LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Ebastin Apofri
(ebastine)

Asp no: 2015-0231, 2015-0232

This module reflects the scientific discussion for the approval of Ebastin Apofri. The procedure was finalised on 2016-01-08. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Ebastin Apofri, 10 mg and 20 mg, orodispersible tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Apofri AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Kestine, 10 mg, film-coated tablet, authorised in Sweden since 1995, with Almirall S.A. as marketing authorisation holder.

The reference product used in the bioequivalence study is Ebastel Forte Flas 20 mg, orodispersible tablet, from Germany with Laboratories Almirall, S.A. as marketing authorisation holder.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

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 have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

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.

CLINICAL ASPECTS

III.2 Pharmacokinetics

Bioequivalence was evaluated in a randomised, two-treatment, four-period, two-sequence fully replicated single-dose crossover study conducted in 82 healthy volunteers, comparing Ebastine Apofri, 20 mg, orodispersible tablet with Ebastrel Forte Flas, 20 mg, orodispersible tablet under fasting conditions. The study was conducted at Lambda Therapeutic Research ltd, India between 17 May and 07 June 2013. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of ebastine and the active metabolite carebastine were determined with an adequately validated LC/MS/MS method. For AUC0-t and Cmax the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for both ebastine and carebastine.

The bioequivalence evaluation were based both on ebastine and the active metabolite carebastine in accordance with the study protocol. For ebastine generics the PKWP has decided that it is acceptable to demonstrate bioequivalence for either the inactive pro-drug ebastine or the active metabolite carebastine. In case both ebastine and carebastine are analysed, the analyte to be used for bioequivalence evaluation should be prospectively defined in the protocol (PKWP Q&A EMA/618604/2008). Thus, evaluation of both compounds is adequate in the current application.

Based on the submitted bioequivalence study, Ebastine Apofri, 20 mg, orodispersible tablet is considered bioequivalent with Ebastrel Forte Flas, 20 mg, orodispersible tablet.

The results from the bioequivalence study with the 20 mg strength can be extrapolated to the additional strength of 10 mg, since all conditions for biowaiver are fulfilled. The study was conducted with the highest strength with is recommended for substances with linear pharmacokinetics. The pharmacokinetics of the active metabolite carebastine is linear within the therapeutic dose range. Since very low plasma concentrations of the parent compound ebastine are obtained after oral administration, published pharmacokinetic is very sparse. Thus information regarding dose linearity for ebastine is lacking. Nevertheless, given that the pharmacokinetics of the active metabolite carebastine is linear demonstration of bioequivalence at the highest strength only is considered acceptable.

Conclusion: Bioequivalence has been satisfactorily demonstrated.

III.3 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.

III.4 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 Ebastin Apofri.

Safety specification

Table 1. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	• Use in patient with severe liver impairment /Hepatic insufficiency. • Use in pregnancy and lactating women

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The RMP is approved.

IV. 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. 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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Ebastin Apofri, 10 mg and 20 mg, orodispersible tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment
N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VI. APPROVAL

Ebastin Apofri, 10 mg and 20 mg, orodispersible tablet was approved in the national procedure on 2016-01-08.

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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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