LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Tiplo
(acetylsalicylic acid/caffeine)

Asp no: 2017-1349

This module reflects the scientific discussion for the approval of Tiplo. The procedure was finalised on 2018-10-09. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Tiplo, 500 mg/50 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, BBS Consult ApS applies for a marketing authorisation in Sweden through a National Procedure.

European Reference Product (ERP)
A European Reference Product is used: Aspirina Plus, 500 mg/50 mg, tablet authorised in Spain since 1949, with Bayer Hispania S.L. as marketing authorisation holder. The justification to use this product is based on information received from ES.

For approved indications, see the Summary of Product Characteristics.

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 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Pharmacokinetic properties of the active substances
Acetylsalicylic acid is rapidly and almost completely absorbed. Acetylsalicylic acid is hydrolysed to salicylic acid (SA), which is also active, in the blood, liver and gut. The half-life for acetylsalicylic acid is 20-30 minutes and salicylic acid has a half-life of approximately 3 hours in low doses (<0.5 g). In high doses, the elimination half-life is increased to 15-30 hours due to saturation of metabolism.

Caffeine is metabolised in the liver followed by renal excretion, with a half-life of 3-4 hours.

BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, *in vitro* dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

Background/Applicant's justification
Acetylsalicylic acid (ASA):
The applicant refers to studies retrieved from the published domain reporting an absolute bioavailability from the gastrointestinal tract of ASA varying within the range of 42-72%. Mass balance and urinary recovery studies, however, clearly indicate the complete absorption of the parent drug from the gastrointestinal system.
Therefore, the low systemic bioavailability of ASA is mainly due to the high first-pass metabolism.

Caffeine:
The applicant refers to studies retrieved from the published domain that consistently report an absolute bioavailability from the gastrointestinal tract of caffeine exceeding 85%.

Discussion and overall conclusion
Acetylsalicylic acid and caffeine are not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with acetylsalicylic acid and caffeine.

Urinary excretion and mass-balance data show that a large fraction (94-98%) of the ASA dose was eliminated in urine, mainly as metabolites, indicating complete absorption of ASA.

Already during the absorption through the intestinal wall, but also in the liver and blood, ASA is hydrolysed to salicylic acid (SA). Although ASA is also hydrolysed to SA without enzymatic assistance, this process appears to be rather slow. Therefore, there is little or no conversion to its active metabolite SA in the intestinal lumen and ASA is mainly absorbed unaltered rather than as SA.

The applicant has submitted references that consistently support high oral bioavailability of caffeine.

It can be concluded that the drug substances have been proven to exhibit high solubility and complete absorption (BCS class I).

It can be concluded that the extent of absorption is above 85% and thus, acetylsalicylic acid and caffeine can be classified as a BCS class I substances from a pharmacokinetic perspective. The qualitative and quantitative composition of the test and the reference product is similar. None of the excipients are known to affect bioavailability. This is considered acceptable for a BCS class I-based biowaiver.

Similar *in vitro* dissolution characteristics of the test and the reference product has been demonstrated.

In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (dated 10.11.2017, version 1), 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 Tiplo.

Safety specification
The proposed safety concerns have been updated according to assessor’s comments, to include the following:

Summary of safety concerns

Important Identified risks	Severe gastrointestinal complications (including ulceration and perforation)
	Major haemorrhages including gastrointestinal haemorrhage and intracranial haemorrhage
	Severe hypersensitivity including anaphylactic reactions
	Maternal, neonatal and foetal toxicity with exposure during the 3rd trimester of pregnancy
	Disturbance in renal function homeostasis in patients with renal, hepatic, or cardiac insufficiency
	Clinically significant drug interactions
	Haemolysis in patients with G-6-PD deficiency
	Severe skin reactions, including Steven-Johnsons syndrome / Toxic Epidermal Necrolysis
Important Potential risks	Reye's syndrome
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 pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The MAH has satisfactory responded to the question raised and updated the RMP accordingly. The submitted Risk Management Plan, version 1.0 signed 2018-04-26 is considered acceptable.

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 MPA;
- 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 for content to Tiplo 500/50 mg effervescent tablets PL approved 18-09-2017 (national procedure Sweden Dnr 5.4.1-2016-43185) and making reference for layout to Kaliumklorid Orifarm 750 mg prolonged-release tablets (DK/H/2347/001/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Tiplo, is found adequate. There are no objections to approval of Tiplo, from a non-clinical and clinical point of view. The product information is acceptable.

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

Tiplo, 500 mg/50 mg, tablet was approved in the national procedure on 2018-10-09.

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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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