COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Kruidvat Acetylsalicylzuur 500 mg, tablets

(acetylsalicylic acid)

NL/H/4033/001/DC

Date: 1 April 2019

This module reflects the scientific discussion for the approval of Kruidvat Acetylsalicylzuur 500 mg, tablets. The procedure was finalised on 22 May 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Kruidvat Acetylsalicylzuur 500 mg, tablets, from Marel B.V.

The product is indicated for the symptomatic treatment of mild to moderate pain and/or fever.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Aspirine 500 mg, tablets (NL License RVG 00613) which has been registered in The Netherlands by Bayer B.V. since 2 October 1968.

The concerned member states (CMS) involved in this procedure were Belgium and Luxembourg.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Kruidvat Acetylsalicylzuur is a white or almost white, round, flat, uncoated tablet. Each tablet contains 500 mg of acetylsalicylic acid.

The tablets are packed in PVC/Alu foil blisters.

The excipients are maize starch and cellulose powder.

II.2 Drug Substance

The active substance is acetylsalicylic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Acetylsalicylic acid is a white or almost white, crystalline powder or colourless crystals. The active substance is slightly soluble in water and freely soluble in ethanol (96%).

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the

corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification adopted by the finished product manufacturer/MAH includes testing as per Ph. Eur. monograph for acetylsalicylic acid together with the additional testing specified in the CEP. The content of acetic acid is limited by the test for loss on drying described in the monograph. This is acceptable. Additionally the finished product manufacturer/MAH controls the particle size of the drug substance. Absence of a specific test for microbiological purity has been sufficiently justified. Batch analysis data for three batches of active substance tested by the finished product manufacturer/MAH have been provided. All results are within specification limits.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained. The test product formulation contains the same excipients as the reference product qualitatively.

The development of the dissolution method for routine testing of the finished product has been adequately described and is based on the United States Pharmacopeia/British Pharmacopoeia method for acetylsalicylic acid tablets. The choice of apparatus, dissolution medium composition and volume and rotation speed have been discussed and justified. The MAH applies for a BCS-based biowaiver.

Comparative dissolution data of 12 units of test and 12 units of reference product in three media have been obtained to justify the waiver. In 0.1M HCl, for the test product less than 85% is dissolved in in 15 min whereas for the reference product more than 85% of active substance is dissolved within 15 minutes. Similarity (f_2) calculation has been performed and resulted in acceptable similarity (f_2 52). At pH 4.5 and pH 6.8 buffers, more than 85% of test and reference product was dissolved in 15 minutes.

Overall, the pharmaceutical development is acceptable.

Manufacturing process

The manufacturing process consists of weighing and sieving, blending, compression and packaging and has been validated according to relevant European guidelines. Critical steps

and intermediates are adequately controlled. Holding times do not apply for any intermediates during the manufacturing process of the finished product. The manufacturing process is considered as being a standard process and has been adequately validated.

Control of excipients

All excipients comply with the specifications of the respective Ph. Eur. monographs current edition. In addition, powdered cellulose complies with the in-house requirements for particle size distribution and bulk density. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, dissolution, uniformity of dosage units, assay, related substances and microbiological test. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data six production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for six production scaled batches stored at 25°C/60% RH (36 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The batches were stored in Al/PVC foil blisters. All results are within currently proposed specification limits and no specific trends have been observed. A photostability study in accordance with applicable guidelines has been performed on one batch of finished product. It showed that the product is not sensitive to light. On basis of the data provided, a shelf life was granted of 36 months. The product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Kruidvat Acetylsalicylzuur has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Kruidvat Acetylsalicylzuur is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Aspirine which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Acetylsalicylic acid is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The MAH has applied for a BSC-based biowaiver. A BCS-based biowaiver is restricted to highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The concept is applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.
The MAH has sufficiently shown that all criteria for a BCS-based biowaiver were met:

- Acetylsalicylic acid is considered to be a BCS-class I drug, i.e. a drug compound with a high permeability (at least 85% absorbed intact) and high solubility.
- Acetylsalicylic acid is not a narrow therapeutic drug.
- The test acetylsalicylic acid 500 mg tablet and the reference Aspirin 500 mg tablet by Bayer contain comparable excipients and no excipients which could be considered critical with regard to absorption.
- Both test and reference formulations dissolves very rapidly or rapidly at pH 1.2, 4.5 and 6.8.

On basis of these the findings above, the justification for BCS (Biopharmaceutics Classification System) - based biowaiver can be accepted.

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 Kruidvat Acetylsalicylzuur.

- Summary table of safety concerns as approved in RMP

Important identified risks	- gastrointestinal disorders (ulcer, perforation - and bleeding) - bleeding - hypersensitivity reactions - deterioration of renal function - bone marrow toxicity due to interaction with - methotrexate - use in third trimester of pregnancy - severe skin reactions (Stevens-Johnson - syndrome, epidermal necrolysis)
Important potential risks	- Reye's syndrome
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Aspirine. No new clinical studies were conducted. A BSC-based biowaiver has been granted. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Celecoxib Apotex. The overall layout, design and writing style of the leaflet being bridged is similar and has been user tested. This includes similar headings, paragraph and sentence structure. In addition the content of the proposed Acetylsalicylic acid Apotex is similar in wording to the already approved version for the innovator product as well as generic acetylsalicylic acid containing products. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Kruidvat Acetylsalicylzuur 500 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Aspirine 500 mg, tablets. Aspirine is a well-known medicinal product with an established favourable efficacy and safety profile.

For this generic application, the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The argumentation included information on the high solubility of acetylsalicylic acid drug substance, almost complete absorption and the rapid dissolution of acetylsalicylic acid tablets. The BCS-based biowaiver is fully justified and accepted.

In a Board meeting of 9 May 2018 the granting of a BCS-based biowaiver was discussed. Initially, it was insufficiently shown that acetylsalicylic acid could be classified as a BCS class I compound. After additional submission of data, it was concluded that the classification is justified and the objected has been solved.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Kruidvat Acetylsalicylzuur with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 May 2018.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/4033/001/IA/001	Replacement or addition of a manufacturer responsible for importation and/or batch release; not including batch control/testing	-	19-11-2018	Approved	-