

Public Assessment Report

Scientific discussion

Acetylsalicylic acid Krka **(acetylsalicylic acid)**

SE/H/1604/01-03/DC

This module reflects the scientific discussion for the approval of Acetylsalicylic acid Krka. The procedure was finalised on 2016-12-19. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Krka d.d., Novo mesto has applied for a marketing authorisation for Acetylsalicylic acid Krka, 75 mg, 100 mg and 160 mg, gastro-resistant tablet. The active substance is acetylsalicylic acid.

For approved indications, see the Summary of Product Characteristics.

The marketing authorisation has been granted pursuant to Article 10a 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

III.1 Introduction

The pharmacology, pharmacokinetics and toxicology of acetylsalicylic acid are well known. The Applicant provided literature based data on these aspects of acetylsalicylic acid, since this application is based on well-established use of the substance.

III.2 Ecotoxicity/environmental risk assessment

Since the products will be used as substitutions to other acetylsalicylic acid products, this will not lead to an increased exposure of ASA to the environment. Therefore, no additional environmental risks are expected for Acetylsalicylic acid Krka.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Two bioequivalence studies (fed and fasted) was submitted to allow bridging of the efficacy/safety data for the applied for products. Bioequivalence has been demonstrated between test and reference product for salicylic acid (SA) in the fasted and fed state. Strict bioequivalence was not demonstrated for acetylsalicylic acid (ASA) in the fasting state, study 091B13 showed a 16% (CI 92-148) increase for both AUC and C_{max} with test compared to reference. The fact that strict bioequivalence for ASA was not demonstrated during fasting conditions is not considered a critical finding as the products are applied as a bibliographic application where the bibliographic clinical data on ASA in the applied indication consists of studies performed with several different formulations and doses. Thus, the presented studies demonstrate that the applied for formulations are sufficiently similar to the formulations used in the bibliographic data referred to.

The pharmacokinetics of SA and ASA have been sufficiently characterised by the submitted literature data.

IV.2 Pharmacodynamics, clinical efficacy, clinical safety

Acetylsalicylic acid (ASA, aspirin) is a non-steroidal anti-inflammatory drug (NSAID) and has a well-characterised antiplatelet effect. There are a large number of randomised trials documenting its efficacy and safety. The primary and secondary pharmacology of acetylsalicylic acid is well-known and it has been adequately summarised by the Applicant.

The use of ASA for secondary prevention in ischemic cardiovascular disease is since long time well accepted. The proposed indications follow the well-established use of the product.

IV.3 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 Acetylsalicylic acid Krka.

Safety specification

Important identified risk	Increased risk of bleeding tendency/haemorrhage
	Gastrointestinal bleeding/ulceration
	Acute renal failure/deterioration of renal function
	Hypersensitivity reactions including bronchospasm and asthma attacks
	Increased serum levels of uric acid
	Stevens-Johnson syndrome
	Lyell's syndrome
Important potential risk	Reye's syndrome
	Interaction with ibuprofen
Missing information	N/A

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 Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine Risk minimisation activities	Additional risk minimisation activities
Important identified risks		
Increased risk of bleeding tendency/haemorrhage	Labelled in SmPC sections	none

	4.3 Contraindications 4.4 Special Warnings and Precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable Effects	
Gastrointestinal bleeding/ulceration	Labelled in SmPC sections 4.3 Contraindications 4.4 Special Warnings and Precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable Effects	none
Acute renal failure/deterioration of renal function	Labelled in SmPC sections 4.3 Contraindications 4.4 Special Warnings and Precautions for use 4.5 Interaction with other medicinal products and other forms of interaction 4.8 Undesirable Effects	none
Hypersensitivity reactions including bronchospasm and asthma attacks	Labelled in SmPC sections 4.3 Contraindications 4.4 Special Warnings and Precautions for use 4.8 Undesirable Effects	none
Increased serum levels of uric acid	Labelled in SmPC sections 4.4 Special Warnings and Precautions for use 4.8 Undesirable Effects	none
Stevens-Johnson syndrome	Labelled in SmPC sections 4.4 Special Warnings and Precautions for use 4.8 Undesirable Effects	none
Lyell's syndrome	Labelled in SmPC sections 4.4 Special Warnings and Precautions for use 4.8 Undesirable Effects	none
Important potential risks		
Reye's syndrome	Labelled in SmPC sections 4.2 Posology and method	none

	of administration 4.4 Special Warnings and Precautions for use	
Interaction with ibuprofen	Labelled in SmPC sections 4.5 Interaction with other medicinal products and other forms of interaction 5.1 Pharmacodynamic properties	none

Summary of the RMP

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 the product Acetylsalicylsyra Kappler, 75 mg, 100 mg, 160 mg, 300 mg, gastro-resistant tablets. The user test of the Acetylsalicylsyra Kappler leaflet was assessed and accepted in the procedure SE/H/1511-01-03/MR. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Acetylsalicylic acid Krka, 75 mg, 100 mg and 160 mg, gastro-resistant tablet is 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

The Decentralised procedure for Acetylsalicylic acid Krka, 75 mg, 100 mg and 160 mg, gastro-resistant tablet was positively finalised on 2016-12-19.

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)