

Public Assessment Report

Scientific discussion

**Cetirizine diHCl Sanias 10 mg,
film-coated tablets**

(cetirizine dihydrochloride)

NL/H/3575/001/DC

Date: 3 April 2017

<p>This module reflects the scientific discussion for the approval of Cetirizine diHCl Sanias 10 mg, film-coated tablets. The procedure was finalised on 17 August 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.</p>
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List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Cetirizine diHCl Sanias 10 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated in adults and paediatric patients 6 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.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zyrtec 10 mg, film-coated tablets which has been registered in Portugal by UCB Pharma (Produtos Farmacêuticos), Lda., since August 1989. The reference product in the Netherlands is Zyrtec 10 mg marketed by UCB Pharma (NL License RVG 13010; IE/H/0209/001).

The concerned member states (CMS) involved in this procedure were Belgium, Germany and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Cetirizine diHCl Sanias is a white to off-white, film-coated, off-rectangular tablet, debossed with '10' on one side and plain on the other side, with a score line between '1' and '0'. The tablet can be divided into equal doses.

The film-coated tablets are packed in PVC/PVdC-Aluminium foil blister packs and HDPE bottle with polypropylene closure.

The excipients are:

Tablet core - lactose monohydrate, cellulose microcrystalline (grade -102), croscarmellose sodium colloidal anhydrous silica, magnesium stearate

Film-coating - hypromellose (5cp), titanium dioxide (E 171), macrogol 400

II.2 Drug Substance

The active substance is cetirizine dihydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is freely soluble in water over the entire physiological pH range. There are no reported polymorphic forms of cetirizine dihydrochloride.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is fully in line with the CEP. Additional specifications are applied for heavy metals, microbial quality, and particle size distribution. The requirements have been adequately justified. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. This re-test period has been substantiated by long-term (72 months) and accelerated (6 months) stability studies.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described. The choice of excipients is justified and their functions explained. The dry compression formulation is the result of several development trials with different formulations. Breakability of the tablets has been demonstrated. The products used in the bioequivalence studies are acceptable. Sufficient comparative dissolution data have been provided.

Manufacturing process

The manufacture of the drug product is straight-forward dry compression process. The process has been described in sufficient detail. The applied in-process controls are appropriate and, where applicable, in line with the release specifications. The process has been adequately validated for the smallest production scale and at full scale.

Control of excipients

Purified water used in manufacture of drug products is tested using a harmonized internal specification (based on Ph.Eur. and USP). The other excipients comply with Ph.Eur. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification, average weight, subdivision of tablets, dissolution, uniformity of dosage units, assay, water content, related substances, thickness, identification colorant and microbial quality. Methods have been adequately described and validated. The applied tests and the limits are acceptable in view of relevant Ph.Eur. monographs and regulatory guidelines. Wider shelf-life limits for Ph.Eur. one impurity, lactose ester, total impurities, and water content are supported by the results of stability studies. Batch analytical data have been provided on three small scale and three full scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three batches, packed in the proposed packaging, stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies demonstrated that the product is not sensitive light. The results support the proposed shelf-life and storage condition (2 years, no special storage condition). In-use stability studies throughout shelf life indicate that a specific in-use shelf-life is not required.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product. Its TSE safety has been substantiated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Cetirizine diHCl Sanias 10 mg, film-coated tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

The MAH argued that an ERA is not required for this product, but also submitted a brief evaluation of the environmental risk. The member states accepted the justification for not providing an in-depth environmental risk assessment, and the submitted brief evaluation of the environmental risk was not further evaluated. Since Cetirizine diHCl Sanias is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zyrtec, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Cetirizine dihydrochloride is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Cetirizine diHCl Sanias 10 mg (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Zirtek Allergy 10 mg film-coated tablets (UCB Pharma Ltd, UK).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-43 years. Each subject received a single dose (10 mg) of one of the 2 cetirizine dihydrochloride formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.67, 0.83, 1.0, 1.25, 1.50, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12, 18, 24, 36 and 48 hours after administration of the products.

The study design is appropriate for testing bioequivalence of cetirizine. The medicine can be taken without food. The blood sampling times are in accordance with the pharmacokinetics of cetirizine.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Twenty six subjects completed both treatments. One subject was withdrawn for a positive urine test on drugs before the start of the second period and one subject did not show up for the second period.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{\max} (median, range)) of cetirizine under fasted conditions

Treatment N=26	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h	t _{1/2} h
Test	3501.785 \pm 921.5855	3708.130 \pm 1047.861	375.877 \pm 71.9487	0.83 (0.50-4.03)	10.5 \pm 2.2
Reference	3398.628 \pm 885.9069	3588.849 \pm 1043.419	364.098 \pm 64.1731	1.00 (0.50-3.00)	10.6 \pm 2.6
*Ratio (90% CI)	1.03 (1.00-1.06)	1.03 (1.00-1.06)	1.03 (0.97-1.09)	--	--
AUC _{0-∞} area under the plasma concentration-time curve from time zero to infinity AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum concentration t _{1/2} half-life CV coefficient of variation					

*In-transformed values

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Cetirizine diHCl Sanias 10 mg is considered bioequivalent with Zirtek Allergy 10 mg film-coated tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The 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 diHCl Sanias.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> Hypersensitivity including anaphylaxis Convulsions, especially in epileptic patients and in patients with predisposing factors Psychiatric disorders including suicidal ideation
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zyrtec. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has not been user tested. The MAH submitted a bridging rationale. The proposed PL (daughter) is in line with Cetirizine Aurobindo 10 mg film-coated tablets (parent) which was approved in DCP SE/H/0845/001/DC. For this PL a user test was successfully conducted and the patients/users are able to act upon the information that it contains. Both products have the same active ingredient, strength, pharmaceutical form and all the important key messages for safe use are similar between the leaflets. Parent and daughter PLs have the same layout and design (same in-house style).

Based on the submitted bridging report, the member states agreed that the PL for Cetirizine diHCL Sanias can be accepted without further user testing.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Cetirizine diHCl Sanias 10 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zyrtec 10 mg, film-coated tablets. Zyrtec is a well-known medicinal product with an established favourable efficacy and safety profile

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Cetirizine diHCl Sanias with the reference product, and have therefore granted a marketing authorisation. The decentralized procedure was finalised with a positive outcome on 17 August 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached