Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zirpine 10mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 10mg cetirizine dihydrochloride.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets
White, round, film-coated tablets embossed with AG on one side, breakline on the reverse.
The tablets can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults and paediatric patients 6 year and above:

- Cetirizine is indicated for the relief of nasal and ocular symptoms of seasonal and perennial allergic rhinitis.
- Cetirizine is indicated for the relief of symptoms of chronic idiopathic 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 patients: Data do not suggest that the dose needs to be reduced in elderly subjects provided that the renal function is normal.

For patients with moderate to severe renal impairment: There are no data to document efficacy/safety ratio in patients with renal impairment. Since cetirizine is mainly excreted via the renal route (see section 5.2), in cases where 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 impairment and renal impairment: Dose adjustment is recommended (see 'For patients with moderate to severe renal impairment' above).

Method of administration: For oral use

4.3 Contraindications

History of hypersensitivity to any of the constituents of the formulation (see section 6.1) or 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

In patients with moderate to severe renal impairment, where no alternative treatment can be used, the dosage should be reduced (see section 4.2) and product used with caution.

In patients with both hepatic impairment and renal impairment, dose adjustment is recommended (see section 4.2).

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.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interactions

Due to the pharmacokinetic, pharmacodynamics 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).

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.

The extent of absorption of cetirizine is not reduced with food, although the rate of absorption is decreased.

Concomitant use of cetirizine with other CNS depressants should be avoided as reduction in alertness and impairment of performance may occur.

4.6 Fertility, pregnancy and lactation

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.

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 10mg.

Patients intending to drive, engage in potentially hazardous activities or operate 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

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.

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

Double blind controlled clinical or pharmacoclinical trials comparing cetirizine to placebo or other antihistamines at the recommended dosage (10mg 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 10mg in the placebo-controlled trails at rates of 1.0% or greater:

Adverse reactions (WHO-ART)	**Cetirizine 10 mg (n = 3260)**	**Placebo (n = 3061)**
Body as whole – general disorders		
Fatigue	1.63%	0.95%
Central and peripheral nervous system disorders		
Dizziness	1.10%	0.98%
Headache	7.42%	8.07%
Gastro-intestinal system 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 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 placebo-controlled clinical trials are:

Adverse reactions (WHO-ART)	**Cetirizine 10 mg (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: thrombocytopenia, haemolytic anaemia

Immune system disorders: anaphylactic shock, hypersensitivity, bronchospasm, photosensitivity

Hepatobiliary disorders: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ-GT and bilirubin)

Metabolism and nutrition disorders: increased appetite, anorexia

Psychiatric disorders: aggression, agitation, confusion, depression, insomnia, hallucination, tics, suicidal ideation

Nervous system disorders: convulsions, dysgeusia, paraesthesia, syncope, tremor, dystonia, dyskinesia, amnesia, memory impairment, movement disorders, incoordination

Eye disorders: oculogyration, accommodation disorder, blurred vision

Ear and labyrinth disorders: Not known: vertigo

Cardiac disorders: tachycardia, palpitations

Gastro-intestinal disorders: diarrhoea, vomiting, constipation

Skin and subcutaneous tissue disorders: angioneurotic oedema, pruritus, rash, urticarial, fixed drug eruption, alopecia

Renal and urinary disorders: micturition difficulty, dysuria, enuresis
Not known: urinary retention

General disorders and administration site conditions: asthenia, malaise, oedema

Investigations: weight increased

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

a) Symptoms
Symptoms observed after an important 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.

b) 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 activated charcoal should be considered if cetirizine has been ingested within 1 hour.

Cetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, Piperazine derivatives, *ATC-Code:* R06A E07

Zirpine is a selective H_1 antagonist with negligible effects on other receptors and is therefore virtually free from anticholinergic and anti-serotonin effects. Zirpine inhibits the histamine-mediated 'early' phase of the allergic reaction and also reduces the migration of inflammatory cells and the release of mediators associated with the 'late' allergic response.

5.2 Pharmacokinetic properties

Peak blood levels of the order of 0.3 micrograms/ml are reached between thirty and sixty minutes after administration of a 10 mg dose of Zirpine. The terminal half-life is approximately 10 hours in adults and 6 hours in children aged between 6 and 12 years and 5 hours in children aged between 2 to 6 years. This data is consistent with the urinary excretion half-life of the drug. The cumulative urinary excretion represents two thirds of the dose given in either adults or children. Consequently, the apparent plasma clearance in children is higher than that measured in adults. Zirpine is strongly bound to plasma proteins.

Patients with mild to severe renal impairment (creatinine clearance < 3.6 L/h) administered Zirpine 10mg, $t_{1/2\beta}$ was prolonged (to ~20 hours) and renal and total body clearances were significantly decreased when compared with volunteers exhibiting normal renal function. In addition, in patients with moderate (creatinine clearance of 0.4 to 1.8 L/h) to severe renal impairment, time to C_{max} was significantly increased (to ~2h) in comparison with those with normal function. These findings indicate that dosage reduction is necessary in patients with moderate or severe renal impairment.

Although the liver does not play a major role in the elimination of Zirpine, significant alterations in the pharmacokinetics of the drug have been reported in humans with hepatic dysfunction, suggesting that dosage reduction may be required in these patients.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber other than those already mentioned in other sections of the SPC. For more information, *see sections 4.3, Contrindications and 4.6, Pregnancy and lactation*.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline Cellulose (E460 (i))
Colloidal anhydrous silica
Magnesium stearate (E572)
Titanium dioxide (E171)
Hypromellose (E464)
Macrogol 400

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 Years

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Zirpine 10mg tablets are supplied in PVC/PVdC/Al blisters in a carton box. A box contains 7 tablets and 30 tablets in 3 blister packs of 10.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd,
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/110/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08 March 2002

Date of last renewal: 16 April 2006

10 DATE OF REVISION OF THE TEXT

July 2015