LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Paracetamol Novum Apofri
(paracetamol)

Asp no: 2018-0193

This module reflects the scientific discussion for the approval of Paracetamol Novum Apofri. The procedure was finalised on 2019-03-01. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Paracetamol Novum Apofri, 500 mg, film-coated tablet, 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 Panodil Zapp, 500 mg, film-coated tablet authorised in SE since 2001-03-23, with Omega Pharma Nordic 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/EC 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 substance

Absorption: Following oral administration, paracetamol is readily absorbed and the maximal plasma concentrations occur at approximately 30 minutes after ingestion irrespective of food intake.

Elimination: The terminal plasma half-life is approximately 2 hours.

BCS-based biowaiver

No bioequivalence study has been submitted in this application since the applicant applies for a BCS-based biowaiver.

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.

Discussion and overall conclusion

It is generally accepted that paracetamol has complete absorption and can be classified as a BCS-class I substance from pharmacokinetic perspective. Data on absolute bioavailability of paracetamol varies between 60 and 90% in published literature (Rawlins et al. 1977, Eandi et al. 1984, Clements et al. 1984, Tukker et al. 1986 and Prescott et al. 1993). It is likely that the incomplete bioavailability is caused by first-pass metabolism, which may be saturated at higher doses. This is supported by the study by Rawlins et al, where the absolute bioavailability was estimated to 0.63, 0.89 and 0.87 after a dose of 500 mg, 1000 mg and 2000 mg respectively.

Since no metabolism is considered to occur in the gastric or intestinal fluid, urinary excretion data could be used to assess fraction absorbed for paracetamol. The fraction absorbed based on urinary excretion data was >85% when urine was collected up to 24 hours after dosing in healthy volunteers (Tukker et al. 1986, Prescott et al. 1993). In another study, the fraction absorbed was estimated to be slightly lower, 70-76%. However in this study urine was only collected up to 12 hours after dose administration and the elimination process may not have

been complete (Goicoechea et al. 1998). Almost complete excretion after oral dosing was confirmed by Lau 1997. After an 20 mg/kg oral dose to 14 healthy subjects, urinary recovery was 94.2 ± 15.4%, of which paracetamol 5.6 ± 1.6%, glucuronide metabolite 54.8 ± 8.9% and sulphate metabolite 33.7 ± 8.0%. Further support is obtained by Perruca and Richens. 1979, showing a urinary recovery of free plus conjugated paracetamol after oral administration (657 mg) was similar to that after intravenous administration (601 mg), which supports the theory that the absorption is complete and that the lower oral bioavailability is caused by first-pass metabolism.

Taken together the data point toward that paracetamol has a fraction absorbed ≥ 85% of the dose, which is the cut-off value used in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). Thus, paracetamol is considered to be a BCS-class I substance.

In addition, the EMA has published a product-specific bioequivalence guidance for paracetamol immediate release formulations for oral use which enters into effect 01/08/2018. According to the product-specific bioequivalence guidance, paracetamol is considered a high solubility compound with >85% absorption and can be classified as a BCS-class I substance from a pharmacokinetic perspective.

Paracetamol is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with paracetamol.

There are both qualitative and quantitative differences in composition between the applied product and the reference product. However, for a BCS-class I substance these differences regarding excipients between the test and reference product are considered acceptable since it is not considered likely that these differences would affect the bioavailability. The amount of sodium hydrogen carbonate is considered most critical for comparison of the bioavailability with the reference product since it can affect gastric emptying. It is noted that the amount of sodium hydrogen carbonate is very similar in both products.

In conclusion, the justification for a BCS (Biopharmaceutics Classification System) based biowaiver can be accepted from a pharmacokinetic and clinical point of view and no bioequivalence study is considered necessary.

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 Novum 500 mg film-coated tablets.

Safety specification

The identified and potential risks of Paracetamol Novum 500 mg film-coated tablets are listed in Table SVIII.1.

Table SVIII.1: Summary of safety concerns	
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 submitted Risk Management Plan, 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 Galpharm 500 mg film-coated tablets (SE/H/1429/01-02/DC) and Natriumklorid Evolan 500 mg capsules (Dnr 5.4.1-2014-5246). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products, Paracetamol Novum Apofri, is found adequate. There are no objections to approval of Paracetamol Novum Apofri, 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/EC 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 Novum Apofri, 500 mg, film-coated tablet was approved in the national procedure on 2019-03-15.

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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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