IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Zirpine 1mg/ml Oral Solution
Cetirizine dihydrochloride
PA0281/178/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Zirpine 1mg/ml Oral Solution, from Pinewood Laboratories Ltd on 7th October 2022, indicated for:

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

The legal basis for the application is Article 10(1) of 2001/83/EC, a generic application.

The reference medicinal product for this application is cetirizine dihydrochloride 1mg/ml oral solution, registered under the brand name Zirtek by UCB (Pharma) Ltd. It was granted a marketing authorisation on 26March 1993.
The product under application, Zirpine, is not subject to a medical prescription as it is authorised in containers up to 200ml only.

The Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Zirpine 1mg/ml Oral Solution
Name(s) of the active substance(s) (INN)	Cetirizine dihydrochloride
Pharmacotherapeutic classification (ATC code)	R06AE07
Pharmaceutical form and strength(s)	Oral solution
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/178/001
Marketing Authorisation Holder	Pinewood Laboratories Ltd,, (0281), Ballymacarbry, Clonmel, Co. Tipperary, Ireland
MRP/DCP No.	CRN008QSH

II. QUALITY ASPECTS

II.1. Introduction

This application is for Zirpine 1mg/ml Oral Solution

II.2 Drug substance

The active substance is Cetirizine dihydrochloride, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product (1 mg/ml active substance).

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Oral solutions, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Zirpine 1mg/ml Oral Solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Zirtek 1 mg/ml oral solution on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of cetirizine are well known. As cetirizine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings are included in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cetirizine dihydrochloride is a well-known active substance with established efficacy and tolerability. Cetirizine, a human metabolite of hydroxyzine, is a potent and selective antagonist of peripheral H1-receptors (ATC-Code: R06A E07).

The content of the SmPC approved during the national procedure is in accordance with that accepted for the reference product Zirtek 1 mg/ml marketed by UCB (Pharma) Ltd.

For this generic application, which concerns an oral immediate release dosage form (oral solution) the applicant has not submitted a bioequivalence study.

The justification for a biowaiver in this case is that the test product and the reference product:

-have the same qualitative and quantitative composition in terms of active substance
-have the same pharmaceutical form
-have the same qualitative formula.
- are highly soluble and highly permeable, therefore BCS-class 1 drug substances.

According to the European Medicine Agency's ''Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), bioequivalence studies are not required to support bioequivalence for this product.

IV.2 Pharmacokinetics

Following oral administration, the steady - state peak plasma concentrations is approximately 300 ng/ml and is achieved within 1.0 ± 0.5 h.. The distribution of 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. 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. 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. Cetirizine exhibits linear kinetics over the range of 5 to 60 mg.

Dosing adjustment is necessary in patients with moderate or severe renal impairment. Dosing adjustment is only necessary in patients with hepatic impairment if concomitant renal impairment is present.

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.

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.

IV.3 Pharmacodynamics

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 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 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 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.

IV.4 Clinical Efficacy

Cetirizine is a well-known active substance. No new clinical efficacy data has been submitted which is acceptable for a generic application.

IV.5 Clinical Safety

Cetirizine is a well-known active substance. No new clinical safety data has been submitted which is acceptable for a generic application.

Risk Management Plan

The applicant 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 Zirpine 1mg/ml Oral Solution.

The RMP (version 1.0, signed August 2019) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.

The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing Information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Cetirizine is a well-known active substance and has been widely marketed. As this is a generic application, no new efficacy or safety data have been submitted, which is acceptable. Efficacy and safety is expected to be similar to the reference product Zirtek 1 mg/ml marketed by UCB (Pharma) Ltd. The product information SmPC and patient leaflet are consistent with those of the reference product.

V. OVERALL CONCLUSIONS

Zirpine 1mg/ml Oral Solution, from Pinewood Laboratories Ltd is a generic form of Zirtek 1mg/ml oral solution by UCB (Pharma) ltd, (PA0891/008/003). Zirtek 1mg/ml oral solution by UCB (Pharma) Ltd is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

This generic application, which concerns an oral immediate release dosage form (oral solution), is acceptable regarding bioequivalence according to the European Medicine Agency's ''Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98)".

The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted, considered that Zirpine 1mg/ml Oral Solution by Pinewood Laboratories Ltd was bioequivalent to the reference product and had a satisfactory risk/benefit profile, and therefore granted a national marketing authorisation.

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
New National	N/A	Section 1 to section 10	7th October 2022	N/A