LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Aspirin
(acetylsalicylic acid)

Asp no: 2015-0454

This module reflects the scientific discussion for the approval of Aspirin. The procedure was finalised on 2016-05-12. 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, coated tablet. 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

The application was supported by three pharmacokinetic studies, including two pivotal bioavailability studies and a food-effect study. In addition, a pharmacodynamic, dental pain study was performed.

IV.2 Pharmacokinetics

The bioavailability studies were phase 1, randomized, open-label, single-dose cross-over studies in fasting, healthy adult male and female subjects. One study compared absorption characteristics of the new coated tablet with those of three previously available effervescent tablets. The second study compared absorption characteristics of the new coated tablet with those of the previously available plain tablet. Blood sampling was performed over 24 hours post-dose and plasma concentrations of acetylsalisylic acid (ASA) and salicylic acid (SA) were determined using a validated LC-MS/MS method. The primary pharmacokinetic parameters were AUCinf, AUC0-t, Cmax and Tmax.

In the fasted state, the Cmax and Tmax for ASA and SA after administration of the new coated tablet were of the same magnitude as after administration of previously available effervescent tablets (Table 1). The total exposure (AUC) of ASA and SA after administration of the coated tablet was of the same magnitude as for the plain tablet (Table 2). As administration of the new coated tablet leads to similar AUC and Cmax values as for previously available acetylsalicylic acid products (plain or effervescent tablets), clinical efficacy or safety data for the coated tablet are not required for approval.

In a third study, the effect of food on the release characteristics of the coated tablet was investigated. The data indicate that concomitant food intake led to a somewhat slower release from the coated tablet, showing as a lower Cmax for ASA and SA than after administration in the fasted state and a longer Tmax, in particular for SA (Table 3).

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for ASA and SA after administration of the new Aspirin coated tablet (treatment A) and three previously available effervescent tablets (treatments B, C and D)

Analyte	PK parameter (unit)	Treatment A (N=29)	Treatment B (N=28)	Treatment C (N=31)	Treatment D (N=31)
ASA	C_{max} (µg/mL)	13.12 (3.092)	9.416 (2.4472)	11.68 (3.268)	11.50 (3.012)
	AUC_{0-t} (µg*hr/mL)	6.599 (1.4261)	4.845 (1.2928)	5.415 (1.3610)	5.831 (1.2687)
	AUC_{0-inf} (µg*hr/mL)	6.669 (1.4168)	4.897 (1.2994)	5.473 (1.3669)	5.904 (1.2832)
	t_{max} (h)	0.330	0.330	0.290	0.330
SA	C_{max} (µg/mL)	31.94 (6.515)	26.98 (5.272)	29.22 (4.951)	27.80 (5.468)
	AUC_{0-t} (µg*hr/mL)	175.2 (51.87)	129.0 (39.90)	143.1 (35.13)	142.9 (43.45)
	AUC_{0-inf} (µg*hr/mL)	183.9 (53.99)	133.5 (40.73)	148.9 (36.94)	147.8 (44.22)
	t_{max} (h)	0.830	0.750	0.750	0.830

A: Aspirin coated tablet 500 mg
B: Alka Seltzer ES effervescent tablet 500 mg
C: Aspirin Migraine effervescent tablet 500 mg
D: Aspirin Aspro effervescent tablet 500 mg.

Table 2: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for ASA and SA after administration of the new Aspirin coated tablet and the previously available Aspirin plain tablet, n=26

Treatment	AUC_{0-t} µg*h/ml	AUC_{0-inf} µg*h/ml	C_{max} µg/ml	t_{max} h
ASA				
Test (Aspirin coated tablet 500 mg)	6.6 ± 1.11	6.7 ± 1.12	13.3 ± 3.36	0.29 (0.21 - 0.58)
Reference (Aspirin plain tablet 500 mg)	6.4 ± 1.53	6.5 ± 1.55	4.4 ± 1.54	0.75 (0.38 - 4.0)
SA				
Test (Fast-release tablet Prototype 2)	193.5 ± 48.62	202.6 ± 51.27	34.1 ± 6.22	0.75 (0.5 - 1.5)
Reference (plain tablet)	177.1 ± 46.08	189.4 ± 50.59	27.0 ± 4.86	3.0 (1.5 - 5.0)
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration				

**calculated based on ln-transformed data*

Table 3: Pharmacokinetic parameters for ASA and SA after administration of the new Aspirin coated tablet in the fasted and the fed state (n=29)

Treatment	Aspirin coated tablet fasted	Aspirin coated tablet fed
ASA		
Cmax (µg/ml)	13.99	5.92
AUCinf (µg*hr/ml)	7.08	6.60
Tmax (min)	20.4	23.1
SA		
Cmax (µg/ml)	30.46	21.84
AUCinf (µg*hr/ml)	187.3	166.6
Tmax (min)	40.2	120.0

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 beneficial 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/minor arthritis pain, and fever associated with infections and common cold.
Compared to the corresponding plain tablets, the coated tablets are expected to provide faster onset of pain relief.
Two multicentre, double-blind, randomized, parallel, placebo controlled trials assessing the analgesic efficacy of a single oral dose of coated Aspirin 650 mg or 1000 mg in postsurgical dental pain, using the dental impaction pain model and including over 1000 patients, were submitted. These demonstrated that first perceptible pain relief was achieved within ca 15-20 minutes. Meaningful pain relief onset was after ca 50 minutes and lasted four to six hours.

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/minor arthritis 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, FR/H/0482/001/DC. 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 beneficial 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/minor arthritis pain, and fever associated with infections and common cold.

Pharmacokinetic studies demonstrated rapid release characteristics of the new fast-release tablets, with Cmax and Tmax for ASA and SA of the same magnitude as for effervescent tablets after intake in the fasted state. Compared with the previously approved plain tablet, Cmax for ASA was on average about 3-fold higher and Tmax for ASA about 2.5 times shorter (18 minutes vs. 45 minutes) for the fast-release tablet.

Compared to the corresponding plain tablet, the coated tablet applied for in the present procedure is expected to provide faster onset of pain relief.

Two multicentre, double-blind, randomized, parallel, Placebo controlled trials assessing the analgesic efficacy of a single oral dose of coated Aspirin 650 mg or 1000 mg in postsurgical dental pain, using the dental impaction pain model and including over 1000 patients, were submitted. These showed that first perceptible pain relief was achieved within ca15-20 minutes. Meaningful pain relief onset was after ca 50 minutes and lasted four to six hours.

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 benefit risk of this product is positive and 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

Aspirin, 500 mg, coated tablet was approved in the national procedure on 2016-05-12.

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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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