LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Acetylsalicylsyra Hexal
(acetylsalicylic acid)

SE/H/1259/01/MR

This module reflects the scientific discussion for the approval of Acetylsalicylsyra Hexal. Please note that the marketing authorisation was first approved with the name Azegetian and therefore this name is used throughout the document. The procedure was finalised at 2012-07-11. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Gentian Generics Limited has applied for a marketing authorisation for Azegetian, gastro-resistant tablet, 100 mg. The active substance is acetylsalicylic acid. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Azegetian is presented in the form of gastro-resistant tablets containing 100 mg. The excipients are cellulose microcrystalline, maize starch, silica colloidal anhydrous, stearic acid, methacrylic acid - ethyl acrylate copolymer, sodium laurilsulfate, polysorbate 80, triethyl citrate and talc. The tablets are packed in PVC/Al blisters and HDPE containers.

II.2 Drug Substance

Acetylsalicylic Acid has a monograph in the Ph Eur.

Acetylsalicylic acid is a white or almost white crystalline powder or colourless crystals, slightly soluble in water and freely soluble in ethanol. 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.

II.3 Medicinal Product

Azegetian gastro-resistant tablets is formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin/has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

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, with storage precautions "Store below 25°C" and "Store in the original package in order to protect from moisture".

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since Acetylsalicylic acid (ASA) has been used clinically for a very long time there is an extensive clinical experience with ASA that largely supersedes non-clinical data. No further non-clinical data have been submitted or are considered necessary. A non-clinical overview, based on submitted publications included in the dossier, is considered to be adequate.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

To support the statement that this formulation is sufficiently similar to the formulations used in the bibliographic data referred to, the applicant has submitted four single-dose bioequivalence studies with the 100 mg tablet strength; one in the fed state and three in the fasting state. The reference product was Aspirin Protect 100 mg gastro-resistant tablet (Bayer).

For all four studies, plasma concentrations of ASA were determined with a validated LC/MS/MS method and plasma concentrations of SA were determined with a validated HPLC method with UV detection. Bioequivalence for SA was considered as supportive evidence only.

Study in the fed state (1268/07)
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted under fed conditions. The 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} and C_{max} for ASA and SA were within the conventional acceptance range of 80-125%.

Study in the fasting state (1267/07)
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted under fasting conditions. The 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} and C_{max} for ASA was outside the conventional acceptance range of 80-125% (for C_{max} also outside the prospectively widened acceptance range of 75-133 %). The 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} and C_{max} for SA were within the conventional acceptance range of 80-125%.

Study in the fasting state (1321/07)
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conducted under fasting conditions. The 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} for ASA was within the conventional acceptance range of 80-125%, but for C_{max} the interval was outside the conventional as well as the prespecified widened acceptance range. The 90% confidence intervals for the test/reference

ratio of the population geometric means for AUC_{0-t} and C_{max} for SA were within the conventional acceptance range of 80-125%.

Study in the fasting state (1747/08)
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study conductedunder fasting conditions. The 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} and C_{max} for ASA was outside the conventional acceptance range of 80-125% (for C_{max} also outside the prospectively widened acceptance range of 75-133 %). For SA, the 90% confidence intervals for the test/reference ratio of the population geometric means for AUC_{0-t} was within the conventional acceptance range of 80-125% and for C_{max} it was just outside the conventional acceptance range.

Study	Ratio (90% CI) for AUC_{0-t} for ASA	Ratio (90% CI) for C_{max} for ASA
1268/07 (fed)	1.14 (1.05-1.23)	1.03 (0.93-1.14)
1267/07 (fasting)	1.18 (1.05-1.33)	1.22 (1.03-1.43)
1321/07 (fasting)	0.98 (0.88-1.10)	0.76 (0.65-0.89)
1747/08 (fasting)	1.12 (0.97-1.29)	1.24 (1.04-1.47)

Pharmacokinetic conclusion
Bioequivalence has been demonstrated between test and reference product for both ASA and SA in the fed state. However, strict bioequivalence has not been demonstrated for ASA in three studies in the fasting state (study 1267/07 showed an 18 % increase in AUC and a 22 % increase in C_{max} with test compared to reference, study 1321/07 was bioequivalent for AUC but showed a 24 % decrease in C_{max} with test compared to reference and study 1747/08 showed a 12 % increase in AUC and a 24 % increase in C_{max} with test compared to reference). This is not considered a critical finding as the products are applied via a bibliographic application where the bibliographic clinical data on ASA in the applied indication consists of studies performed with several different formulations and doses. Our conclusion is that the presented studies demonstrate that the formulation is sufficiently similar to the formulations used in the bibliographic data referred to.

IV.2 Pharmacodynamics

No new data has been submitted, however, an overview on published data on the pharmacodynamics of acetylsalicylic acid has been provided.

The mechanism of action and pharmacodynamics of ASA is well known and has been adequately summarised by the applicant. ASA inactivates COX irreversibly. Since platelets do not have a cell nucleus they cannot synthesise new proteins. Therefore, the action of ASA on platelet COX is permanent, lasting for the life of the platelet (7 to 10 days). Repeated, low, doses of ASA therefore produce a cumulative inhibitory effect on platelet function. Via the effect on COX, ASA also has an inhibitory action on prostacyclin biosynthesis. This potentially counteractive effect, however, may be limited due to the rapid recovery of the synthetic capacity of vascular endothelium. The anti inflammatory properties of ASA may have an additive effect in the prevention of cardiovascular disease.

A comprehensive review of the known pharmacodynamic interactions has been provided. These interactions are reflected in the SPC.

IV.3 Clinical efficacy

The applicant has provided an overview based on published literature to support the efficacy of ASA in the sought indications. The most important publication is the large meta-analysis carried out by the Antithrombotic Trialists' Collaboration, which summarises the main studies concerning the use of ASA in the sought indications and also forms the basis for the current European guidelines for the prevention of cardiovascular diseases.

The data provided supports the well-established efficacy in the approved indications:

Since the current application concerns a gastro-resistant formulation which is not suitable in acute conditions, the indication "Acute myocardial infarction" is not included in the approval.

As pointed out by the applicant, there are no regular dose-finding studies for ASA available in these indications. Over time, the recommended dose for the prevention of cardiovascular events has been adjusted towards lower levels (75-150 mg daily) for all indications except after coronary bypass, where the lowest recommended dose is 150 mg daily.

The dosing recommendation in the treatment and prevention of cerebrovascular events is still a matter of debate; however, a recommendation of a daily dose between 75 and 320 mg is supported by both clinical and pharmacodynamic data as well as current guidelines.

The SPC has been updated to reflect the posology as recommended in the submitted publications and current European guidelines.

IV.4 Clinical safety

The safety profile for ASA is well known and has been extensively described in the literature. The applicant has provided a comprehensive summary of the data. The applicant has also provided safety data from the four bioavailability studies performed with the product under assessment which supports that the product has a similar safety profile as already described for other ASA products.

The safety aspects are adequately reflected in the SPC.

IV.5 Discussion on the clinical aspects

The efficacy and safety characteristics of ASA are well documented through the longstanding clinical experience.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

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 Acetylsalicylsyra

Actavis, SE/H/1020/02-05/DC. The bridging report submitted by the applicant has been found acceptable.

The risk/benefit ratio is considered positive and Azegetian, 100 mg, gastro-resistant tablet is recommended for approval.

VI. APPROVAL

The Mutual recognition procedure for Azegetian, 100 mg, gastro-resistant tablet was successfully finalised on 2012-07-11.

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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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