Medicines & Healthcare products Regulatory Agency

Public Assessment Report

National Procedure

Phenoxymethylpenicillin 500 mg film-coated tablets
phenoxymethylpenicillin (as phenoxymethylpenicillin potassium)

PL 25298/0376

Brown & Burk UK Ltd

LAY SUMMARY

Phenoxymethylpenicillin 500 mg film-coated tablets
phenoxymethylpenicillin (as phenoxymethylpenicillin potassium)

This is a summary of the Public Assessment Report (PAR) for Phenoxymethylpenicillin 500 mg film-coated tablets. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Phenoxymethylpenicillin film-coated tablets in this lay summary for ease of reading.

For practical information about using Phenoxymethylpenicillin film-coated tablets, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What are Phenoxymethylpenicillin film-coated tablets and what are they used for?
This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised, called Penicillin VK 250 mg Tablets, PL 08215/0178, albeit with certain differences. In this case, Phenoxymethylpenicillin 500 mg film-coated tablets is for change in strength.

Phenoxymethylpenicillin film-coated tablets are used for treating an infection which is caused by bacteria which are sensitive to penicillin antibiotics.

How do Phenoxymethylpenicillin film-coated tablets work?
Phenoxymethylpenicillin film-coated tablets belong to a family of medicines called antibiotics, in a group called 'penicillins'. Antibiotics are used to kill the bacteria or "germs" which cause infections.

How are Phenoxymethylpenicillin film-coated tablets used?
The pharmaceutical form of this medicine is film coated tablet and the route of administration is oral (by mouth).

Each dose should be swallowed with a drink of water, at least 30 minutes before food. Try to space the doses as evenly as possible throughout the day.
The recommended dose is:

Adults:
250 mg or 500 mg (i.e. one or two tablets) every 6 hours. This may vary depending on the type of infection the patient has.
If the patient has poor kidney function the dose may be lowered.

Children and adolescents:
For children aged 6 - 12 years of age the recommended dose is 250 mg (i.e. one tablet) every 6 hours.
For children aged 1 - 5 years of age the recommended dose is 125 mg (i.e. half a tablet) every 6 hours.

For further information on how Phenoxymethylpenicillin film-coated tablets is used, refer to the PIL and Summary of Product Characteristics (SmPC)available on the Medicines and

Healthcare Products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should always take this medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Phenoxymethylpenicillin film-coated tablets have been shown in studies?
Because Phenoxymethylpenicillin film-coated tablets is a hybrid medicine, studies in healthy volunteers consist of tests to determine that it is therapeutically equivalent to the reference medicine.

What are the possible side effects of Phenoxymethylpenicillin film-coated tablets?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Because Phenoxymethylpenicillin film-coated tablets is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

Why was Phenoxymethylpenicillin film-coated tablets approved?
It was concluded that Phenoxymethylpenicillin film-coated tablets has been shown to be bioequivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Phenoxymethylpenicillin film-coated tablets?
As for all newly authorised medicines, a Risk Management Plan (RMP) has been developed for Phenoxymethylpenicillin film-coated tablets. The RMP details the important risks of Phenoxymethylpenicillin film-coated tablets, how these risks can be minimised, any uncertainties about Phenoxymethylpenicillin film-coated tablets (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Phenoxymethylpenicillin film-coated tablets.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Phenoxymethylpenicillin film-coated tablets are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Phenoxymethylpenicillin film-coated tablets
A Marketing Authorisation for Phenoxymethylpenicillin film-coated tablets was granted in the United Kingdom (UK) on 21 March 2024.

The full PAR for Phenoxymethylpenicillin film-coated tablets follows this summary.

This summary was last updated in April 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Phenoxymethylpenicillin 500 mg film-coated tablets(PL 25298/0376) could be approved.

The product is approved for the following indication:

For use in the treatment of mild to moderately severe infections caused by penicillin sensitive organisms.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

The name of the active substance is phenoxymethylpenicillin that belongs to the Pharmacotherapeutic group of Beta lactamase sensitive penicillins.

Mechanism of action

Phenoxymethylpenicillin is a broad-spectrum beta-lactam antibiotic with bactericidal action against Gram-positive bacteria and Gram-negative cocci. Its antimicrobial action is similar to that of benzyl penicillin. Phenoxymethylpenicillin is usually active against the following organisms:

Gram-positive aerobes and anaerobes including

Bacillus anthracis
Clostridium perfringens
Clostridium tetani
Corynebacterium diphtheriae
Erysipelothrix rhusiopathiae
Listeria monocytogenes
Peptostreptococcus spp.
*Streptococcus agalactiae (*Group *B)*
Streptococcus pneumoniae
*Streptococcus pyogenes (*Group *A)*

Gram-negative including
Neisseria meningitidis
Neisseria gonorrhoeae

Phenoxymethylpenicillin is inactivated by penicillinase and other beta-lactamases.

Phenoxymethylpenicillin binds to penicillin-binding proteins located on the inner membrane of the bacterial cell wall. Phenoxymethylpenicillin binds to and inactivates these proteins resulting in weakening of the bacterial cell wall and lysis.

This application was approved under Regulation 52B, of The Human Medicines Regulation 2012, as amended (previously Article 10(3) of Directive 2001/83/EC, as amended), claiming to be a hybrid medicinal product of a suitable originator product, Penicillin VK 250 mg Tablets, that has been licensed for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is acceptable given that the application is for a hybrid medicinal product of a suitable reference product.

Data from one bioequivalence study was submitted with this application. This study was conducted in-line with current Good Clinical Practice (GCP).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the United Kingdom (UK) on 21 March 2024.

II QUALITY ASPECTS

II.1 Introduction

This product consists of a film-coated tablet; each tablet contains 500 mg of phenoxymethylpenicillin (as phenoxymethylpenicillin potassium).

In addition to phenoxymethylpenicillin (as phenoxymethylpenicillin potassium), this product also contains the excipients calcium hydrogen phosphate dihydrate, maize starch, microcrystalline cellulose, magnesium stearate, macrogol polyvinyl alcohol graft copolymer, talc, titanium dioxide, GMCC Type 1, and polyvinyl alcohol-part. hydrolyzed.

The finished product is packaged in a white opaque PVC-Al blister pack of pack sizes containing 10,14, 20, 28, 30, 50, 56,60, 84, 98 and 100's tablets.
Not all pack sizes may be marketed.

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

II.2 ACTIVE SUBSTANCE

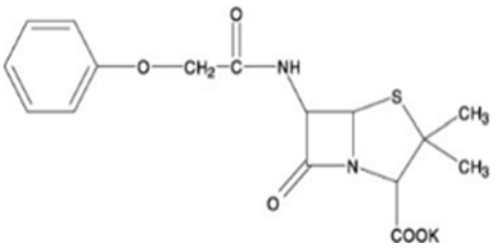
rINN: phenoxymethylpenicillin (as phenoxymethylpenicillin potassium)

Chemical Name:

Potassium salt of (2S,5R,6R)-3,3-dimethyl-7-oxo-6-[(phenoxyacetyl)amino]- 4-thia-1- azabicyclo[3.2.0]heptane-2-carboxylic acid

Molecular Formula: $C_{16}H_{17}KN_2O_5S$

Chemical Structure:



Molecular Weight: 388.5
Appearance: White or almost white, crystalline powder.
Solubility: Freely soluble in water, practically insoluble in ethanol (96 per cent).

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

Suitable specifications have been provided for all packaging used. The primary packaging complies with the current regulations concerning materials in contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMOs).

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have 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.

Finished Product Specifications
The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years, with the storage conditions to not store above 25°C, is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of phenoxymethylpenicillin (as phenoxymethylpenicillin potassium) is well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided, and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided, and none were required for this application.

III.4 Toxicology
No new toxicology data were provided, and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

In accordance with the regulatory requirements, data from one bioequivalence study has been submitted with this application. This study was conducted in-line with current Good Clinical Practice (GCP).

IV. 2 Pharmacokinetics

In support of the application, the applicant submitted the following BIOEQUIVALENCE STUDY No. 097-21. This study was an open-label, balanced, randomized, two-treatment, two-sequence, two-period, two-way cross-over, single dose, comparing the test product Phenoxymethylpenicillin 500 mg film-coated tablets versus the reference product Penicillin VK 250 mg Tablets (250×2=500mg) in healthy, adult, human subjects, under fasting conditions.
Subjects were administered orally a single dose of test or reference product. Blood samples were taken pre-dose and up to 9 hours post-dose, with a washout period of 7 days between the treatment periods.

A summary of the pharmacokinetic results is presented below:

PK Parameter (Units)	Phenoxymethylpenicillin	
	Test	Reference
C_{max} (µg/mL)	8.618±2.918	9.469±2.668
AUC_{0-t} (µg·hr/mL)	11.943±3.648	12.329±3.496
$AUC_{0-\infty}$ (µg·hr/mL)	12.167±3.628	12.539±3.474
#T_{max} (hr)	0.670 (0.330-1.250)	0.670(0.500-1.250)
K_{el} (hr)	0.881±0.216	0.920±0.204
$t_{1/2}$ (hr)	0.833±0.205	0.840±0.504
AUC_%Extrap_obs	2.090±1.390	1.856±1.343
AUC_{0-t}/ $AUC_{0-\infty}$	97.910±1.390	98.144±1.343

#T_{max} is represented in median (min-max) value.

Parameter	GLSMR	GLSMT	(T/R) Ratio (%)	90% CI Lower	90% CI Upper	Power (%)	ISCV (%)	BE
C_{max}	9.082	8.165	89.91%	82.72%	97.73%	99.63%	22.07%	YES
AUC_{0-t}	11.874	11.411	96.09%	90.28%	102.28%	99.99%	16.43%	YES

In accordance with the regulatory requirements, the Test/Reference ratios and their 90% confidence intervals were within the specified limits to show bioequivalence between the test product and the reference product.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety
With the exception of the safety data from the clinical study submitted with this application, no new safety data were submitted. The safety data submitted showed that the product was well-tolerated. No new or unexpected safety issues were raised from these data.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION
A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with phenoxymethylpenicillin (as phenoxymethylpenicillin potassium) is considered to have demonstrated the therapeutic value of the product.

The benefit/risk is, therefore, considered to be positive.

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

In accordance with legal requirements, the current approved versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N