Public Assessment Report

UKPAR

Cetirizine dihydrochloride 10 mg film-coated tablets

(cetirizine dihydrochloride)

UK Licence No: PL 20416/0278

Crescent Pharma Limited.
LAY SUMMARY

Cetirizine dihydrochloride 10 mg film-coated tablets
(cetirizine dihydrochloride, film-coated tablet, 10 mg)

This is a summary of the Public Assessment Report (PAR) for Cetirizine dihydrochloride 10 mg film-coated tablets (PL 20416/0278). It explains how Cetirizine dihydrochloride 10 mg film-coated tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Cetirizine dihydrochloride 10 mg film-coated tablets.

The product will be referred to as Cetirizine dihydrochloride tablets throughout the remainder of this public assessment report.

For practical information about using Cetirizine dihydrochloride tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Cetirizine dihydrochloride tablets and what are they used for?
Cetirizine dihydrochloride tablets are a generic medicine. This means that Cetirizine dihydrochloride tablets are similar to a reference medicine already authorised in the UK called Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542).

Cetirizine dihydrochloride tablets are used to treat people who have hay fever (seasonal allergic rhinitis), year round allergies such as dust or pet allergies (perennial allergic rhinitis) and urticaria (swelling, redness and itchiness of the skin).

How do Cetirizine dihydrochloride tablets work?
Cetirizine dihydrochloride tablets contain the active ingredient cetirizine dihydrochloride which belongs to a group of medicines called antihistamines. Cetirizine dihydrochloride blocks the effects of a substance called histamine which occurs naturally in the body. Histamine is involved in allergic reactions.

Antihistamines such as cetirizine dihydrochloride relieve the unpleasant symptoms and discomfort associated with these conditions such as sneezing, irritated, runny and blocked nose, itchy, red and watering eyes and skin rashes.

Cetirizine dihydrochloride tablets can be obtained without prescription.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

For further information on how Cetirizine dihydrochloride tablets are used, please see the Summary of Product Characteristics and package leaflet available on the MHRA website.

How are Cetirizine dihydrochloride tablets used?
The pharmaceutical form of Cetirizine dihydrochloride tablets is a film-coated tablet and the route of administration is via the mouth (oral).

The recommended dose of Cetirizine dihydrochloride tablets is as follows:

Children aged 6 to 12:
Take half a tablet twice a day.
Adults and children aged 12 years and over:
Take one tablet daily. If the tablets make the patient feel drowsy or dizzy, taking half a tablet twice a day may be better than taking one tablet once a day. Cetirizine dihydrochloride tablets are not suitable for children under 6.

This medicine should be taken with a glass of water. The patient MUST NOT take more than one tablet each day. If the patient does not feel better within a few days, the patient should consult their doctor.

What benefits of Cetirizine dihydrochloride tablets have been shown in studies?
Because Cetirizine dihydrochloride tablets are a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Cetirizine dihydrochloride tablets?
As Cetirizine dihydrochloride tablets are a generic medicine that is bioequivalent to Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542), its benefits and risks are taken as being the same as those for Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542).

Why are Cetirizine dihydrochloride tablets approved?
It was concluded that, in accordance with EU requirements, Cetirizine dihydrochloride tablets have been shown to have comparable quality to Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542). Therefore, the view was that, as for Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited; PL 00039/0542), the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Cetirizine dihydrochloride tablets?
A Risk Management Plan has been developed to ensure that Cetirizine dihydrochloride tablets are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Cetirizine dihydrochloride tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Cetirizine dihydrochloride tablets
A Marketing Authorisation was granted in the UK on 14 April 2015.

The full PAR for Cetirizine dihydrochloride tablets follows this summary. For more information about using Cetirizine dihydrochloride tablets, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
Cetirizine dihydrochloride 10 mg film-coated tablets

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I. Introduction

The Medicines and Healthcare products Regulatory Agency (MHRA) granted a Marketing Authorisation to Crescent Pharma Limited for the medicinal product Cetirizine dihydrochloride tablets (PL 20416/0278) on 14 April 2015. This product is a General Sales List Medicine (GSL) indicated in adults and paediatric patients 6 years and above for the relief of:

- nasal and ocular symptoms of seasonal and perennial allergic rhinitis
- symptoms of chronic idiopathic urticaria.

This application was submitted as a national abridged application under Article 10(1) of Directive 2001/83/EC, as amended. The applicant has cross-referred to Zirtek allergy 10 mg film-coated tablets which was first authorised to UCB S.A on 16 August 1988 (PL 05221/0001) and underwent change of ownership procedures leading to the current licence holder UCB Pharmaceuticals Limited, granted on 19 January 2006 (PL 00039/0542).

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.

One bioequivalence study was submitted to support this application comparing the applicant’s test product Cetirizine dihydrochloride tablets (Crescent Pharma Limited) with the reference product Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited) under fasting conditions. The applicant has stated that the bioequivalence study was conducted in compliance with the requirements of ICH (Step 5) ‘Guideline for Good Clinical Practice’, the principles enunciated in the Declaration of Helsinki, Good Laboratory Practice (GLP), Schedule Y (2005) of Indian Drugs and Cosmetics Act, ICMR Guidelines (2006) and EMEA guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on a product being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that the benefits of taking Cetirizine dihydrochloride tablets outweigh the risks and a Marketing Authorisation was granted.
II Quality aspects

II.1 Introduction

This product is a film-coated tablet and contains 10 mg cetirizine dihydrochloride as an active ingredient. The pharmaceutical excipients are microcrystalline cellulose, lactose monohydrate, colloidal anhydrous silica, magnesium stearate, and the film coating Opadry II OY GM 28900 white (consisting of hypromellose 15cP, polydextrose, titanium dioxide (E 171) and macrogol 4000). Appropriate justification for the inclusion of each excipient has been provided.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of the film coating Opadry II OY GM 28900 white which is controlled to suitable in-house specifications.

Satisfactory Certificates of Analysis have been provided for all excipients, showing compliance with the proposed specifications.

The finished product is packaged in clear, colourless polyvinylchloride (PVC)/ polyvinylidene chloride (PVDc) blisters closed with aluminium foil and packed into cardboard boxes containing 7 or 30 tablets. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with applicable European regulations.

II.2 Drug Substance

INN: Cetirizine dihydrochloride
Chemical name: (RS)-2-[2-[(4-Chlorophenyl)phenylmethyl]piperazin-1-yl]ethoxy]acetic acid dihydrochloride

Structure:

\[
\text{Cl} \quad \text{H} \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{CO}_2\text{H}
\]

\[\text{and enantiomer}\]

Molecular formula: \(\text{C}_{21}\text{H}_{25}\text{ClN}_{2}\text{O}_{3}\cdot2\text{HCl}\)
Molecular weight: 461.8 g/mol
Appearance: White or almost white powder.
Solubility: Freely soluble in water and practically insoluble in acetone and methylene chloride.

Cetirizine dihydrochloride is the subject of a European Pharmacopoeia monograph.
All aspects of the manufacture and control of the active substance, cetirizine dihydrochloride, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate robust, stable, tablets containing 10 mg cetirizine dihydrochloride per tablet that could be considered as a generic medicinal product of Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited).

Comparative impurity and in-vitro dissolution profiles have been provided for the proposed and originator product.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot-scale batch size and has shown satisfactory results. The marketing authorisation holder (MAH) has committed to perform additional process validation on future commercial-scale batches.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 3 years, with no special storage conditions. This is satisfactory.

Suitable post approval stability commitments have been provided to continue stability studies on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cetirizine dihydrochloride are well-known, no further non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Cetirizine dihydrochloride tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on Cetirizine dihydrochloride tablets being a generic medicinal product of an originator product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of cetirizine dihydrochloride is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of cetirizine dihydrochloride.

Based on the data provided, Cetirizine dihydrochloride tablets (Crescent Pharma Limited) can be considered bioequivalent to Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following bioequivalence study:

STUDY
An open label, randomised, two-sequence, two-treatment, two-period, single oral dose, crossover, bioequivalence study comparing the pharmacokinetics of the test product Cetirizine dihydrochloride tablets (Crescent Pharma Limited) with the reference product Zirtek allergy 10
mg film-coated tablets (UCB Pharmaceuticals Limited) in healthy, adult, human subjects under fasting conditions.

The subjects were administered a single dose (10 mg) of either the test or the reference product after an overnight fast of at least 10 hours.

Blood samples were collected before and up to 48 hours post-dose. The washout period between treatment phases was 7 days. The pharmacokinetic results are presented below:

**Geometric Least Square Mean, Ratios and 90% Confidence Interval for Cetirizine:**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (T)</th>
<th>Reference</th>
<th>% Ratio</th>
<th>90% Confidence Interval for Log-data transformed</th>
<th>Intrasubject CV (%)</th>
<th>Power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ln C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>347.358</td>
<td>358.093</td>
<td>97.00</td>
<td>91.96 - 102.33</td>
<td>10.8</td>
<td>100.0</td>
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<tr>
<td>(ng/mL)</td>
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<tr>
<td>Ln AUC&lt;sub&gt;0-4&lt;/sub&gt;</td>
<td>2885.2257</td>
<td>2875.7163</td>
<td>100.33</td>
<td>96.60 - 104.21</td>
<td>7.7</td>
<td>100.0</td>
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<tr>
<td>(ng*h/mL)</td>
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</table>

AUC<sub>0-4</sub> area under the plasma concentration-time curve from zero to t hours

C<sub>max</sub> maximum plasma concentration

The 90% confidence intervals of the test/reference ratio for AUC<sub>0-4</sub>, and C<sub>max</sub> values for cetirizine lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited).

**IV.3 Pharmacodynamics**

No new data have been submitted and none are required for applications of this type.

**IV.4 Clinical efficacy**

No new data on efficacy have been submitted and none are required for this type of application.

**IV.5 Clinical safety**

No new safety data were submitted and none are required.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cetirizine dihydrochloride tablets.

A summary table of safety concerns and risk minimisation measures as approved in the RMP is listed as follows:
Summary table of Safety concerns

<table>
<thead>
<tr>
<th>Summary of safety concerns</th>
<th>Important identified risks</th>
<th>Important potential risks</th>
<th>Missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td>• Renal and urinary disorders (e.g. urinary retention)</td>
<td>• Nervous system disorders (e.g. epilepsy, convulsions, amnesia, memory impairment)</td>
<td>• Pregnancy</td>
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<td>• Hepatic disorders: (e.g. increased transaminases, alkaline phosphatase, γ-GT and bilirubin)</td>
<td>• Inhibition of allergy skin tests</td>
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<td>• Immune system disorders (e.g. anaphylactic shock)</td>
<td>• Overdose</td>
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<td>• Children under 6 years-old</td>
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<td></td>
<td>• Use in patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption</td>
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<td></td>
<td>• Thrombocytopenia</td>
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<td></td>
<td>• Psychiatric disorders (e.g. depression, somnolence, suicidal ideation)</td>
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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**IV.7 Discussion on the clinical aspects**

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

Bioequivalence has been demonstrated between the applicant’s product Cetirizine dihydrochloride tablets (Crescent Pharma Limited) and the reference product Zirtek allergy 10 mg film-coated tablets (UCB Pharmaceuticals Limited), under fasting conditions.

The grant of a marketing authorisation is recommended for this application.

**V User consultation**

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended. The language used for the purpose of user testing the PIL was Portuguese.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI Overall conclusion, benefit/risk assessment and recommendation**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with cetirizine dihydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Cetirizine dihydrochloride tablets is presented below:
Cetirizine dihydrochloride 10 mg film-coated tablets

7 Tablets

Each tablet contains 10mg of cetirizine dihydrochloride

Contains lactose. See package leaflet for further information.

7 Tablets

Relief of symptoms of hay fever and allergic rhinitis (e.g. dust and pet allergens), such as sneezing, itchy and watery eyes. Also relieves itching of skin (pruritus), such as itchy eczema, scabies, and insect bites. Also relieves itching and scaling of skin due to psoriasis and atopic dermatitis.

Adults and children aged 12 years and over: Take one tablet (10mg) once daily or half a tablet (5mg) twice daily.

Children aged 6-12 years: Take half a tablet (5mg) twice a day or a tablet (10mg) once a day.

Children under 6 years of age: Do not use.

If symptoms persist consult your doctor. Do not exceed the recommended dose.

Do not use if affected by drug allergies.

Keep out of the sight and reach of children.

Product licence holder:
Crescent Pharma Limited,
Units 3 & 4, Goldsmiths Business Park,
Pillington Lane, Overton, Lancashire, BL5 2BD, United Kingdom

PL 20416/0278

UKPAR Cetirizine dihydrochloride 10 mg film-coated tablets
Cetirizine dihydrochloride 10 mg film-coated tablets

Each tablet contains 10 mg of Cetirizine Dihydrochloride.

See pack leaflet for further information.

30 Tablets
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