LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Acetylsalicylsyra ABECE
(acetylsalicylic acid)

Asp no: 2016-1378

This module reflects the scientific discussion for the approval of Acetylsalicylsyra ABECE. The procedure was finalised on 2016-11-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Acetylsalicylsyra ABECE, 500 mg, tablet, is generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies for marketing authorisations in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Aspirin, 500 mg, tablet, authorised in Sweden since 1935, 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 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

No studies have been conducted. The Applicant claims that acetylsalicylic acid belongs to BCS class I and that bioequivalence studies can be waived.

From a clinical/pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same. It should also be confirmed that the substance is not a narrow therapeutic index drug. From a quality perspective, a BCS-class I based biowaiver is acceptable if the solubility of the substance is high and if very rapid or similarly rapid dissolution characteristics of the test and reference products have been demonstrated.

The Applicant refers to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ and has provided a thorough discussion regarding the above mentioned requirements.

Absorption
The absolute bioavailability of ASA following oral administration is approximately 50-70 % (Dressman et al 2012, Nagelschmitz et al 2014). According to the SmPC of Aspirin, ASA is absorbed rapidly and almost completely. Already during the absorption through the intestinal wall, but also in the liver and blood, ASA is hydrolyzed to salicylic acid, which has substantially the same pharmacological properties as ASA (SmPC: Aspirin Bayer 2013). The liver is the major site of first-pass metabolism.

The urinary excretion and mass-balance data show that a large fraction (94-98%) of the ASA dose was eliminated in urine, mainly as metabolites (Montgomery 1986, Hutt 1982), indicating complete absorption of ASA. Furthermore, the conversion of ASA to salicylic acid primarily occurs in the gut wall and liver after absorption. Therefore, it may be concluded that the fraction absorbed ASA is most probably above 85% and consequently fulfil the demands for complete absorption according to the EMA demands.

In vitro permeability results from Caco-2 models also indicate high permeability with apparent permeability coefficients (Papp) above $10x10^{-6}$ cm/sec (Artursson and Karlsson 1991, Yee 1997), which may be considered as supportive evidence in the evaluation of a BCS-biowaiver.

Solubility
It has been satisfactorily demonstrated that the highest dose of 1000 mg acetylsalicylic acid is dissolved in 250 mL buffers in the range of pH 1.2-6.8.

In vitro dissolution
Similar in vitro dissolution behavior of the test- and reference drug products at pH 1.2-6.8 has been demonstrated.

Excipients
The qualitative composition of the test and the reference product is very similar. None of the excipients are known to affect bioavailability. This is considered acceptable for a BCS class I.

Therapeutic index
ASA is not considered to be a narrow therapeutic index drug.

Conclusion
A BCS class I biowaiver can be accepted.

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 Acetylsalicylsyra ABECE.

The safety concerns are updated as follow:

Important Identified risks	Gastrointestinal disorders(including gastric or duodenal ulcers) Increased bleeding of various origin including gastrointestinal bleeding and other haematological disorders Hypersensitivity reactions(bronchospasm, aspirin-induced asthma(AIA), angioedema, anaphylactic shock) Use in pregnancy Renal impairment Interactions
Important Potential risks	Reyes syndrome
Missing Information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed at current stage.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed at current stage.

The RMP is approved.

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 Polish.
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.

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 Ranitidin Apofri MA-nr 48746. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Acetylsalicylsyra ABECE, is found adequate. There are no objections to approval of Acetylsalicylsyra ABECE, from a non-clinical and clinical point of view. 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

Acetylsalicylsyra ABECE, 500 mg, tablet was approved in the national procedure on 2016-11-18.

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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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