent Pharmaceuticals Ltd.

32 No. Middle Camp, NH-10, East District, Gangtok. Sikkim-737 135.

11. Details of permission or licence number with date

Mfg Licence No.: M/563/2010 issued on 22.11.2017

12. Date of revision

Not available

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ZYNCET 10mg /APR-20/01/PI