Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zirpine 1mg/ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution contains 1 mg cetirizine dihydrochloride.

Excipients with known effect:
- one ml of solution contains 50.152 mg Propylene glycol
- one ml of solution contains 1.35 mg Methyl parahydroxybenzoate (E218)
- one ml of solution contains 0.15 mg Propyl parahydroxybenzoate (E216)
- one ml of solution contains 450 mg Liquid Sorbitol (E420)
- one ml of solution contains 0.00525 mg of alcohol (ethanol)
- one ml of solution contains 0.00001575 mg Benzyl alcohol

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Oral Solution

Clear or almost clear, colourless solution with taste and odour of banana.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Cetirizine dihydrochloride 1mg/ml oral solution is indicated in adults and children aged 2 years 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 (10 ml oral solution (2 full spoons)).

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 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.

Dosing adjustments for adult patients with impaired renal function

Group	Estimated Glomerular Filtration Rate (eGFR) (ml/min)	Dosage and frequency
Normal renal function	≥90	10 mg once daily
Mildly decreased renal function	60 - < 90	10 mg once daily
Moderately decreased renal function	30 - < 60	5 mg once daily
Severely decreased renal function	15 - < 30 not requiring dialysis	5 mg once every 2 days
End-stage renal disease	< 15 requiring dialysis treatment	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 Renal impairment above).

Paediatric population

Children aged from 2 to 6 years: 2.5 mg twice daily (2.5 ml oral solution twice daily (a half spoon twice daily)).

Children aged from 6 to 12 years: 5 mg twice daily (5 ml oral solution twice daily (a full spoon twice daily)).

Adolescents over 12 years of age: 10 mg once daily (10 ml oral solution (2 full spoons)).

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 solution can be swallowed as such.

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 end-stage renal disease with an eGFR (estimated Gomerular Filtration Rate) below 15 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.

Methyl parahydroxybenzoate and Propyl parahydroxybenzoate:
Methylparahydroxybenzoate and propylparahydroxybenzoate may cause allergic reactions (possibly delayed).

Sorbitol:
This medicine contains 450 mg sorbitol in each ml. Patients with hereditary fructose intolerance (HFI) should not take or be given this medicinal product. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account. The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.
Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Propylene glycol:
This medicine contains 50.152 mg propylene glycol in each ml.

Sodium:
This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say essentially 'sodium-free'.

Benzyl alcohol:
This medicine contains 0.00001575 mg benzyl alcohol in each ml. Benzyl alcohol may cause allergic reactions. Do not use for more than a week in young children (less than 3 years old), unless advised by your doctor or pharmacist. Ask your doctor or pharmacist for advice if you are pregnant or breast-feeding. This is because large amounts of benzyl alcohol can build-up in our body and may cause side effects (called "metabolic acidosis"). Ask your doctor or pharmacist for advice if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called

"metabolic acidosis").

Ethanol:
This medicine contains 0.00525 mg of alcohol (ethanol) in each ml which is equivalent to 0.000525 w/v%. The amount in 10 ml of this medicine is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

Response to 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
Due to the amount of some excipients in the formulation, the use of the product is not recommended in children aged less than 2 years.

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 nevertheless be exercised when prescribing to pregnant women.

Breast-feeding
Cetirizine passes into breast milk. A risk of side effects in breastfed infants cannot be excluded. 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.

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 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 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.

- *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 events were reported for cetirizine 10 mg in the placebo- controlled trials at rates of 1.0% or greater.

Adverse reactions (WHO-ART)	**Cetirizine10 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 placebo-controlled clinical or pharmacoclinical trials are:

Adverse drug 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 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)

System Organ Class	Frequency	Undesirable effects
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	dysgeusia, syncope, tremor, dystonia, dyskinesia
	Not known	amnesia, memory impairment
Eye disorders	Very rare	accommodation disorder, blurred vision, oculogyric crisis
Ear and labyrinth disorders	Not known	vertigo
Cardiac disorders	Rare	tachycardia
Gastrointestinal disorders	Uncommon	diarrhoea
Hepatobiliary disorders	Rare	hepatic function abnormal (increased transaminases, alkaline phosphatase, gamma-GT and bilirubin)
	Not known	hepatitis
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, myalgia
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 events

Withdrawal symptoms: after discontinuation of cetirizine, pruritus (intense itching) and/or urticaria have been reported.

Reporting of suspected adverser eactions

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, Website: www.hpra.ie.

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 H1-receptors. *Invitro*receptor binding studies have shown no measurable affinity for other than H1-receptors.

Pharmacodynamic effects
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.

Clinical efficacy and safety
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 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 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.

Paediatric population
In a 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.

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 (Cmax) 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 normals. 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 the normal 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

Propylene glycol
Glycerol
Methyl parahydroxybenzoate (E218)
Propyl parahydroxybenzoate (E216)
Sodium acetate
Acetic acid
Saccharin sodium
Liquid Sorbitol (E420)
Banana flavour
Purified water

6.2 Incompatibilities

None known.

6.3 Shelf life

Shelf life before opening – 3 years
Shelf life after opening – 6 months

6.4 Special precautions for storage

Do not store above 25˚C.

6.5 Nature and contents of container

Type III amber glass bottles with a tamper evident screw cap having a polypropylene outer layer and a polyethylene inner layer.

Dosing device - double-measuring spoon 2.5/5ml

Bottle size: 100ml and 200 ml

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Pinewood Laboratories Ltd
Ballymacarbry
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0281/178/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorisation: 7th October 2022

10 DATE OF REVISION OF THE TEXT

January 2025