LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Naproxen Apofri
(naproxen)

Asp no: 2016-0186-87

This module reflects the scientific discussion for the approval of Naproxen Apofri. The procedure was finalised on 2017-02-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Naproxen Apofri, 250 mg, 500 mg, tablet, is ageneric application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Apofri AB applied 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 Naprosyn, 250 mg, tablet authorised in Sweden in 1975, with Roche AB as marketing authorisation holder. The MA was withdrawn in 2006.

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 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

Naproxen is quickly and completely absorbed. Following an oral dose of naproxen maximal plasma concentrations occur at approximately 2 hours. The absorption of naproxen is usually not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. Plasma concentrations of naproxen increase proportionally with dose up to about 500 mg daily; at higher doses there is an increase in clearance caused by saturation of plasma proteins. The terminal half-life is 10-17 hours.

The applicant has submitted two single dose bioequivalence studies with the 500 mg tablet strength, one in the fasted and one in the fed state. According to guideline, one study in the fasted state would have been sufficient since this is an immediate release tablet and the SmPC recommends intake irrespective of food intake. However, bioequivalence was demonstrated in both studies and the fed study is considered as supportive.

Fasted study 15-VIN-609:
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Naproxen, 500 mg, tablet with Naprosyn, 500 mg, tablet under fasting conditions. The study was conducted at Veeda Clinical Research Pvt. Ltd., Ahmedabad, India between 30th March and 10th April 2016. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of naproxen were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Fed study 15-VIN-610:
Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 26 healthy volunteers, comparing Naproxen, 500 mg, tablet with Naprosyn, 500 mg, tablet under fed conditions. The study was conducted at Veeda Clinical Research Pvt. Ltd., Ahmedabad, India between 1st and 16th April 2016. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of naproxen were determined with an adequately validated LC-MS/MS method. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

From a pharmacokinetic point of view, absence of studies with the additional strength 250 mg is acceptable, as the pharmacokinetics of naproxen is linear between 250 mg and 500 mg.

Based on the submitted bioequivalence studies, Naproxen Apofri tablets is considered bioequivalent with Naprosyn tablets.

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.

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 Naproxen Apofri and duplicate.

The following table is suggested (taken from the clinical AR/RMP as submitted by applicant):

Safety specification

Summary of safety concerns	
Important identified risks	Gastrointestinal ulcers Liver failure Renal failure Heart failure Gastrointestinal bleeding Hypersensitivity reactions Use in pregnancy
Important potential risks	None
Missing information	Use in children

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.

Safety specification
Summary table of safety concerns as approved in RMP

Updated safety concerns:

Important identified risk	Gastrointestinal ulcers Liver failure Renal failure Heart failure Gastrointestinal bleeding Use in pregnancy
Important potential risks	Drug Interactions
Missing information	Use in children

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly.

The RMP is approved

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 RMS;
- 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

Naproxen Apofri

Full User test

The package leaflet (for Rx use) 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.

Bridging

A user consultation with target patient groups on the package leaflet (for OTC use) has been performed on the basis of a bridging report making reference to the PL for Rx use.

A user consultation with target patient groups regarding the layout of the package leaflet has been performed on the basis of a bridging report making reference to Ranitidin Apofri 150 mg tablets, Dnr 111:2012/79828 (“In House Style”).

The bridging reports submitted by the applicant have been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Naproxen Apofri, is found acceptable. There are no objections to approval of Naproxen Apofri, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore 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

VII. APPROVAL

Naproxen Apofri, 250 mg, 500 mg, tablet was approved in the national procedure on 2017-02-21.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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