LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Kalcium/Magnesium Apofri

(calcium carbonate, magnesium hydroxide)

2019-0673

This module reflects the scientific discussion for the approval of Kalcium/Magnesium Apofri. The procedure was finalised on 2020-11-23. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Kalcium/Magnesium Apofri, 180 + 43.7 mg, chewable tablet is a hybrid application made according to Article 10(3) 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 Rennie, 680 mg + 80 mg, chewable tablet, authorised in SE since 1976, with Bayer AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

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.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The applicant did not submit any bioequivalence studies. The applicant is referring to Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1, Corr.1*), that for antacids, *in vitro* methodology based on dynamic and static neutralizing tests is considered a surrogate methodology for therapeutic equivalence demonstration. The Guideline also states that plasma levels cannot be used, in principle, as a surrogate of equivalence in efficacy for products acting locally in the stomach exclusively because the sites of action in the stomach are reached first and are different to the sites of absorption in the intestine.

Composition of the drug product
The applicant compared the composition of the drug product with two antacids approved in Sweden where Rennie is the formal reference product with which similarity should be shown. Whereas Kalcium/Magnesium Apofri contains calcium carbonate and magnesium hydroxide, the reference product contains calcium carbonate and magnesium carbonate. When the daily ingested calcium and magnesium doses were calculated for the applied product and Rennie, based on the maximal daily dose of 11 tablets, the applied product contained less calcium, but about 113 % more magnesium than Rennie.

Discussion and overall conclusion
It can be agreed with the applicant that bioequivalence studies may not be suitable for products acting locally in the stomach according to Guideline on equivalence studies for the demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev.1, Corr.1*).

For antacids, in vitro methodology based on dynamic and statistic neutralizing tests is considered a surrogate methodology for therapeutic equivalence demonstration.

The same Guideline also states that, in those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety, unless otherwise justified. The amount of calcium carbonate in each tablet is lower for the test product than for the reference product, and thus it is not considered likely that formulation differences would result in higher systemic calcium exposure following ingestion of the test product than the reference product. Regarding magnesium, the applicant explained that there are approved products in Sweden with higher daily magnesium consumption. Thus, there is no concern regarding safety for magnesium.

IV.2 Discussion on the clinical aspects

No new studies have been provided to support the clinical efficacy, only literature data and a discussion in the clinical overview. That is acceptable for a locally acting medicinal product when therapeutic equivalence has been shown to the reference product. An in vitro test for acid neutralizing capacity has been performed and compared to the reference product.

No new safety studies have been submitted but the safety is discussed in the overview based on literature. This is acceptable for this locally active medicinal product. The content of magnesium is higher than in the reference product, but literature data has been provided to support the safety of the relevant amounts for this product and the intended use.

IV.3 Risk Management Plan

The MAH has in response to the LoQ submitted an updated risk management plan, version 0.2, 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 Kalcium/Magnesium Apofri, chewable tablet.

Safety specification

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

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
Since all important identified risks and important potential risks are well known and managed with routine risk minimisation activities only the table “summary of safety concerns” is empty. The RMP is acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the MPA;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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. The language used for the purpose of user testing the PIL was English. Furthermore, a bridging report has been submitted regarding the layout of the package leaflet with reference to the nationally approved medicinal product Natriumklorid Evolan 500 mg capsules.

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

For locally active products, bioequivalence is generally not a suitable way to show therapeutic equivalence since plasma levels are not relevant for local efficacy, although they may play a role with regards to safety. In this case there are certain differences in composition between the test and reference products but an *in vitro* test for acid neutralizing capacity has been performed showing a difference of only slightly larger than 10% and this is acceptable.

The content of magnesium is higher than in the reference product, but literature data has been provided to support the safety of the relevant amounts for this product and the intended use.
A waiver of the need to provide equivalence data could thus be granted.

The benefit/risk ratio is therefore considered positive and Kalcium/Magnesium Apofri, 180 + 43.7 mg, chewable tablet is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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

VII. APPROVAL

Kalcium/Magnesium Apofri, 180 + 43.7 mg, chewable tablet was approved in the national procedure on 2020-11-23.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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