

IRISH MEDICINES BOARD ACT 1995, as amended

Medicinal Products (Control of Placing on the Market) Regulations, 2007, as amended

PA0577/085/001

Case No: 2085502

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

McDermott Laboratories Ltd t/a Gerard Laboratories

35-36 Baldoyle Industrial Estate, Grange Road, Dublin 13, Ireland

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Cetirizine 10 mg film-coated tablets

the particulars of which are set out in the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **30/07/2010**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cetirizine 10 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 10mg cetirizine dihydrochloride.

Excipients: one film-coated tablet contains 74.3mg lactose-monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets.

White, capsule shaped, film coated tablet with breakline and marked 'CZ' and '10' on one side and marked 'G' on the reverse.

The breakline is to facilitate breaking for ease of swallowing and not to divide 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 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 (see section 5.2), 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:

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

Dosing adjustments for adult patients with impaired renal function

Group	Creatinine Clearance (ml/min)	Doasge and frequency
Normal	≥80	10 mg once daily
Mild	50 – 79	10 mg once daily
Moderate	30 – 49	5mg 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, 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

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

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

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take cetirizine film-coated tablet.

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

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 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.

4.6 Pregnancy and lactation

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 or breast feeding women because cetirizine passes into breast milk.

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 these 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 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

Double blind controlled clinical or pharmacoclinical 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 event (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	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 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 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 effects reported during clinical studies and listed above, isolated cases of the following adverse drug reactions have been reported in post-marketing experience. For these less frequently reported undesirable effects, the estimated frequencies (uncommon: $\geq 1/1,000$ to $1/100$, rare: $\geq 1/10,000$ to $1/1,000$, very rare: $1/10,000$) are made based on post-marketing experience.

Blood and lymphatic disorders:

Very rare: thrombocytopenia

Immune system disorders:

Rare: hypersensitivity

Very rare: anaphylactic shock

Psychiatric disorders:

Uncommon: agitation

Rare: aggression, confusion, depression, hallucination, insomnia

Very rare: tic

Nervous system disorders:

Uncommon: paraesthesia

Rare: convulsions, movements disorders

Very rare: dysgeusia, syncope, tremor, dystonia, dyskinesia

Eye disorders:

Very rare: accommodation disorder, blurred vision, oculogyration

Cardiac disorders:

Rare: tachycardia

Gastro-intestinal disorders:

Uncommon: diarrhoea

Hepatobiliary disorders:

Rare: hepatic function abnormal (increased transaminases, alkaline phosphatase, γ -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

General disorders and administration site conditions:

Uncommon: asthenia, malaise

Rare: oedema

Investigations:

Rare: weight increased

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. Cetirizine is not effectively removed by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Piperazine derivatives, ATC code: R06A E07

Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H₁-receptors. *In vitro* receptor binding studies have shown no measurable affinity for other than H₁-receptors.

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 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.

5.2 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 (C_{max}) 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 normals. 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.

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

Tablet core:

Lactose Monohydrate,
Pregelatinised Maize Starch,
Povidone K29/32,
Magnesium Stearate,

Tablet coating

Opadry-Y-1-7000, containing:
Titanium Dioxide (E171),
Hypromellose 5cP (E464),
Macrogol 400.

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polypropylene container with tamper-evident polyethylene cap: 30, 100, 250 tablets.

PVdC coated PVC blister with aluminum foil lidding: 7, 10, 14, 15, 20, 30, 50, 60, 90, 100, 100 (10x10x1) and 50 (50 x 1) unit-dose.

Not all pack sizes may be marketed.

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

McDermott Laboratories Limited (t/a Gerard Laboratories)
35/36 Baldoyle Industrial Estate
Grange Road,
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 0577/085/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 13 June 2006

Date of last renewal: 30 November 2007

10 DATE OF REVISION OF THE TEXT

December 2009