LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Fenoximetylpenicillin
Generic Specialty Pharma
(phenoxymethylpenicillin potassium)

Asp no: 2018-0005, 2018-0006

This module reflects the scientific discussion for the approval of Fenoximetylpenicillin Generic Specialty Pharma. The procedure was finalised on 2019-01-31. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Fenoximetylpenicillin Generic Specialty Pharma 800 and 1000 mg film-coated tablets, are generic applications made according to Article 10(1) of Directive 2001/83/EC. The applicant, Generic Specialty Pharma 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 Kåvepenin, film-coated tablets 800 mg authorised in Sweden since 1973, and Kåvepenin film-coated tablet 1000 mg authorised in Sweden since 1979, both with Meda AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Kåvepenin, 1000 mg, film-coated tablet from Sweden with Meda 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

To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Phenoxymethylpenicillin potassium, 1000 mg, film-coated tablets with the reference product Kåvepenin, 1 g, film-coated tablets.

Pharmacokinetic properties of the active substance
Absorption: Phenoxymethylpenicillin has an oral bioavailability of approximately 50 %. Following an oral dose of phenoxymethylpenicillin maximal plasma concentrations occur at approximately 0.5-1 hour.

Concomitant food intake decreases the C_{max} and degree of absorption and therefore phenoxymethylpenicillin should be administered on an empty stomach (one hour before or two hours after a meal).

Linearity: According to a study by Josefsson and Bergan (1982) AUC increased almost linearly with increasing dose in the dose interval 0.4 to 3 g. There was only a 10% difference in dose-adjusted AUC between the doses 0.4 and 1g in the study. According to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1), pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUC is no more than 25 % when comparing the studied strength and the strength for which a waiver is sought. Thus, linear kinetics can be concluded in the dose interval relevant for biowaiver.

Elimination: The terminal half-life is approximately 30 minutes.

Study 14-053
Methods
This was a single-dose, two-way crossover study conducted in 42 (40 completed) healthy volunteers, comparing Phenoxymethylpenicillin potassium, 1000 mg, film-coated tablets, with Kåvepenin, 1 g, film-coated tablets under fasting conditions. Blood samples for concentration analysis was collected pre-dose and up to 9 hours post-dose. Serum concentrations of phenoxymethylpenicillin 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 12th and 21st August 2015.

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 phenoxymethylpenicillin, n=40.

Treatment	AUC_{0-t} µg*h/ml	C_{max} µg/ml	t_{max} h
Test	**21.213±4.435**	**14.665±5.041**	**0.830 (0.33-1.75)**
Reference	**21.279±5.238**	**14.485±4.115**	**0.670 (0.33-1.25)**
***Ratio (90% CI)**	**100.61 (94.64-106.96)**	**98.86 (89.71-108.94)**	**-**

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%.

A biowaiver was sought for the additional strength of 800 mg.

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.

Absence of studies with the additional strength of 800 mg is acceptable, as all conditions for biowaiver for additional strengths, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of phenoxymethylpenicillin is linear between 0.4 and 1g.

Based on the submitted bioequivalence study, Phenoxymethylpenicillin potassium film-coated tablets are considered bioequivalent with Kåvepenin.

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 Fenoximetylpenicillin Generic Specialty Pharma.

The active pharmaceutical ingredient has a safety profile that can be considered as well established and is therefore not expected to find new unknown experience when marketed. Therefore, no additional risk management activities are considered necessary.

Safety specification
The MAH has submitted the version 0.1 RMP dated 2018-01-04 and proposed the following summary safety concerns:"
Important identified risks
- Allergic reactions (e.g. anaphylactic shock, angioedema);
- Cross-allergy between penicillins and cephalosporins;
- Colitis and pseudomembranous colitis;
- Interaction with methotrexate

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, version 0.1 signed 2018-01-04 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 (PL) has been performed on the basis of a bridging report making reference to Avopenin 800 mg and 1 g filmdragerade tabletter, SE/H/1207/01-02/DC for the key safety messages and Kaliumklorid Orifarm 750 mg depottabletter, DK/H/2347/001 for the layout issues. 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, Fenoximetylpenicillin Generic Specialty Pharma, is found adequate. There are no objections to approval of Fenoximetylpenicillin Generic Specialty Pharma, 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/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

Fenoximetylpenicillin Generic Specialty Pharma 800 and 1000 mg film-coated tablets was approved in the national procedure on 2019-01-31.

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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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