LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Paracetamol Accord (paracetamol)

SE/H/1763/01/DC 2017-1209

This module reflects the scientific discussion for the approval of Paracetamol Accord. The procedure was finalised on 2018-12-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Paracetamol Accord, 500 mg, effervescent tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Accord Healthcare Ltd. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BE, BG, CZ, ES, FR, RO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Panadol, 500 mg, effervescent tablet, authorised in Belgium since 1992, with GlaxoSmithKline Consumer Healthcare s.a/n.v. as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS CZ, RO and ES referring to the reference product in the RMS: Panodil Brus, 500 mg, effervescent tablet, authorised in Sweden since 1974, with Omega Pharma Nordic AB as current marketing authorisation holder. *The MA was transferred from GlaxoSmithKline Consumer Healthcare A/S to Omega Pharma Nordic AB on 2016-01-14.*

The justification to use this product is based on RMS's own files and the ERP information was circulated to CMS during the validation period.

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

No bioequivalence study has been submitted. The applicant claims that since this medicinal product is an effervescent preparation, submission of a bioequivalence study is not applicable. According to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1), bioequivalence studies may be waived if the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution. However if the excipients may affect gastrointestinal transit (e.g. sorbitol, mannitol, etc.), absorption (e.g. surfactants or excipients that may affect transport proteins), in vivo solubility (e.g. co-solvents) or in vivo stability of the active substance, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. The same requirements for similarity in excipients apply for oral solutions as for Biowaivers (see Appendix III, Section IV.2 Excipients). PKWP has published a clarification how to apply this reference to Appendix III when waiving in vivo studies for oral solutions (6.3 Biowaivers: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000179.jsp&mid=WC0b01ac0580aff2ec#). It is stated that differences in excipients could be handled more flexible with BCS class I drug substances. In addition the Q&A regarding effect of sorbitol on the PK (6.1 Biowaivers: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000179.jsp&mid=WC0b01ac0580aff2ec) should be considered.

Paracetamol is classified as a BCS class I substance and hence the differences in excipients could be handled more flexible. The quantitative and qualitative differences in all excipients except sorbitol are considered acceptable without further justification. However there is a difference in the amount of sorbitol and this difference needs to be adequately justified by reference to other data. The applied product contains 100 mg sorbitol and the reference product 50 mg according to the SmPC of Panodil Brus. The corresponding amounts at maximal single dose (2 tablets) are 200 mg and 100 mg sorbitol, respectively.

According to Q&A regarding effect of sorbitol on the PK (6.1 Biowaivers) and the article by Chen et al an estimated single dose threshold for the sorbitol effect on drug bioavailability is probably around 1 g. In addition reference can be made to a previously approved paracetamol oral solution (Pinex, IS/H/0175/DC) and the published PAR of the product (https://mri.cts-mrp.eu/Human/Downloads/IS_H_0175_001_PAR.pdf). Pinex oral solution has a sorbitol concentration of 140 mg/ml corresponding to 2.8 g at maximal dose. The approval was based on a bioequivalence study comparing with a reference product including no sorbitol. Bioequivalence was demonstrated indicating that a difference of 2.8 g between test and reference have no influence on the bioavailability of paracetamol.

Based on the results above and the small amount of sorbitol in the applied product, it is considered unlikely that the amount of sorbitol (and the difference in amount of sorbitol) will have an effect on the bioavailability of paracetamol. Waiving bioequivalence studies is therefore considered acceptable.

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, 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 Paracetamol Accord.

Safety specification
The MAH has submitted the version 1.2 RMP dated 11 October 2018 and proposed the following summary safety concerns:

List of important risks and missing information	
Important identified risks	• Hepatotoxicity in overdose • Severe skin reactions
Important potential risks	None
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 RMP

The applicant has updated the RMP in line with the request by RMS. All relevant sections of the RMP, including the Annexes, has been updated accordingly. The submitted Risk Management Plan, version 1.2, dated 11 October 2018 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 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. For content the reference is Paracetamol Galpharma 500 mg Tablets (SE/H/1429/01/DC) and for layout the reference is Mycophenolic acid 180 mg, 360 mg gastro-resistant Tablets (ES/H/0183/001-002/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, Paracetamol Accord, is found adequate. There are no objections to approval of Paracetamol Accord, 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

The Decentralised procedure for Paracetamol Accord, 500 mg, effervescent tablet was positively finalised on 2018-12-05.

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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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