LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Cetirizin Apofri
Cetirizine hydrochloride

Asp no 2009-1109

This module reflects the scientific discussion for the approval of Cetirizin Apofri. The procedure was finalised 2010-06-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Evolan Pharma AB has applied for a marketing authorisation for Cetirizin Apofri, film-coated tablet, 10 mg claiming essential similarity to “Zyrlex, filmdragerade tabletter, 10 mg” marketed in Sweden by UCB Nordic A/S. The product contains cetirizine hydrochloride as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is “Zirtek, tablet, 10 mg” marketed by UCB Pharma Ltd in UK.

II. QUALITY ASPECTS

II.1 Introduction

Cetirizin Apofri is presented in the form of tablets containing 10 mg of “cetirizine dihydrochloride” which corresponds to 8.42 mg of cetirizine . The excipients are lactose monohydrate, magnesium stearate, maize starch, pregelatinised starch, talc, titanium dioxide, hypromellose and macrogol. The tablets are packed in PVC/aluminium blister.

II.2 Drug Substance

Cetirizine dihydrochloride has a monograph in the Ph Eur.

Cetirizine dihydrochloride is a white, powder which is freely soluble in water and practically insoluble in acetone and in methylene chloride. The structure of cetirizine dihydrochloride has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Cetirizin Apofri, film-coated tablet, is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin except for lactose. For lactose is demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 30 °C.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Following oral administration cetirizine reaches its peak plasma levels within one hour. Extent of absorption of cetirizine is not reduced by food intake, although the rate of absorption is decreased. Cetirizine does not undergo extensive first pass metabolism. About two third of the dose are excreted unchanged in urine. The terminal half life is around 10 hours in adults and 6 hours in children.

To support the application, the applicant has submitted one single-dose, two-way crossover bioequivalence study where Cetirizin Apofri 10 mg film-coated tablets are compared with Zirtek 10 mg tablets following a dose of 20 mg. The study was performed in healthy volunteers under fasting conditions. The results are shown below.

Based on the submitted bioequivalence study Cetirizine Apofri is considered bioequivalent with Zirtek.

Pharmacokinetic parameters for cetirizine (n=23). Non-transformed values; arithmetic mean ± SD, tmax median (range).

Treatment	C_{max} (ng/ml)	AUC_{0-t} (ng·h/ml)	$AUC_{0-\infty}$ (ng·h/ml)	t_{max}* (h)
Cetirizin Apofri	**524.6±120.3**	**4698.3±887.8**	**5080.1±947.7**	**1.094 (0.5-3.00)**
Zirtek	**560.9±116.4**	**4637.0±752.6**	**4985.3±809.9**	**0.918 (0.5-2.00)**
Ratio (90% CI)**	**94.1 86.7-102.1%**	**102.0 96.7-107.6%**	**102.5 97.1-108.2%**	

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 plasma concentration

** t_{max} which is given as median (range)*
*** calculated using ln-transformed values*

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Cetirizin Aurobindo, SE/H/845/01/DC (content) and Paracetamol Apofri, 111/2007:72776 (lay-out). The bridging report submitted by the applicant has been found acceptable.

Bioequivalence has been properly demonstrated between Cetirizin Apofri and the reference product Zirtek.

The risk/benefit ratio is considered positive and Cetirizin Apofri, film-coated tablet, is recommended for approval.

VI. APPROVAL

Cetirizin Apofri, 10 mg film-coated tablet, was approved in the national procedure on 20100621.

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Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)

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