Public Assessment Report
Generic applications
Scientific discussion

Acetylsalicylsyra/Koffein Apofri
(Acetylsalicylic acid and Caffeine)

This module reflects the scientific discussion for the approval of Acetylsalicylsyra/Koffein Apofri. The procedure was finalised at 2012-04-26. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

Apofri AB has applied for a marketing authorisation for Acetylsalicylsyra/Koffein Apofri, effervescent tablet, 500 mg/50mg claiming essential similarity to Bamyl koffein, effervescent tablet, 500 mg/50 mg marketed in Sweden by Meda AB. The product contains acetylsalicylic acid and caffeine as active substance. For approved indications see the Summary of Product Characteristics. No bio-equivalence study is performed.

II. QUALITY ASPECTS

II.1 Introduction

Acetylsalicylsyra/Koffein Apofri is presented in the form of effervescent tablets containing 500 mg of acetylsalicylic acid and 50 mg of caffeine. The excipients are anhydrous citric acid, sodium hydrogen carbonate, anhydrous sodium carbonate, sodium dihydrogen citrate, sodium citrate, mannitol, docusate sodium, simeticone and povidone. The tablets are packed in polypropylene tubes with stoppers containing desiccant.

II.2 Drug Substance

Acetylsalicylic acid
Acetylsalicylic acid has a monograph in the Ph Eur. The drug substance is a white or almost white, crystalline powder or colourless crystals which is slightly soluble in water. The structure of acetylsalicylic acid 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.

Caffeine
Caffeine has a monograph in the Ph Eur. The drug substance is a white or almost white, crystalline powder or colourless crystals which is sparingly soluble in water. The structure of caffeine 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

Acetylsalicylsyra/Koffein Apofri effervescent tablet is formulated using excipients described in the current Ph Eur, except for sodium dihydrogen citrate which is controlled according to
acceptable in house specifications. All raw materials used in the product are of vegetable origin. 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 in the original package in order to protect from moisture.

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 effervescent tablet is quickly dissolved which leads to a fast absorption. Acetylsalicylic acid is hydrolysed to salicylic acid, which is also active, in the blood, liver and gut. The half-life for acetylsalicylic acid is 20-30 minutes and salicylic acid has a half-life of approximately 3 hours in low doses (<0.5 g). In high doses, the elimination half-life is increased to 15-30 hours due to saturation of metabolism. Caffeine is metabolised in the liver followed by renal excretion, with a half-life of 3-4 hours.

Generally, for a product claiming essential similarity bioequivalence with the reference product must be shown. For the applied product, the applicant has not submitted any bioequivalence study but claims that the applied product fulfils the criteria for exemption of in vivo bioequivalence studies since both the applied product and the reference product are aqueous oral solutions at time of administration and since the qualitative composition of the excipients of the applied product is identical compared to the reference product.

According to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1), bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution. However, if there are differences regarding excipients that may affect the bioavailability, a study should be conducted unless the differences in the amounts of these excipients can be adequately justified.

The applied product is an aqueous oral solution at time of administration, and contains the same concentration of acetylsalicylic acid and caffeine as Bamyl koffein 500 mg/50 mg effervescent tablets. In addition, the excipients are qualitatively the same and it is has been
judged unlikely that the amount mannitol in the applied product could affect the bioavailability of the active substances. Mannitol is specially mentioned in the guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) as an excipient that could affect the gastrointestinal transit time.

Thus no bioequivalence study is considered necessary according to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/ Rev. 1 Corr).

**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**

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.

The risk/benefit ratio is considered positive and Acetylsalicylsyra/Koffein Apofri, 500 mg/50 mg, effervescent tablet is recommended for approval.

**VI. APPROVAL**

Acetylsalicylsyra/Koffein Apofri, 500 mg/50 mg, effervescent tablet was approved in the national procedure on 2012-04-26.
# Public Assessment Report – Update

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