**PHENOXYMETHYLPENICILLIN 125 MG/5 ML AND 250MG/5ML ORAL SOLUTION**

PL 17907/0034-5

**UKPAR**

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PHENOXYMETHYL-PENICILLIN 125 MG/5 ML AND 250 MG/5 ML ORAL SOLUTION

PL 17907/0034-5

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency granted Bristol Laboratories Limited Marketing Authorisations (licences) for the medicinal products Phenoxymethylpenicillin 125 mg/5 mL Oral Solution (PL 17907/0034) and Phenoxymethylpenicillin 250 mg/5 mL Oral Solution (PL 17907/0035) on 22 June 2011. These are prescription-only medicines (POM) and are used to treat mild to moderately severe infections associated with microorganisms whose susceptibility to penicillin is within range of serum levels attained with the dosage form.

Phenoxymethylpenicillin Oral Solution contains the active ingredient, phenoxymethylpenicillin potassium and belongs to a group of medicines called beta-lactamase resistant penicillins (antibiotics).

Phenoxymethylpenicillin 125 mg/5 mL and 250 mg/5 mL Oral Solution are used to treat infections caused by bacteria that are sensitive to penicillins. These infections include:

- Infections of the lungs (such as pneumonia and bronchitis)
- Ear and throat infections (such as otitis media and pharyngitis)
- Other infections (such as infections of the skin and soft tissue, scarlet fever and erysipelas).

Phenoxymethylpenicillin is also used for:

- Prevention of recurrent attacks of rheumatic fever and chorea

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Phenoxymethylpenicillin 125 mg/5 mL and 250 mg/5 mL Oral Solution outweigh the risks; hence Marketing Authorisations have been granted.
# Scientific Discussion

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INTRODUCTION

The UK granted Marketing Authorisations for the medicinal products Phenyoxymethylpenicillin 125 mg/5 mL Oral Solution and Phenyoxymethylpenicillin 250 mg/5 mL Oral Solution (PL 17907/0034-35) to Bristol Laboratories Limited on 22 June 2011. These products are prescription-only medicines.

These applications were submitted as abridged applications according to Article 10(1) of Directive 2001/83/EC. The applications cross-refer to Phenyoxymethylpenicillin Oral Solution BP 125 mg/5 mL (PL 06453/0024) and Phenyoxymethylpenicillin Oral Solution BP 250 mg/5 mL (PL 06453/0025), licensed to Athlone Laboratories Limited, on 9 June 1997. The reference products have been authorised in the EEA for over 10 years.

Phenoxymethylpenicillin is used in the treatment of infections caused by susceptible staphylococci, pneumococci, gonococci, and haemolytic streptococci. Unless very large doses are given, phenoxymethylpenicillin administered by mouth is less effective than parenterally administered benzylpenicillin in the treatment of severe acute infections.

The pharmacovigilance system, as described by the MAH, fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

The MAH has provided adequate justification for not submitting a Risk Management Plan (RMP). As the application is for a generic version of an already authorised reference product, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference product has been in use for many years and the safety profile of the active is well established.

No new non-clinical or clinical studies were performed, which is acceptable given that the proposed products are generic medicinal products of the reference products that have been licensed for over 10 years.

No new or unexpected safety concerns arose during the review of information provided by the Marketing Authorisation Holder (MAH) and it was, therefore, judged that the benefits of taking Phenyoxymethylpenicillin 125 mg/5 mL Oral Solution and Phenyoxymethylpenicillin 250 mg/5 mL Oral Solution outweigh the risks; hence Marketing Authorisations have been granted.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Phenoxymethylpenicillin potassium
INN: Phenoxymethylpenicillin potassium

Chemical name: Potassium (6R)-6-(2-phenoxyacetamindo) penicillanate

Structure:

Molecular mass: 388.5
Molecular formula: C\textsubscript{16}H\textsubscript{17}KN\textsubscript{2}O\textsubscript{5}S

General Properties

Description: A white homogeneous, crystalline powder, odourless or with a slight characteristic odour.

Solubility: Freely soluble in water, practically insoluble in ethanol (96%).

Phenoxymethylpenicillin potassium is the subject of a European Pharmacopoeia monograph (Ph Eur).

Manufacture

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

DRUG PRODUCT

Description and Composition

Phenoxymethylpenicillin 125 mg/5 mL and 250 mg/5 mL Oral Solution are both presented as light pink coloured powders for reconstitution. Each 5 mL of reconstituted solution contains either 125 mg or 250 mg, respectively, of phenoxymethylpenicillin as the active ingredient.

Other ingredients consist of pharmaceutical excipients, sucrose, strawberry flavour 17.41.0549, colour red dye (Anstead) 1578 (E124) (Spectracol Ponceau 4R), saccharin sodium, industrial methylated spirit. Appropriate justification for the inclusion of each excipient has been provided. All excipients used comply with their relevant European Pharmacopoeia (Ph. Eur) monographs with the exception of the strawberry flavouring and
the colorant, red dye (Anstead) 1578 (E124) (Spectracol Ponceau 4R), which are controlled to satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process of the proposed product. Furthermore, none of the excipients are sourced from genetically modified organisms.

**Pharmaceutical Development**

Suitable pharmaceutical development data have been provided for these applications.

The objective of the development programme was to formulate robust, stable acceptable formulations of phenoxyemethylpenicillin oral solutions which are comparable in performance to the reference products, V-Cil-K 125mg/5ml and 250 mg/5ml, PL 00006/5128R and PL 00006/5129R, licensed to Eli Lilly & company Ltd in 1985 and 1990, respectively. The physico-chemical properties of the drug product have been compared with the originator products. These data demonstrate that the proposed products can be considered as generic medicinal products to the reference products.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided.

In-process controls were considered appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are accepted. Satisfactory analytical results from 2 pilot scale batches for both strengths of the product.

**Finished Product Specification**

The finished product specifications are satisfactory; they provide an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data are provided for 3 batches of both strengths of the product and demonstrate that the batches are compliant with the proposed release specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

Both strengths of the finished product are licensed for marketing in natural high density polyethylene bottles with polypropylene or high density polyethylene (HDPE) polypropylene tamper evident/child resistant cap containing 100 mL of oral solution on reconstitution.

Each 100 mL bottle is packaged with a combined label-leaflet.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), Ph Eur requirements and is suitable for contact with oral solution products. The caps comply with child resistant packaging legislation.
**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set for unopened containers, which is satisfactory. Storage conditions are ‘Do not store above 25°C’ and ‘Store in a dry place’. Once opened and reconstituted the oral solution has a shelf-life of 7 days; the storage conditions for the reconstituted product are ‘Store for 7 days in a refrigerator’.

**Bioequivalence Study**
The products are aqueous oral solutions at the time of administration and contain the same concentration of the active substance as the reference products, V-Cil-K 125mg/5ml and 250 mg/5ml; bioequivalence studies from a quality perspective can be waived.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels**
The SmPCs and combined labels and leaflets are pharmaceutically acceptable. Colour mock-ups of the labelling and PIL have been provided. The labelling is satisfactory and fulfils the statutory requirements for Braille.

A user consultation with target patient groups on the combined label/patient information leaflet (PIL) has been performed on the basis of a bridging report making reference to three products; Phenoxymethylpenicillin 250 mg Tablets (PL 17907/0033), Amoxicillin Capsules 250 mg and 500 mg (PL 17907/0044-5) and Amoxicillin 125 mg/5 mL and 250 mg/5 mL oral suspension BP (PL 17907/0008-9). The bridging report submitted by the applicant has been found acceptable.

**Quality Overall Summary**
A satisfactory quality overview is provided and has been prepared by an appropriately qualified expert. The *curriculum vitae* of the expert has been provided.

**Conclusion**
It is recommended that Marketing Authorisations are granted for these applications.
NON-CLINICAL ASSESSMENT

This application was submitted as an abridged, standard application, according to Article 10.1 of Directive 2001/83/EC, as amended.

The pharmacodynamic, pharmacokinetic and toxicological properties of phenoxymethylpenicillin potassium are well-known. Therefore, no further studies are required and the applicant has provided none.

The non-clinical overview was written by a suitably qualified person and is satisfactory. The curriculum vitae of the expert has been provided.

A suitable justification has been provided for the non-submission of an environmental risk assessment.
CLINICAL ASSESSMENT

Pharmacokinetics
No new data have been submitted and none are required for applications of this type.

Phenoxymethylpenicillin 125 mg/5 mL and Phenoxymethylpenicillin 250 mg/5 mL Oral Solutions are generic versions Phenoxymethylpenicillin Oral Solution BP 125 mg/5 mL (PL 06453/0024) and Phenoxymethylpenicillin Oral Solution BP 250 mg/5 mL (PL 06453/0025), licensed to Athlone Laboratories Limited, on 9 June 1997. The use of the reference products is well-established in the UK. Both the proposed products and the reference products contain the same quantitative and qualitative composition of the active ingredient, phenoxymethylpenicillin.

In accordance with the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev.1/Corr**) the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous oral solution containing the same active substance, in the same concentration as the currently authorised product; the applicant has submitted none which is satisfactory.

Pharmacodynamics
No new data have been submitted and none are required for applications of this type.

Clinical efficacy
No new data have been submitted and none are required for applications of this type.

Clinical safety
No new safety data have been submitted or required for these generic applications. As phenoxymethylpenicillin is a well-known product with an acceptable adverse event profile, this is satisfactory.

Expert Report
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC and PIL are medically acceptable, and consistent with those for the reference product. The labelling is medically acceptable and in-line with current requirements.

MAA form
The MAA form is medically satisfactory.

Conclusion
There are no objections to approval of Phenoxymethylpenicillin 125 mg/5 mL Oral Solution and Phenoxymethylpenicillin 250 mg/5 mL Oral Solution from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Phenoxympenicillin 125 mg/5 mL Oral Solution and Phenoxympenicillin 250 mg/5 mL Oral Solution 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 preclinical data were submitted and none are required for applications of this type.

EFFICACY
The applicant’s Phenoxympenicillin 125 mg/5 mL and 250mg/5 mL Oral Solutions have been demonstrated to be generic versions of the reference products, Phenoxympenicillin Oral Solution BP 125 mg/5 mL and 250mg/ 5 mL (PL 06453/0024-5), licensed to Athlone Laboratories Limited, on 9 June 1997.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The SmPCs and combined PIL and labels are acceptable, and consistent with those for the reference products. The labelling is acceptable and in-line with current requirements.

A user consultation with target patient groups on the combined label/patient information leaflet (PIL) has been performed on the basis of a bridging report. The bridging report is in accordance with the requirements of Article 59(3) and 61(1) of Directive 2001/83/EC.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant’s Phenoxympenicillin 125 mg/5 mL and 250mg/5 mL Oral Solution and the reference products Phenoxympenicillin Oral Solution BP 125 mg/5 mL and 250mg/ 5 mL (Athlone Laboratories Limited) are interchangeable. Extensive clinical experience with phenoxympenicillin potassium is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk is, therefore, considered to be positive.
### STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the marketing authorisation application on 19 September 2008</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 2 October 2008.</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the quality dossiers on 27 February 2009, 23 September 2010 and 23 February 2011.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on the quality dossier on 14 July 2009, 14 January 2011 and 14 March 2011</td>
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<td>5</td>
<td>The application was determined on 22 June 2011.</td>
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PHENOXYMETHYL PENICILLIN 125 MG/5 ML AND 250 MG/5 ML ORAL SOLUTION

PL 17907/0034-5

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Application type</th>
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The UK Summary of Product Characteristics (SmPC) for Phenoxy methylpenicillin 125 mg/5 mL Oral Solution (PL 17907/0034) is as follows:

1 NAME OF THE MEDICINAL PRODUCT
Phenoxy methylpenicillin 125 mg/5 mL Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5 mL of reconstituted solution contains 125 mg of Phenoxy methylpenicillin as Phenoxy methylpenicillin Potassium as the active ingredient.
For excipients, see 6.1

3 PHARMACEUTICAL FORM
Powder for oral solution.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Phenoxy methylpenicillin and phenoxy methylpenicillin potassium are indicated in the treatment of mild to moderately severe infections associated with micro-organisms whose susceptibility to penicillin is within the range of serum levels attained with the dosage form.
Note: Severe empyema, bacteraemia, pericarditis, meningitis and arthritis should not be treated with Penicillin V during the acute phase.

The following infections will usually respond to adequate doses:

Streptococcal infections (without bacteraemia): Mild to moderate infections of the upper respiratory tract, scarlet fever and mild erysipelas.
Pneumococcal infections: mild to moderately severe infections of the respiratory tract.
Staphylococcal infections sensitive to penicillin: mild infections of the skin and soft tissues.
Fusospirochaetosis (Vincent's gingivitis and pharyngitis): mild to moderately severe infections of the oropharynx usually respond to therapy with oral penicillin.

Prophylactic use: prophylaxis with oral penicillin has proved effective in preventing recurrence of rheumatic fever and chorea.

Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered.
Note: oral penicillin should not be used as adjunctive prophylaxis for genito - urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and child birth.

4.2 Posology and method of administration
Dosage

Adults: 125 or 250 mg every four to six hours depending on the severity of the condition. The elderly: as for adults. Reduce dosage if renal function is markedly impaired.

Children over 5 years: The adult dose.

Children 5 years or less: 125 mg every six hours.
Infants (up to 1 year): 62.5 mg every six hours.
In all but the most serious cases the last dose of the day may be doubled to avoid disturbing sleep. Ideally, each dose should be given half an hour before (or at least three hours after) a meal.

Prophylactic use: 250 mg twice daily is recommended for long term prophylaxis of rheumatic fever.

For oral administration only.

4.3 Contraindications
Phenoxymethylpenicillin is contraindicated in patients known to be hypersensitive to Penicillin and should be used with caution in patients with known histories of allergy.

4.4 Special warnings and precautions for use
Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Oral penicillin should not be used as adjunctive prophylaxis for genito-urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and childbirth. Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered. Severe empyema, bacteraemia, pericarditis, meningitis and arthritis should not be treated with Penicillin V during the acute phase.

All degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin. These reactions are more likely to occur in individuals with a history of sensitivity to penicillins, cephalosporins and other allergens. Enquiries should be made for such a history before therapy is begun. If any allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline and other pressor amines, antihistamines and corticosteroids). Oral therapy should not be relied upon for patients with severe illness, or with nausea, vomiting, gastric dilatation, achalasia or intestinal hypermotility. Occasionally patients do not absorb therapeutic amounts of orally administered penicillin. Administer with caution in the presence of markedly impaired renal function, as safe dosage may be lower than the usually recommended. Streptococcal infections should be treated for a minimum of 10 days, and post therapy cultures should be performed to confirm the eradication of the organisms. Prolonged use of antibiotics may promote the over growth of non-susceptible organisms, including fungi. If super infection occurs, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of interaction
Guar gum: Reduced absorption of phenoxymethylpenicillin
Probenicid: Reduced excretion of phenoxymethylpenicillin by competing with it for renal tubular secretion.
Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bacteriocidal activity of penicillins and concomitant use is not recommended.
Neomycin is reported to reduce the absorption of phenoxymethylpenicillin.
Penicillin may reduce the efficacy of combined oral contraceptives.
Use of Phenoxymethylpenicillin while taking methotrexate can cause reduced excretion of methotrexate and thus increasing the risk of toxicity.

4.6 Fertility, Pregnancy and lactation
Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing to the pregnant patient. Phenoxymethylpenicillin is excreted in breast milk.

4.7 Effects on ability to drive and use machines
None known.

4.8 Undesirable effects
Although reactions have been reported much less frequently after oral than after parenteral therapy, it should be remembered that all forms of hypersensitivity, including fatal anaphylaxis have been observed with oral penicillin. The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhoea and black hairy tongue.
The hypersensitivity reactions noted are skin eruptions (ranging from maculopapular to exfoliative dermatitis); urticaria (rashes); angioedema; antibiotic-associated colitis; reactions resembling serum sickness including interstitial nephritis, neutropenia, chills, fever, oedema, arthralgia (joint pains) and prostration; coagulation disorders.

Central nervous system toxicity has been reported (especially with high doses or in severe renal impairment); paraesthesia with prolonged use; laryngeal oedema; and anaphylaxis. Fever and eosinophilia may frequently be the only reactions observed. Haemolytic anaemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.

4.9 Overdose

**Signs and Symptoms:** A large oral overdose of penicillin may cause nausea, vomiting, stomach pain, diarrhoea, and rarely, major motor seizures. If other symptoms are present, consider the possibility of an allergic reaction. Hyperkalaemia may result from over dosage, particularly for patients with renal insufficiency.

**Treatment:** No specific antidote is known. Symptomatic and supportive therapy is recommended. Activated charcoal with a cathartic, such as sorbitol may hasten drug elimination. Penicillin may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC code: J01CE02

Phenoxymethylpenicillin is used in the treatment of infections caused by susceptible staphylococci, pneumococci, gonococci, and haemolytic streptococci. Unless very large doses are given, phenoxymethylpenicillin administered by mouth is less effective than parenterally administered benzylpenicillin in the treatment of severe acute infections. It is inactivated by penicillinase.

5.2 Pharmacokinetic properties

**Absorption:** Rapidly but incompletely adsorbed after oral administration. Calcium and potassium salts are better adsorbed than the free acid. Absorption appears to be reduced in patients with coeliac disease. Absorption appears to be more rapid in fasting than non-fasting subjects. Blood concentration: after an oral dose of 125mg, peak serum concentrations of 200 to 700ng/ml are attained in 2 hours. After an oral dose of 500mg, peak serum concentrations reach 2 to 5µg/ml in 2 to 4 hours.

**Half-life:** Biological half-life is about 30 minutes.

**Distribution:** Widely distributed throughout the body and enters pleural and ascitic fluids and also in cerebrospinal fluid when the meninges are inflamed; Phenoxymethylpenicillin crosses the placenta and is secreted in the milk; (protein binding 50 to 80% bound plasma proteins).

**Metabolic reactions:** Hydroxylation may occur.

**Excretion:** 20% to 35% of an oral dose is excreted in the urine in 24 hours

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Strawberry Flavour 17.41.0549
**Colour Red Dye (Anstead) 1578 (E124) (Spectracol Ponceau 4R)**
Saccharin Sodium
Industrial Methylated Spirit
6.2 **Incompatibilities**
None

6.3 **Shelf life**
*Unopened container*: 24 months
*Reconstituted oral solution*: 7 days

6.4 **Special precautions for storage**
*Unconstituted powder*: Do not store above 25°C. Store in a dry place.
*Reconstituted oral solution*: Store for 7 days in a refrigerator

6.5 **Nature and contents of container**
Natural high density polyethylene bottle with a polypropylene tamper evident or HDPE/polypropylene, tamper evident/child resistant cap containing 100ml of oral solution on reconstitution.

6.6 **Special precautions for disposal**
None.

7 **MARKETING AUTHORISATION HOLDER**
BRISTOL LABORATORIES LIMITED
Unit 3, Canalside, Northbridge Road
Berkhamsted, Herts, HP4 1EG
United Kingdom

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 17907/0034

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
22/06/2011

10 **DATE OF REVISION OF THE TEXT**
22/06/2011
The UK Summary of Product Characteristics (SmPC) for Phenoxymethylpenicillin 250 mg/5 mL Oral Solution (PL 19707/0035) is as follows:

1  NAME OF THE MEDICINAL PRODUCT
Phenoxymethylpenicillin 250 mg/5ml Oral Solution.

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 5ml of reconstituted solution contains 250mg of Phenoxymethylpenicillin as Phenoxymethylpenicillin Potassium as the active ingredient.

For excipients, see 6.1

3  PHARMACEUTICAL FORM
Powder for oral solution.

4  CLINICAL PARTICULARS
4.1 Therapeutic indications
Phenoxymethylpenicillin and phenoxymethylpenicillin potassium are indicated in the treatment of mild to moderately severe infections associated with micro-organisms whose susceptibility to penicillin is within the range of serum levels attained with the dosage form.

Note: Severe empyema, bacteraemia, pericarditis, meningitis and arthritis should not be treated with Penicillin V during the acute phase.

The following infections will usually respond to adequate doses:

- Streptococcal infections (without bacteraemia): Mild to moderate infections of the upper respiratory tract, scarlet fever and mild erysipelas.
- Pneumococcal infections: mild to moderately severe infections of the respiratory tract.
- Staphylococcal infections sensitive to penicillin: mild infections of the skin and soft tissues.
- Fusospirochaetosis (Vincent's gingivitis and pharyngitis): mild to moderately severe infections of the oropharynx usually respond to therapy with oral penicillin.

Prophylactic use: prophylaxis with oral penicillin has proved effective in preventing recurrence of rheumatic fever and chorea.

Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered.

Note: oral penicillin should not be used as adjunctive prophylaxis for genito - urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and child birth.

4.2 Posology and method of administration
Dosage

Adults: 125 or 250 mg every four to six hours depending on the severity of the condition. The elderly: as for adults. Reduce dosage if renal function is markedly impaired.

Children over 5 years: The adult dose.

Children 5 years or less: 125 mg every six hours.

Infants (up to 1 year): 62.5 mg every six hours.

In all but the most serious cases the last dose of the day may be doubled to avoid disturbing sleep. Ideally, each dose should be given half an hour before (or at least three hours after) a meal.

Prophylactic use: 250 mg twice daily is recommended for long term prophylaxis of rheumatic fever.

For oral administration only.
4.3 **Contraindications**
Phenoxymethylpenicillin is contraindicated in patients known to be hypersensitive to Penicillin and should be used with caution in patients with known histories of allergy.

4.4 **Special warnings and precautions for use**
Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma. Oral penicillin should not be used as adjunctive prophylaxis or genito-urinary instrumentation or surgery, lower intestinal tract surgery, sigmoidoscopy and childbirth. Patients with a past history of rheumatic fever receiving continuous prophylaxis may harbour penicillin-resistant organisms. In these patients, the use of another prophylactic agent should be considered. Severe empyema, bacteraemia, pericarditis, meningitis and arthritis should not be treated with Penicillin V during the acute phase.

All degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin. These reactions are more likely to occur in individuals with a history of sensitivity to penicillins, cephalosporins and other allergens. Enquiries should be made for such a history before therapy is begun. If any allergic reaction occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. adrenaline and other pressor amines, antihistamines and corticosteroids). Oral therapy should not be relied upon for patients with severe illness, or with nausea, vomiting, gastric dilation, achalasia or intestinal hypermotility. Occasionally patients do not absorb therapeutic amounts of orally administered penicillin. Administer with caution in the presence of markedly impaired renal function, as safe dosage may be lower than the usually recommended. Streptococcal infections should be treated for a minimum of 10 days, and post therapy cultures should be performed to confirm the eradication of the organisms. Prolonged use of antibiotics may promote the overgrowth of non-susceptible organisms, including fungi. If super infection occurs, appropriate measures should be taken.

4.5 **Interaction with other medicinal products and other forms of interaction**
- Guar gum: Reduced absorption of phenoxymethylpenicillin
- Probenecid: Reduced excretion of phenoxymethylpenicillin by competing with it for renal tubular secretion.
- Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bacteriocidal activity of penicillins and concomitant use is not recommended.
- Neomycin is reported to reduce the absorption of phenoxymethylpenicillin.
- Penicillin may reduce the efficacy of combined oral contraceptives.
- Use of Phenoxymethylpenicillin while taking methotrexate can cause reduced excretion of methotrexate and thus increasing the risk of toxicity.

4.6 **Pregnancy and lactation**
Although laboratory and clinical studies have shown no evidence of teratogenicity, caution should be exercised when prescribing to the pregnant patient. Phenoxymethylpenicillin is excreted in breast milk.

4.7 **Effects on ability to drive and use machines**
None known.

4.8 **Undesirable effects**
Although reactions have been reported much less frequently after oral than after parenteral therapy, it should be remembered that all forms of hypersensitivity, including fatal anaphylaxis have been observed with oral penicillin. The most common reactions to oral penicillin are nausea, vomiting, epigastric distress, diarrhoea and black hairy tongue. The hypersensitivity reactions noted are skin eruptions (ranging from maculopapular to exfoliative dermatitis); urticaria (rashes); angioedema; antibiotic-associated colitis; reactions resembling serum sickness including interstitial nephritis, neutropenia, chills, fever, oedema, arthralgia (joint pains) and prostration; coagulation disorders. Central nervous system toxicity has been reported (especially with high doses or in severe renal impairment); paraesthesia with prolonged use; laryngeal oedema; and anaphylaxis. Fever and eosinophilia may frequently be the only reactions observed. Haemolytic anaemia, leucopenia, thrombocytopenia, neuropathy and nephropathy are infrequent reactions and are usually associated with high doses of parenteral penicillin.
4.9 Overdose

Signs and Symptoms: A large oral overdose of penicillin may cause nausea, vomiting, stomach pain, diarrhoea, and rarely, major motor seizures. If other symptoms are present, consider the possibility of an allergic reaction. Hyperkalaemia may result from over dosage, particularly for patients with renal insufficiency.

Treatment: No specific antidote is known. Symptomatic and supportive therapy is recommended. Activated charcoal with a cathartic, such as sorbitol may hasten drug elimination. Penicillin may be removed by haemodialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Phenoxymethylpenicillin is used in the treatment of infections caused by susceptible staphylococci, pneumococci, gonococci, and haemolytic streptococci. Unless very large doses are given, phenoxymethylpenicillin administered by mouth is less effective than parenterally administered benzylpenicillin in the treatment of severe acute infections. It is inactivated by penicillinase.

5.2 Pharmacokinetic properties

Absorption: Rapidly but incompletely adsorbed after oral administration. Calcium and potassium salts are better adsorbed than the free acid. Absorption appears to be reduced in patients with coeliac disease. Absorption appears to be more rapid in fasting than non-fasting subjects. Blood concentration: after an oral dose of 125mg, peak serum concentrations of 200 to 700ng/ml are attained in 2 hours. After an oral dose of 500mg, peak serum concentrations reach 2 to 5µg/ml in 2 to 4 hours.

Half-life: Biological half-life is about 30 minutes.

Distribution: Widely distributed throughout the body and enters pleural and ascitic fluids and also in cerebrospinal fluid when the meninges are inflamed; Phenoxymethylpenicillin crosses the placenta and is secreted in the milk; (protein binding 50 to 80% bound plasma proteins).

Metabolic reactions: Hydroxylation may occur.

Excretion: 20% to 35% of an oral dose is excreted in the urine in 24 hours

5.3 Preclinical safety data

Not applicable

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Strawberry Flavour 17.41.0549
 Colour Red Dye (Anstead) 1578 (E124) (Spectracol Ponceau 4R)
Saccharin Sodium
Industrial Methylated Spirit

6.2 Incompatibilities

None

6.3 Shelf life

Unopened container: 24 months
Reconstituted oral solution: 7 days

6.4 Special precautions for storage

Unconstituted powder: Do not store above 25°C. Store in a dry place.
Reconstituted oral solution: Store for 7 days in a refrigerator
6.5 Nature and contents of container
Natural high density polyethylene bottle with a polypropylene tamper evident or HDPE/polypropylene, tamper evident/child resistant cap containing 100ml of oral solution on reconstitution.

6.6 Special precautions for disposal
None.

7 MARKETING AUTHORISATION HOLDER
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