LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fenoximetylpenicillin EQL
(phenoxymethylpenicillin potassium)

SE/H/2263/01-02/DC

This module reflects the scientific discussion for the approval of Fenoximetylpenicillin EQL. The procedure was finalised on 2025-04-23. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Fenoximetylpenicillin EQL, 800 mg, 1000 mg, Film-coated tablet.

The active substance is phenoxymethylpenicillin potassium. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Fenoximetylpenicillin EQL, 800 mg, 1000 mg, Film-coated tablet, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and IS as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Kåvepenin, 800 mg, film-coated tablet authorised in Sweden since 1973, 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.

European Reference Product (ERP)
A European Reference Product is used in CMS DK and IS: Kåvepenin, 800 mg, film-coated tablet authorised in Sweden since 1973, with Meda AB as marketing authorisation holder.

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

Potential similarity with orphan medicinal products
N/A

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

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of phenoxymethylpenicillin are well known. As phenoxymethylpenicillin is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Fenoximetylpenicillin EQL is a generic product, it is not expected to lead to an increased exposure to the environment as long as the indications do not differ from the reference product. Provided that SmPC section 4.1 with indications is harmonised with the reference product, an environmental risk assessment is therefore not deemed necessary.

Provided that SmPC section 4.1 is harmonised with the reference product there are no objections to approval of Fenoximetylpenicillin EQL from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Fenoximetylpenicillin EQL with the reference product Kåvepenin.

Pharmacokinetic properties of the active substance
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).

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.

The terminal half-life is approximately 30 minutes.

Study ARL/10/479
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing

Phenoxymethylpenicillin, 1000 mg, film-coated tablets with Kåvepenin, 1 g, film-coated tablets under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 10 hours post-dose. Plasma 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 24th 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 phenoxymethylpenicillin, n=27.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**20502.65±7668.63**	**14928.82±3930.40**	**0.67 (0.50-1.50)**
Reference	**19604.68±6929.32**	**14646.79±4600.43**	**0.67 (0.50-1.33)**
***Ratio (90% CI)**	**105.13 (96.17-114.92)**	**104.05 (93.65-115.62)**	**-**
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).

This study was performed before the Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009, came into force in February 2012 but the bioanalytical method is considered adequately validated. ISR was performed with acceptable results.

Absence of studies with the additional strength of 800 mg is acceptable, as all conditions for biowaiver for additional strength(s), 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.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Discussion and overall conclusion
The Applicant's review of the clinical literature is acceptable. The key pharmacodynamic, clinical efficacy and clinical safety aspects for Phenoxymethylpenicillin are well-known, being essentially the same as those for the refence product, Kåvepenin, which has been authorised and used for several decades in the RMS.

The proposed indications are acceptable. The applicant has harmonised SmPC section 4.1 with the text in the SmPC of the reference medicinal product, "cutaneus Borrelia infections" and deleted

“acrodermatitis”. As a consequence of the update, updates have also been made in SmPC section 4.2.

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 EQL.

Safety specification

Summary of safety concerns	
Important identified risks	None
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, version 0.1 signed 14-Feb-2022 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

Content
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 Pilum Pharma A/S and Primve 50 mg/ml 2care4 ApS. The user test of the Avopenin leaflet was assessed and accepted in SE/H/1207/01-02/DC. The user test of the Primve leaflet was assessed and accepted in DK/H/2578/001.

Layout
The applicant has proposed a bridging to a user test carried out on the product Acetazolamid EQL Pharma 250 mg tablets.

A comparison between the parent PL and the daughter PL (including lay-out) together with a critical discussion hereof has been provided.

The proposed bridging regarding content and layout is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Fenoximetylpenicillin EQL, is found adequate. There are no objections to approval of Fenoximetylpenicillin EQL, 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 benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Fenoximetylpenicillin EQL, 800 mg, 1000 mg, Film-coated tablet was positively finalised on 2025-04-23.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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