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

ZYNCET

1. Generic Name

Cetirizine Syrup I.P.

2. Qualitative and quantitative composition

Each 5ml contains:
Cetirizine Hydrochloride I.P. …..5mg
Flavoured Syrupy base……q.s.
The excipients used are Propyl Paraben, Methyl Paraben, Sodium Acetate Anhydrous, Glacial Acetic acid, Glycerine, Sucrose and Essence Banana.

3. Dosage form and strength

Dosage form: Syrup

Strength: 5mg/5ml

4. Clinical particulars

4.1 Therapeutic indication

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

4.2 Posology and method of administration

For oral use only.

Adults and children 6 years and above: 10 mg daily.

Adults and children aged 12 years and above: 10 ml once daily.

Children aged between 6 to 11 years: Either 5 ml twice daily or 10 ml once daily.

Children aged between 2-5 years: 5 mg daily.

Either 5 ml once daily or 2.5 ml twice daily.

At present there is insufficient clinical data to recommend the use of Cetirizine in children under 2 years of age.

Elderly subjects: There is no data to suggest that the dose should be reduced in elderly patients, provided that the renal function is normal.

For 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 eliminated via renal route (see section 5.2), in cases no alternative treatment can be used, the dosing intervals must be individualised 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 (CLcr) in ml/min is needed. The CLcr (ml/min) may be estimated from serum creatinine (mg/dl) determination using the following formula:

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

Dosing adjustments for adult patients with impaired renal function

Group	**Creatinine clearance (ml/min)**	**Posology 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

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, their age and their body weight.

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

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

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients, to hydroxyzine or to any piperazine derivatives.

Cetirizine is also contraindicated in patients with severe renal impairment at less than 10 ml/min creatinine clearance.

4.4 Special warnings and precautions for use

(See also section 4.7 Effects on Ability to Drive and Use Machines).

Dosage adjustment is necessary in patients with moderate or severe renal impairment (*see section 4.2 Posology and Method of Administration*).

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.

For patients whose symptoms persist, it is advised to consult a doctor or pharmacist.

At therapeutic doses, no clinically signification 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.

Allergy skin tests are inhibited by antihistamines and a wash-out period (of 3 days) is required before performing them.

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 product is not recommended in children aged less than 2 years.

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.

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 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/foetal 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. Caution therefore 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.

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

Clinical studies

• *Overview*

Reported clinical studies have shown that cetirizine at the recommended dosage has minor adverse 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. Affected patients may divide their daily dose, i.e. take as 5 mg in the morning and 5 mg in the evening.

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*

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)**
General disorders and administration site conditions		
Fatigue	1.63%	0.95%
Nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastro-intestinal disorders		
Abdominal pain	0.98%	1.08%
Dry mouth	2.09%	0.82%
Nausea	1.07%	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.

Paediatric population

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

Adverse drug reactions	**Cetirizine**	**Placebo**

(WHO-ART)	(n=1656)	(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 administrative 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 system 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: syncope, dysgeusia, 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

Gastrointestinal disorders:

Uncommon: diarrhoea

Hepatobiliary disorders:

Rare: abnormal hepatic function (increased transaminases, alkaline phosphatase, gamma-GT and bilirubin)

Not known: hepatitis

Skin and subcutaneous tissue disorders:

Uncommon: rash, pruritus

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.

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

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. In addition, active charcoal should be considered if cetirizine has been ingested within 1 hour.

Cetirizine is not effectively removed by dialysis.

5. Pharmacological properties

5.1 Mechanism of Action

Cetirizine, a human metabolite of hydroxyzine, is a potent antihistamine, selective H1 receptor antagonist. The histamine-mediated 'early' phase of the allergic reaction is inhibited by cetirizine, which also reduces the migration of inflammatory cells and the release of mediators associated with the 'late' allergic responses. Effects on other receptors are negligible and consequently cetirizine is unlikely to cause undesirable anti-cholinergic and anti-serotonin effects.

5.2 **Pharmacodynamic properties**

Pharmacotherapeutic classification: Piperazine derivatives

R06A E07 (ATC classification system)

Cetirizine, a human metabolite of hydroxyzine, is a potent antihistamine, selective H1 receptor antagonist. The histamine-mediated 'early' phase of the allergic reaction is inhibited by cetirizine, which also reduces the migration of inflammatory cells and the release of mediators associated with the 'late' allergic responses. Effects on other receptors are negligible and consequently cetirizine is unlikely to cause undesirable anti-cholinergic and anti-serotonin effects. At the recommended therapeutic dose of 10 mg daily, impairment of CNS function has not been found to be greater than with the placebo.

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 eosinophils, in the skin and conjunctiva of atopic subjects submitted to allergen challenge.

Studies in healthy volunteers show that cetirizine, at doses of 5 mg 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 reported 35-day study in children aged 5 to 12, no tolerance to the antihistaminic effect (suppression of the 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 reported 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 reported placebo-controlled study, cetirizine given at the high daily dose of 60 mg for seven days did not cause statistically significant prolongation of the 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

Cetirizine is rapidly absorbed from the gastrointestinal tract; absorption is not reduced by food, though the rate may be decreased slightly. Peak blood levels in the order of 0.3 micrograms/ml are attained between 30 and 60 minutes following administration of a 10 mg oral dose of cetirizine. Apparent plasma clearance is greater in children than in adults: the terminal elimination half-life in healthy adult volunteers ranges between 6.7 – 10.7 hours; in children 6.1 – 7.1 hours; and in children aged under 4 years 5.55 hours. Cetirizine is mainly excreted unchanged in the urine (approximately 70% over 5 days compared with 10% in the faeces). The half-life is increased in renal dysfunction: half-lives of 19 and 21 hours in patients with mild to moderate renal impairment respectively have been reported. This may have implications for elderly patients. Cetirizine binds strongly to plasma proteins

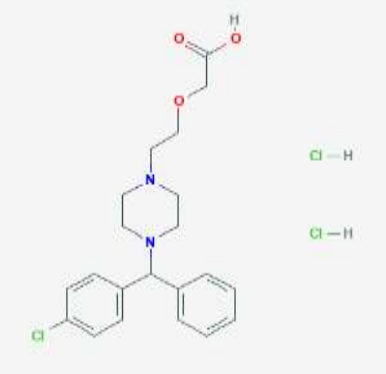
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

No relevant information additional to that contained elsewhere in the document.

7. Description

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 Syrup is clear, colourless to pale yellow coloured, banana flavoured, slightly viscous liquid. The excipients used are Propyl Paraben, Methyl Paraben, Sodium Acetate Anhydrous, Glacial Acetic acid, Glycerine, Sucrose and Essence Banana.

8. Pharmaceutical particulars

8.1 Incompatibilities

None known.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

ZYNCET is available in bottle of 60ml.

8.4 Storage and handing instructions

Store protected from light at a temperature not exceeding 30ºC.

9. Patient Counselling Information

PATIENT INFORMATION LEAFLET

ZYNCET SYRUP 5 mg/5 ml

Cetirizine hydrochloride

Read all of this leaflet carefully because it contains important information for you.

This medicine is available without prescription, however, you still need to take your medicine carefully to get the best results from it.

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

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

- You must contact a doctor if your symptoms worsen or do not improve after a few days.

- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

9.1. WHAT ZYNCET SYRUP IS AND WHAT IT IS USED FOR

ZYNCET SYRUP 5 mg/5 ml Oral Solution belongs to a group of medicines called antihistamines. It works by counteracting the effects of histamine which is produced naturally by your body's defence system, but may be over-produced in allergic reactions.

ZYNCET SYRUP is used to relieve the symptoms of Seasonal rhinitis and conjunctivitis, perennial allergic rhinitis, pruritis and urticaria.

9.2. Before you take ZYNCET

DO NOT TAKE ZYNCET SYRUP if you:

• are allergic to ZYNCET, hydroxyzine or any of the other ingredients of ZYNCET, or to any piperazine derivatives.

• are breast-feeding, as ZYNCET SYRUP can pass into breast milk.

• have severe kidney failure (creatinine clearance less than 10 ml/min).

Take special care with ZYNCET SYRUP if:

• you have kidney problems. Your dose should be adjusted as recommended by a doctor.

• you have problems passing urine (like spinal cord problems or prostate or bladder problems), ask your doctor for advice.

• you are pregnant.

• you suffer from epilepsy or are at risk of convulsions.

• you have hereditary intolerance to some sugars.

• your symptoms persist; you should get advice from your doctor or pharmacist.

• you are due to have an allergy test, as this medicine may affect your allergy test result.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Especially tell your doctor if you are taking:

• theophylline which is taken for some heart conditions or breathing disorders like asthma or bronchitis.

• central nervous system depressants e.g. barbiturates which are used as sedatives or anaesthetics.

Taking ZYNCET SYRUP with food and drink

Food does not affect absorption of ZYNCET. You must avoid alcohol consumption while you are taking this medicine, as with all antihistamine medicines.

Pregnancy and breast-feeding

Ask your doctor or pharmacist for advice before taking any medicine during pregnancy.

• Do not take ZYNCET SYRUP if you are breast-feeding.

• Only take this medicine during pregnancy if advised to do so by your doctor.

Driving and using machines

ZYNCET SYRUP does not usually cause drowsiness at the recommended dose. However, individuals react differently, so do not drive or operate machinery until you know how it affects you.

9.3. How to take ZYNCET

Always take this medicine exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. ZYNCET SYRUP is to be taken only by mouth, and is not to be taken by children aged under 2 years. The measuring spoon provided is double-ended. The larger spoon holds 5 ml of your medicine, and the smaller spoon holds 2.5 ml. Each 5 ml spoonful of solution contains 5 mg ZYNCET. The usual dose is:

Adults, the elderly and children aged 12 years and above:	Two 5 ml spoonful's once daily (to a maximum of 10 mg daily).
Children aged 6 to 11 years:	Either two 5 ml spoonful once daily, or one 5 ml spoonful twice daily (to a maximum of 10 mg daily).

Children aged 2 to 5 years:	Either one 5 ml spoonful once daily or one 2.5 ml spoonful twice daily (to a maximum of 5 mg daily).

If you have kidney problems, your dose should be adjusted as recommended by a doctor.

If you take more ZYNCET SYRUP than you should:

If you or your child may have taken too much of this medicine, talk to a doctor or pharmacist immediately. You or the child may feel drowsy or dizzy. In children, agitation or restlessness may occur before drowsiness.

If you forget to take ZYNCET

If you forget to take a dose, take it as soon as you remember, but wait at least 24 hours before taking the next dose.

If you stop taking ZYNCET

Rarely, pruritus (intense itching) and/or urticaria may return if you stop taking ZYNCET.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

9.4. POSSIBLE SIDE EFFECTS

Like all medicines, ZYNCET SYRUP can cause side effects, although not everybody gets them.

The following side effect are rare or very rare, but you must stop taking the medicine and speak to your doctor immediately if you notice these symptoms:

• Allergic reactions, including severe reactions and angioedema (serious allergic reaction which causes swelling of the face or throat).

These reactions may start soon after you first take the medicine, or might start later.

The following side effects have also been reported.

Common side effects (may affect up to 1 in 10 people)

• Somnolence (sleepiness)

• Pharyngitis, rhinitis (in children)

• Diarrhoea, nausea, dry mouth

• Dizziness, headache

• Fatigue

Uncommon side effects (may affect up to 1 in 100 people)

• Agitation

• Paresthesia (abnormal feelings of the skin)

• Abdominal pain

• Pruritus (itchy skin), rash

• Asthenia (extreme fatigue), malaise

Rare side effects (may affect up to 1 in 1000 people)

• Allergic reactions, some severe (very rare)

• Depression, hallucination, aggression, confusion, insomnia

• Convulsions

• Tachycardia (heart beating too fast)

• Liver function abnormal

• Urticaria (hives)

• Oedema (swelling)

• Weight increased

Very rare side effects (may affect up to 1 in 10,000 people)

• Thrombocytopenia (low levels of blood platelets)

• Tics (habit spasm)

• Syncope, dyskinesia (involuntary movements), dystonia (abnormal prolonged muscular contractions), tremor, dysgeusia (altered taste)

• Blurred vision, accommodation disorder (difficulty focusing), oculogyration (eyes having uncontrolled circular movements)

• Angioedema (serious allergic reaction which causes swelling of the face or throat), fixed drug eruption

• Abnormal elimination of urine (bed wetting, pain and/or difficulty passing water)

Not known (frequency cannot be estimated from the available data)

• Increased appetite

• Suicidal ideation (recurring thoughts of or preoccupation with suicide), nightmare

• Amnesia, memory impairment

• Vertigo (sensation of rotation or movement)

• Urinary retention (inability to completely empty the urinary bladder)

• Pruritus (intense itching) and/or urticaria upon discontinuation

• Joint pain

• Rash with blisters containing pus

• Hepatitis (inflammation of the liver)

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 medicine.

9.5. HOW TO STORE ZYNCET

Store protected from light at a temperature not exceeding 30ºC.

9.6. FURTHER INFORMATION

What ZYNCET SYRUP contains

• The **active ingredient** is cetirizine: 5 mg in each 5 ml of solution.

• The **other ingredients** are: Propyl Paraben, Methyl Paraben, Sodium Acetate Anhydrous, Glacial Acetic acid, Glycerine, Sucrose and Essence Banana.

10. Details of manufacturer

Manufactured in India by:

The Madras Pharmaceuticals

No. 137-B, Old Mahabalipuram Road, Karapakkam, Chennai – 600096, Tamil Nadu.

11. Details of permission or licence number with date

Mfg Lic No. 247 issued on 01.12.2015.

12. Date of revision

Not available

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ ZYNCET SYRUP/APR-20/01/PI