LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Aspirin
(acetylsalicylic acid)

Asp no: 2015-0618

This module reflects the scientific discussion for the approval of Aspirin. The procedure was finalised on 2016-06-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Bayer AB has applied for a marketing authorisation for Aspirin, 500 mg, granules. The active substance acetylsalicylic acid is the same as in Aspirin, tablets, marketed by Bayer AB since 1935.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC.

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

No new non-clinical studies were submitted for this application. Pharmacodynamics, pharmacokinetic and toxicological properties of acetylsalicylic acid are considered well-known. Since Aspirin 500 mg coated tablets can be expected to result in similar systemic exposure and clinical safety profile as other Aspirin products, the lack of additional studies is considered acceptable.

III.1 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) in accordance with the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (CHMP/SWP /4447/00) was submitted. Overall, the environmental risk assessment shows no environmental concerns. It can be concluded that acetylsalicylic acid is unlikely to represent a risk to the environment under the proposed conditions of use.

IV. CLINICAL ASPECTS

IV.1 Introduction

IV.2 Pharmacokinetics

In order to demonstrate the release characteristics of the new granule formulation and to bridge between the new formulation and previously approved formulations four bioavailability studies have been conducted.

Study PH-28658

A randomised, 3-way, single-dose, cross-over study to evaluate the relative bioavailability of Aspirin dry granules 500 mg and a new Aspirin tablet in comparison to the 500 mg Aspirin plain tablet.

The results demonstrate comparable AUC and Cmax for SA and comparable AUC for ASA following administration of Aspirin granules and tablet. Not unexpectedly the rate of absorption was slightly faster for the granules resulting in an approx. 50% higher Cmax for ASA.

Table 1. Pharmacokinetic parameters (non-transformed values; geometric mean (CV%), tmax median, range) for ASA, n=17.

Treatment	$AUC_{0-\infty}$ mg*h/L	AUC_{norm} kg*h/L	C_{max} mg/L	$C_{max,norm}$ kg/L	t_{max} h
Granules (Test A)	**4.97 (17.4)**	**0.790 (16.8)**	**5.34 (24.3)**	**0.850 (21.6)**	**0.333 0.333-1**
Tablet (Reference C)	**4.25 (44.3)**	**0.676 (43.0)**	**3.63 (74.0)**	**0.577 (73.0)**	**0.5 0.333-2**
***Ratio (90% CI)**	**-**	**1.18 (1.03-1.34)**	**-**	**1.46 (1.13-1.87)**	**-**

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; geometric mean (CV%), t_{max} median, range) for SA, n=17.

Treatment	$AUC_{0-\infty}$ mg*h/L	AUC_{norm} kg*h/L	C_{max} mg/L	$C_{max,norm}$ kg/L	t_{max} h
Granules (Test A)	**106 (27.8)**	**22.0 (23.5)**	**21.5 (19.0)**	**4.46 (14.8)**	**1.5 0.833-2**
Tablet (Reference C)	**107 (26.7)**	**22.2 (23.4)**	**20.1 (22.4)**	**4.18 (20.1)**	**2 0.833-3.06**
***Ratio (90% CI)**	**-**	**0.99 (0.93-1.07)**	**-**	**1.07 (0.98-1.16)**	**-**

**calculated based on ln-transformed data*

Study PH-3110

A randomised, 2-way, single-dose, cross-over study to evaluate the relative bioavailability of Aspirin granules 2x500 mg and Aspirin effervescent tablet 2x500 mg.

With respect to ASA the total exposure (AUC) was similar but the rate of absorption slower resulting in 45% lower Cmax after administration of the granules compared to the effervescent tablet. This is expected since the effervescent tablet is in solution at time of administration. For SA both AUC and Cmax were similar with 90% CI of the T/R-ratio within the conventional bioequivalence acceptance limits after administration of granules in comparison to effervescent tablets.

Table 3. Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, t_{max} median, range) for ASA, n=12.

Treatment	$AUC_{0-\infty}$ mg*h/L	C_{max} mg/L	t_{max} h
Granules (Test)	**9.44 ± 1.26**	**9.61 ± 1.27**	**0.42 0.17-0.67**
Effervescent tablet (Reference)	**9.66 ± 1.19**	**17.2 ± 1.31**	**0.33 0.17-0.50**
***Ratio (90% CI)**	**0.9776 (0.8938-1.0692)**	**0.5598 (0.4856-0.6452)**	**-**

**calculated based on ln-transformed data*

Table 4. Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, t_{max} median, range) for SA, n=12.

Treatment	$AUC_{0-\infty}$ mg*h/L	C_{max} mg/L	t_{max} h
Granules (Test)	**262 ± 1.26**	**41.3 ± 1.20**	**1.50 0.67-3.00**
Effervescent tablet (Reference)	**259 ± 1.21**	**46.8 ± 1.14**	**0.83 0.33-1.00**
***Ratio (90% CI)**	**1.0131 (0.9275-1.1065)**	**0.8819 (0.8448-0.9207)**	**-**

**calculated based on ln-transformed data*

Study PH-32192
A randomised, 2-way, single-dose, cross-over study to evaluate the relative bioavailability of Aspirin granules 500 mg given with and without water.

For SA the 90% CI of the T/R-ratio for AUC and Cmax were within the conventional bioequivalence acceptance limits of 80-125% and also for ASA AUC. ASA Cmax was slightly lower after administration without water. This is unlikely to be of any clinical relevance. The proposed method of administration in the SmPC:" The granules should be poured directly on the tongue and allowed to dissolve in the saliva before swallowing. A little fluid can be taken afterwards", is supported.

Table 5. Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, t_{max} median, range) for ASA, n=23.

Treatment	$AUC_{0-\infty}$ mg*h/L	C_{max} mg/L	t_{max} h
Without water	**5.14 ± 1.19**	**4.02 ± 1.47**	**0.667 0.167-1.50**
With water	**4.83 ± 1.22**	**4.68 ± 1.38**	**0.500 0.330-2.00**
***Ratio (90% CI)**	**1.0619 (1.0026-1.1247)**	**0.8582 (0.7632-0.9650)**	**-**

**calculated based on ln-transformed data*

Table 6. Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, t_{max} median, range) for SA, n=23.

Treatment	$AUC_{0-\infty}$ mg*h/L	C_{max} mg/L	t_{max} h
Without water	**108 ± 1.29**	**21.5 ± 1.24**	**1.50 0.834-3.00**
With water	**111 ± 1.28**	**21.9 ± 1.20**	**1.50 1.50-3.00**
***Ratio (90% CI)**	**0.9715 (0.9210-1.0248)**	**0.9794 (0.9173-1.0456)**	**-**

**calculated based on ln-transformed data*

Voelker&Hammer 2012; study 1
A randomised, single-dose, cross-over study to evaluate PK of 500 mg fast-release tablet with 500 mg granules and 500 mg Aspirin tablets.

The full study report which forms the ground for the published study by Voelker and Hammer (2012) has not been provided and a detailed assessment thus not possible. The general study design does however seem to be in line with the other studies described in this report. The results are in accordance with study PH-28658 with comparable AUC and Cmax for SA and comparable AUC for ASA and with approx. 50% higher Cmax for ASA following administration of Aspirin granules compared to the plain tablet.

Overall conclusions on pharmacokinetics
The overall exposure of ASA and SA after administration of the new Aspirin granule formulation was similar compared to both Aspirin conventional tablets and Aspirin effervescent tablets. The rate of absorption of ASA from the granule formulation was

somewhere in between the conventional tablet and the effervescent tablet resulting in Cmax values higher than for the tablet but lower than for the effervescent tablet. The exposure of ASA and SA was similar when the granules were administered with and without water. ASA Cmax was slightly lower after administration without water. This is unlikely to be of any clinical relevance. In conclusion, the product is considered to be sufficiently similar to the already approved formulations (tablet and effervescent tablet) to be approvable based on pharmacokinetic data alone.

IV.3 Pharmacodynamics

ASA belongs to the group of acidic nonsteroidal anti-inflammatories (NSAIDs), and has been in medical use for over 100 years. ASA exerts its analgetic, anti-inflammatory and antipyretic effect by inhibition of cyclooxygenase (COX)-catalysed conversion of arachidonic acid into prostaglandins, prostacyclin and thromboxane.

IV.4 Clinical efficacy

The submitted literature data provides an overview of the current knowledge of the effects of ASA. The available data supports the use of ASA for the applied therapeutic indications, i.e. the symptomatic relief of headache, menstrual pain, toothache, muscular and joint pain and fever associated with infections and common cold.

IV.5 Clinical safety

The use of ASA for the applied therapeutic indications, i.e. the symptomatic relief of headache, menstrual pain, toothache, muscular and joint pain and fever associated with infections and common cold, is well-established. The vast amount of patients that have been exposed to ASA since it was first marketed provide a substantial base for the assessment of the drug´s safety. Safety of ASA has also been thoroughly explored in a large amount of published studies.
The Applicant presents an adequate and relevant overview of adverse events, safety in special populations and interactions involving ASA.
Overall, literature data suggests that ASA is well-tolerated when used in line with the proposed posology. The safety profile is well-known and no new safety concerns can be identified.

IV.6 Risk Management Plans

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 Aspirin.

Safety specification
Summary table of safety concerns as approved in RMP

Important identified risks	• gastrointestinal disorders (ulcer, perforation and bleeding) • bleeding • hypersensitivity reactions • disturbance in renal function homeostasis in patients with renal, hepatic or cardiac insufficiency • hemolysis in patients with G-6-PD deficiency • interaction with drugs highly bound to plasma proteins and drugs with addtive toxicity potential • use in third trimester of pregnancy may expose o the foetus to cardiopulmonary toxicity (with premature

	closure of of the ductus arteriosus and pulmonary hypertension), and renal dysfunction. o the mother and child to: ▪ possible prolongation of bleeding time due to an anti- aggregating effect on the platelets which may occur even after very low doses ▪ inhibition of uterine contractions resulting in delayed or prolonged labour.
Important potential risks	Reye's syndrome
Important 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 Risk Minimisation Plan
The MAH proposed safety specification includes relevant safety issues, however, one can debate if all of the proposed risks are considered as "important" in the RMP perpsective. However, with a PSUSA soon coming up (DLP 1 Febr 2016) there will be an opportunity to discuss within the PRAC and harmonize the safety concerns to be followed, that is the risks defined in a RMP. Therefore is the proposed safety spcification acceptable for the time beeing.

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

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 Asproflash 500 mg coated tablet (FR/H/0482/001/DC) for the content and reference to Aspirin Plus C 400 mg/240 mg effervescent tablet regarding layout (assessed and accepted by German BfArM in 29 June 2009). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

ASA is a well-established non-steroid anti-inflammatory agent with analgetic, anti-pyretic and anti-inflammatory properties which has been in medical use for over 100 years. Its mechanism of action is well understood, as it is one of the most widely studied drugs ever.

The submitted literature data provides an overview of the current knowledge of the effects of ASA. The available data supports the use of ASA for the applied therapeutic indications, i.e. the symptomatic relief of headache, menstrual pain, toothache, muscular and joint pain and fever associated with infections and common cold.

The Applicant presents an adequate and relevant overview of the safety profile for ASA. Overall, literature data suggests that ASA is well-tolerated when used in line with the proposed posology. The safety profile is well-known and no new safety concerns can be identified.

The overall exposure of ASA and SA after administration of the new Aspirin granule formulation was similar compared to both Aspirin conventional tablets and Aspirin effervescent tablets. The rate of absorption of ASA from the granule formulation was somewhere in between the conventional tablet and the effervescent tablet resulting in Cmax values higher than for the tablet but lower than for the effervescent tablet. In conclusion, the product is considered to be sufficiently similar to the already approved formulations (tablet and effervescent tablet) to be approvable based on pharmacokinetic data alone.

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

Aspirin, 500 mg, granules was approved in the national procedure on 2016-06-09.

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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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