LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Paracetamol ABECE, 24 mg/ml, oral solution (paracetamol)

Asp no: 2017-0683

This module reflects the scientific discussion for the approval of Paracetamol ABECE. The procedure was finalised on 2018-03-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Paracetamol ABECE, 24 mg/ml, oral solution, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Evolan Pharma AB applies for a marketing authorisation in Sweden through a National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Alvedon, 24 mg/ml, oral solution, authorised in Sweden since 1959, with GlaxoSmithKline Consumer Healthcare AB as marketing authorisation holder.

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

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Paracetamol, 24 mg/ml oral solution with the reference product Alvedon, 24 mg/ml oral solution.

Study C11-0029

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Paracetamol, 24 mg/ml oral solution with Alvedon, 24 mg/ml oral solution under fasting conditions. After an overnight fast a single oral dose of 20 mL of 24 mg/mL (480 mg) of either test or reference was administered together with 240 ml of water. Fasting continued until 4 hours after drug administration. Blood samples for concentration analysis were collected pre-dose and up to 14 hours post-dose. Plasma concentrations of paracetamol were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 26th and 31st January 2011.

Results

The results from the pharmacokinetic and statistical analysis are presented in **Table 1** below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for paracetamol, n=23.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**22915 ± 7083**	**8536 ± 2175**	**0.50 0.33-2.00**
Reference	**22464 ± 6371**	**8878 ± 2892**	**0.33 0.167-1.25**
***Ratio (90% CI)**	**101.08 (97.73-104.55)**	**97.26 (87.06-108.65)**	**-**
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*

For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Paracetamol ABECE, 24 mg/ml oral solution is considered bioequivalent with Alvedon, 24 mg/ml oral solution.

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 22 Sep 2016, 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 Apofri 500 mg filmdragerade tabletter; Paracetamol Apofri 500 mg brustabletter and Paracetamol Apofri 24 mg/ml oral lösning.

Safety specification
The summary table of proposed safety concerns for Paracetamol Apofri (RMP Part II: Module SVIII).

Table 1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Hepatotoxicity in overdose - Severe skin reactions
Important potential risks	- None
Important missing information	- None

Pharmacovigilance Plan

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, dated 22 Sep 2016 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 to Paracetamol Apofri, Dnr 111:2011/45089. 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 ABECE, is found adequate. There are no objections to approval of Paracetamol ABECE, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. 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

Paracetamol ABECE, 24 mg/ml, oral solution was approved in the national procedure on 2018-06-18.

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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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