Public Assessment Report

Decentralised Procedure

Phenoxymethylpenicillin 250mg Film-coated Tablets
(Phenoxymethylpenicillin potassium)

UK/H/1852/001/DC

UK Licence No: PL 20117/0121

Morningside Healthcare Limited
Phenoxymethylpenicillin 250mg Film-coated Tablets

(Lay Summary)

This is a summary of the Public Assessment Report (PAR) for Phenoxymethylpenicillin 250mg Film-coated Tablets (PL 20117/0121, UK/H/1852/001/DC). It explains how the application for Phenoxymethylpenicillin 250mg Film-coated Tablets was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Phenoxymethylpenicillin 250mg Film-coated Tablets.

For practical information about using Phenoxymethylpenicillin 250mg Film-coated Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Phenoxymethylpenicillin Tablets’ in this report.

What are Phenoxymethylpenicillin Tablets and what are they used for?

Phenoxymethylpenicillin Tablets are a ‘generic medicine’. This means that Phenoxymethylpenicillin Tablets are similar to a ‘reference medicine’ already authorised in the UK called Penicillin VK Tablets 250 mg (also named as Phenoxymethylpenicillin 250 mg Film-Coated Tablets; PL 04520/0005), which was granted to Sandoz GmbH, Austria on 05 November 1986.

Phenoxymethylpenicillin Tablets can be used to treat a range of infections of the ear, throat, lungs, skin and soft tissues. The tablets may also be used:

- to prevent infections such as rheumatic fever
- for the prevention of infection in patients without a spleen or patients with sickle cell disease.

How do Phenoxymethylpenicillin Tablets work?

Phenoxymethylpenicillin Tablets contain an active substance called phenoxymethylpenicillin, which is an antibiotic (antibacterial medicine) for treating infections. It belongs to a group of antibiotics called ‘Penicillins’. Phenoxymethylpenicillin works by killing the bacteria that cause infections. It can also be used to prevent infections.

How are Phenoxymethylpenicillin Tablets used?

Phenoxymethylpenicillin Tablets are taken by mouth. The tablets are swallowed whole with water, at least 30 minutes before food.

The medicine should always be taken as advised by the doctor. If unsure, the patient or caregiver should check with the doctor or pharmacist.

For children with difficulty in swallowing or 6r infants and children under the age of 6, an oral solution containing phenoxymethylpenicillin is recommended.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Phenoxymethylpenicillin Tablets can only be obtained with a prescription.
Phenoxymethylpenicillin Tablets have been shown in studies?
As Phenoxymethylpenicillin Tablets are a generic medicine, studies in patients have been limited to tests to determine that Phenoxymethylpenicillin Tablets are bioequivalent to the reference medicine, Penicillin VK Tablets 250 mg (Sandoz GmbH, Austria). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (Morningside Healthcare Limited) has provided data from the published literature on phenoxymethylpenicillin.

What are the possible side effects of Phenoxymethylpenicillin Tablets?
Because Phenoxymethylpenicillin Tablets are a generic medicine and are bioequivalent to the reference medicine Penicillin VK Tablets 250 mg (Sandoz GmbH, Austria), the benefits and possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Phenoxymethylpenicillin Tablets, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet.

Why are Phenoxymethylpenicillin Tablets approved?
In accordance with the EU requirements, Phenoxymethylpenicillin Tablets have been shown to have comparable quality and clinical characteristics to the originator Penicillin VK Tablets 250 mg (Sandoz GmbH, Austria). Based on this evaluation, the MHRA concluded that the benefits of Phenoxymethylpenicillin Tablets outweigh the identified risks and recommended Phenoxymethylpenicillin Tablets for approval.

What measures are being taken to ensure the safe and effective use of Phenoxymethylpenicillin Tablets?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Phenoxymethylpenicillin Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Phenoxymethylpenicillin Tablets
Ireland and the UK agreed to grant a Marketing Authorisation for Phenoxymethylpenicillin Tablets on 09 January 2011. A Marketing Authorisation was granted in the UK to Morningside Healthcare Limited on 01 February 2011.

The full PAR for Phenoxymethylpenicillin Tablets follows this summary.

For more information about treatment with Phenoxymethylpenicillin Tablets
This summary was last updated in February 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the application for Phenoxymethylpenicillin 250mg Film-coated Tablets (PL 20117/0121, UK/H/1852/001/DC) could be approved. The product is a prescription-only medicine (POM) indicated in the treatment or prophylaxis of mild to moderately severe infections caused by penicillin sensitive organisms, i.e. those microorganisms whose susceptibility to phenoxymethylpenicillin is within the range of serum levels attained. Phenoxymethylpenicillin is indicated for the treatment of the following infections:

- Streptococcal infections:
  - pharyngitis
  - scarlet fever
  - skin and soft tissue infections (e.g. erysipelas)

- Pneumococcal infections:
  - pneumonia
  - otitis media
  - Vincent's gingivitis and pharyngitis

- Phenoxymethylpenicillin is also indicated for the prophylaxis of:
  - rheumatic fever and/or chorea
  - pneumococcal infection (e.g. in asplenia and in patients with sickle cell disease).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Penicillin VK Tablets 250mg (Sandoz GmbH, Austria; PL 04520/0005) for which a licence was granted in the UK on 05 November 1986.

Phenoxymethylpenicillin exerts a bactericidal action against penicillin-susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptide rendering the cell wall osmotically unstable. It is not active against the penicillinase-producing bacteria, which include many strains of staphylococci.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for this application as the pharmacology of phenoxymethylpenicillin potassium is well-established. The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP).

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
II QUALITY ASPECTS

II.1 Introduction

The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The tablets are white, circular, biconvex and film coated, with a break line on one side and ‘1 04’ on the other. Each tablet contains 250 mg phenoxymethylpenicillin (as phenoxymethylpenicillin potassium). The product also contains calcium hydrogen phosphate dihydrate, maize starch, microcrystalline cellulose (E460), magnesium stearate (E572), basic butylated methacrylate, macrogol 6000, sodium laurilsulfate (E487), stearic acid (E570), titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is supplied in aluminium/polyvinylchloride blisters, in pack sizes of 14, 28, 42, 56, 70 and 140 film-coated tablets.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.

II.2 DRUG SUBSTANCE

Phenoxymethylpenicillin potassium

Nomenclature:
INN: Phenoxymethylpenicillin potassium
Chemical name: (2S, 5R, 6R)-3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)-amino]4-thia-1-azobicyclo[3.2.0]heptane-2-carboxylic acid, potassium salt

Structure:

\[
\text{Molecular formula: } C_{16}H_{17}KN_{2}O_{5}S \\
\text{ Molecular weight: } 388.5 \text{ g/mol} \\
\text{ Physical form: } \text{White, or almost white, crystalline powder, slightly hygroscopic.} \\
\text{ Solubility: } \text{Freely soluble in water, practically insoluble in ethanol (96 percent).}
\]

The active substance, phenoxymethylpenicillin potassium, is the subject of a European Pharmacopeia (EP) monograph.

All aspects of the manufacture and control of the active substance, phenoxymethylpenicillin potassium, except for stability data, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Appropriate stability data have been generated for the active substance stored in the proposed commercial packaging. These data demonstrate the stability of the active substance and appropriate retest periods have been set.
II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to produce a safe, efficacious product containing phenoxymethylpenicillin potassium that could be considered a generic medicinal product of Penicillin VK Tablets 250mg (Sandoz GmbH, Austria) for which a licence was granted in the UK on 05 November 1986 to Sandoz GmbH.

The applicant has provided suitable product development information. Justifications for the use and amounts of each excipient have been provided and are valid.

Comparative in vitro dissolution profiles have been provided for the proposed and reference product.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. The suppliers of the excipients have provided declarations that neither the excipients nor any material used in the production of the excipients pose a TSE risk.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided. The results are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability of the Product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 2 years with storage instructions ‘Do not store above 25°C’ which is satisfactory.

Bioequivalence/Bioavailability
Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study. The bioequivalence study is discussed in Section III.3, Clinical Aspects.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for the application for Phenoxymethylpenicillin 250mg Film-coated Tablets, from a quality point of view.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL are available on the MHRA website. The current labelling is presented below:
Phenoxymethylpenicillin 250mg Film-coated Tablets

Each tablet contains Phenoxymethylpenicillin 250mg (as Phenoxymethylpenicillin potassium).

Dosage: To be taken as directed by the doctor.

Oral use.

Read the package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

Do not store above 25°C.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Strength</th>
<th>Formulation</th>
<th>Code</th>
</tr>
</thead>
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<tr>
<td><strong>Phenoxymethylpenicillin</strong></td>
<td>250 mg</td>
<td>Film-coated Tablets</td>
<td>KR/UG/05/KTC/28/037/2003</td>
</tr>
<tr>
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<td>KR/UG/05/KTC/28/037/2003</td>
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</tr>
</tbody>
</table>
III NON-CLINICAL ASPECTS

III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of phenoxymethylpenicillin are well known. As phenoxymethylpenicillin potassium is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required.

III.2 The non-clinical overview provides a satisfactory review of the pharmacological and toxicological properties of phenoxymethylpenicillin.

III.3 Pharmacodynamics
Not applicable, see Section III.1 Introduction, above.

III.4 Pharmacokinetics
Not applicable, see Section III.1 Introduction, above.

III.5 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.6 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for generic substitution with a product that is already marketed, no increase in environmental exposure to phenoxymethylpenicillin is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.7 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Phenoxymethylpenicillin 250mg Film-coated Tablets, from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction
The clinical pharmacology of Phenoxymethylpenicillin is well-known. With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

IV.2 Pharmacokinetics
The application is supported by a bioequivalence study presented by the applicant comparing the pharmacokinetic profile of Phenoxymethylpenicillin 250mg Film-coated Tablets (test product) and Penicillin VK Tablets 250mg (Sandoz GmbH; reference product).

A single-dose, open-label, randomised, balanced, two-treatment, two-period, crossover study to compare the pharmacokinetics of the test product Phenoxymethylpenicillin 250mg Film-coated Tablets versus the reference product Penicillin VK Tablets 250mg (Sandoz GmbH, Austria) in healthy subjects under fasting conditions.

Blood samples were taken pre- and up to 12 hours post dose. There was a washout period of seven days between each treatment period. Pharmacokinetic parameters were measured from the plasma and statistically analysed. Results for phenoxymethylpenicillin are presented below as log-transformed values:
<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_{0-t}) (ng.h/mL)</th>
<th>AUC(_{0-\infty}) (ng.h/mL)</th>
<th>C(_{\text{max}}) (ng/ml)</th>
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<tbody>
<tr>
<td>Phenoxymethylpenicillin:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test (T)</td>
<td>4655.4880</td>
<td>5093.7283</td>
<td>3398.0480</td>
</tr>
<tr>
<td>Reference (R)</td>
<td>5294.3936</td>
<td>5610.9461</td>
<td>3710.1984</td>
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<tr>
<td>T/R Ratio (90% CI)</td>
<td>87.93</td>
<td>90.78</td>
<td>91.59</td>
</tr>
</tbody>
</table>

AUC\(_{0-t}\)  area under the plasma concentration-time curve from time zero to \(t\) hours  
AUC\(_{0-\infty}\) area under the plasma concentration-time curve from time zero to infinity  
C\(_{\text{max}}\) maximum plasma concentration

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC\(_{0-t}\) and C\(_{\text{max}}\) for phenoxymethylpenicillin lie within acceptable limits. Thus, bioequivalence has been shown between the test and reference products in this study.

IV.3 Pharmacodynamics

The clinical pharmacodynamic properties of phenoxymethylpenicillin are well-known. No novel pharmacodynamic data are supplied or required for this application.

IV.4 Clinical Efficacy

No new efficacy data were submitted with this application and none were required.

IV.5 Clinical Safety

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

IV.6 Risk Management Plan

Suitable justification has been provided for non-submission of a Risk Management Plan. No additional risk minimisation activities were required beyond those included in the product information.

IV.7 Discussion of the clinical aspects

All issues have been adequately addressed by the applicant. The bioequivalence study demonstrates the bioequivalence of the test product (Phenoxymethylpenicillin 250mg Film-coated Tablets) and reference (Penicillin VK Tablets 250mg; Sandoz GmbH; Austria) product.

Sufficient clinical information has been submitted to support this application. A Marketing Authorisation was, therefore, granted on medical grounds.

V. USER CONSULTATION

The package leaflet has been evaluated in a user consultation study in accordance with current requirements. The language used for the purpose of user testing the package leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Phenoxymethylpenicillin 250mg Film-coated Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

EFFICACY
Bioequivalence has been demonstrated between the applicant’s Phenoxymethylpenicillin 250mg Film-coated Tablets and the reference product Penicillin VK Tablets 250mg (Sandoz GmbH, Austria).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC, and PIL and labelling are satisfactory and consistent with those for the reference product.

The Marketing Authorisation Holder (MAH) has committed to submitting mock-ups for all packaging and PILs for assessment before those packs are commercially marketed.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with phenoxymethylpenicillin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type Ib/II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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</thead>
<tbody>
<tr>
<td>To submit a new fasting bioequivalence study to confirm that the product under investigation (Phenoxymethylpenicillin 250mg Film-coated Tablets) is bioequivalent to the reference product Penicillin VK Tablets 250mg (Sandoz GmbH, Austria).</td>
<td>UK/H/1852/001/II/002</td>
<td>None</td>
<td>10/11/2015</td>
<td>08/01/2016</td>
<td>Approval</td>
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</tr>
</tbody>
</table>
Annex 1.1

**Our Reference:** PL 20117/0121, Application 6
**Product** Phenoxymethylpenicillin 250mg Film-coated Tablets
**Marketing Authorisation Holder:** Morningside Healthcare Limited
**Active Ingredient(s):** Phenoxymethylpenicillin potassium

**Type of Procedure:** Mutual Recognition
**Submission Type:** Variation
**Submission Category:** Type II
**Submission Complexity:** Standard
**EU Procedure Number (if applicable):** UK/H/1852/001/II/002

**Reason:**
To submit a new fasting bioequivalence study to confirm that the product under investigation (Phenoxymethylpenicillin 250mg Film-coated Tablets) is bioequivalent to the reference product Penicillin VK Tablets 250mg (Sandoz GmbH, Austria).

**Supporting Evidence**
The Applicant has submitted the results of an open-label, randomised, single-dose, two-period, two-treatment, cross-over bioequivalence study in healthy adult human subjects under fasting conditions.

**Evaluation**
The subjects were administered a single dose of either the test or the reference product with 240 ml of water, after at least a 10-hour overnight fast. Blood sampling was performed pre-dose and up to seven hours post-dose in each treatment period. The washout period between the two treatment arms was seven days. The pharmacokinetic results are presented below:

The Guidance on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1, Corr**) defines the 90% confidence limits as 80.00% to 125.00% for \(C_{\text{max}}\) and AUC values. The 90% confidence intervals of the test/reference ratio for \(C_{\text{max}}\) and AUC values lie within the acceptable limits for phenoxymethylpenicillin. Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Penicillin VK Tablets 250mg (Sandoz GmbH, Austria), under fasting conditions.
Safety
No new or unexpected safety issues arose during the bioequivalence study.

Conclusion
Bioequivalence has been demonstrated between the applicant’s Phenoxymethylpenicillin 250mg Film-coated Tablets and the reference product (Penicillin VK Tablets 250mg, Sandoz GmbH) under fasting conditions. The new bioequivalence study is acceptable. No other changes are proposed.

The benefit-risk balance remains positive.

Decision – Approved 08 January 2016.