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

PL 17907/0034-5

UKPAR

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PHENOXYMETHYLPENICILLIN 125 MG/5 ML AND 250MG/5ML 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 Phenyoxymethylpenicillin 125 mg/5 mL Oral Solution (PL 17907/0034) and Phenyoxymethylpenicillin 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.

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

Phenyoxymethylpenicillin 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).

Phenyoxymethylpenicillin 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 Phenyoxymethylpenicillin 125 mg/5 mL and 250 mg/5 mL Oral Solution outweigh the risks; hence Marketing Authorisations have been granted.

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

PL 17907/0034-5

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

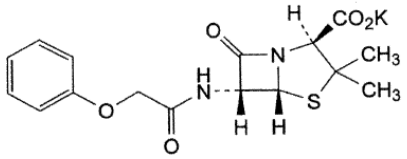
DRUG SUBSTANCE

Phenoxymethylpenicillin potassium

INN: Phenoxymethylpenicillin potassium

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

Structure:



Molecular mass: 388.5

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

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 phenoxymethylpenicillin potassium 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 phenoxymethylpenicillin 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^{o}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 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 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 Phenoxymethylpenicillin 125 mg/5 mL Oral Solution and Phenoxymethylpenicillin 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 Phenoxymethylpenicillin 125 mg/5 mL and 250mg/5 mL Oral Solutions have been demonstrated to be generic versions of the reference products, Phenyoxymethylpenicillin 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 Phenoxymethylpenicillin 125 mg/5 mL and 250mg/5 mL Oral Solution and the reference products Phenyoxymethylpenicillin Oral Solution BP 125 mg/5 mL and 250mg/ 5 mL (Athlone Laboratories Limited) are interchangeable. Extensive clinical experience with phenyoxymethylpenicillin potassium is considered to have demonstrated the therapeutic value of the active substance. The benefit:risk is, therefore, considered to be positive.

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

PL 17907/0034-5

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation application on 19 September 2008
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 2 October 2008.
3	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.
4	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
5	The application was determined on 22 June 2011.

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

PL 17907/0034-5

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

PHENOXYMETHYLPENICILLIN 125 MG/5 ML AND 250MG/5ML ORAL SOLUTION
PL 17907/0034-5

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SmPC) for Phenoxymethylpenicillin 125 mg/5 mL Oral Solution (PL 17907/0034) is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Phenoxymethylpenicillin 125 mg/5ml Oral Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5ml of reconstituted solution contains 125mg 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 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 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 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 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 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 17907/0035

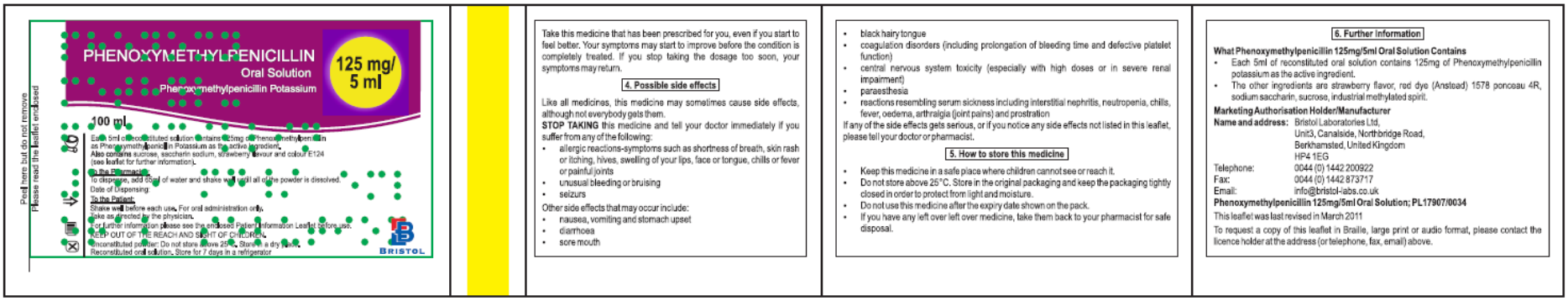
9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22/06/2011

10 DATE OF REVISION OF THE TEXT

22/06/2011

PATIENT INFORMATION LEAFLET COMBINED WITH LABEL



Take this medicine that has been prescribed for you, even if you start to feel better. Your symptoms may start to improve before the condition is completely treated. If you stop taking the dosage too soon, your symptoms may return.

4. Possible side effects

Like all medicines, this medicine may sometimes cause side effects, although not everybody gets them.
STOP TAKING this medicine and tell your doctor immediately if you suffer from any of the following:

- allergic reactions-symptoms such as shortness of breath, skin rash or itching, hives, swelling of your lips, face or tongue, chills or fever or painful joints
- unusual bleeding or bruising
- seizurs

Other side effects that may occur include:

- nausea, vomiting and stomach upset
- diarrhoea
- sore mouth
- black hairy tongue
- coagulation disorders (including prolongation of bleeding time and defective platelet function)
- central nervous system toxicity (especially with high doses or in severe renal impairment)
- paraesthesia
- reactions resembling serum sickness including interstitial nephritis, neutropenia, chills, fever, oedema, arthralgia (joint pains) and prostration

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store this medicine

- Keep this medicine in a safe place where children cannot see or reach it.
- Do not store above 25°C. Store in the original packaging and keep the packaging tightly closed in order to protect from light and moisture.
- Do not use this medicine after the expiry date shown on the pack.
- If you have any left over left over medicine, take them back to your pharmacist for safe disposal.

6. Further Information

What Phenoxymethylpenicillin 125mg/5ml Oral Solution Contains

- Each 5ml of reconstituted oral solution contains 125mg of Phenoxymethylpenicillin potassium as the active ingredient.
- The other ingredients are strawberry flavor, red dye (Anstead) 1578 ponceau 4R, sodium saccharin, sucrose, industrial methylated spirit.

Marketing Authorisation Holder/Manufacturer

Name and address: Bristol Laboratories Ltd,
Unit3, Canalside, Northbridge Road,
Berkhamsted, United Kingdom
HP4 1EG
Telephone: 0044 (0) 1442 200922
Fax: 0044 (0) 1442 873717
Email: info@bristol-labs.co.uk

Phenoxymethylpenicillin 125mg/5ml Oral Solution; PL 17907/0034

This leaflet was last revised in March 2011

To request a copy of this leaflet in Braille, large print or audio format, please contact the licence holder at the address (or telephone, fax, email) above.

Read this entire leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What this medicine is and what it is used for

Phenoxymethylpenicillin belongs to a group of medicines called penicillin, which are used to treat mild to moderate severe infections associated with microorganisms whose susceptibility to penicillin is within the range of serum levels attained with the dosage form.

The name of your medicine is phenoxymethylpenicillin potassium. It is available as a powder for reconstitution. The powder for reconstitution is prepared by the pharmacist before dispensing by adding water to the powder to give 100ml of oral solution.

2. Before you take this medicine

Do not take this medicine if you:

- Ever had a bad reaction or allergic reaction to Phenoxymethylpenicillin, any other penicillin or cephalosporins or any other ingredients (these listed in Section 6, Further Information)

Take special care with this medicine

Tell your doctor before taking this medicine if you have any medical conditions, and especially if you:

- Suffer from kidney problems

Taking other medicines

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed, for example, herbal remedies and health supplements from a pharmacy, supermarket or health food shop, as they may interact with this medicine.

- Probenecid, which is used to treat gout
- Other antibiotics (such as erythromycin, neomycin or tetracycline)
- Oral contraceptives
- Beta-blockers (used to lower blood pressure)

Pregnancy and breast-feeding

- Do not take this medicine if you are pregnant, think you have become pregnant or intend to become pregnant whilst taking this medicine or are breast-feeding.
- Always ask your doctor or pharmacist for advice before taking any other medicines.

3. How to take this medicine

- Always take this medicine exactly as advised by your doctor. You should check with your doctor or pharmacist if you are not sure.
- The dosage and duration of treatment will depend on the type and severity of the infection.
- It should be given in divided doses (3 to 4 times a day) and preferably half an hour before meals.

The following dosage schedule applies to Phenoxymethylpenicillin Oral Solution BP.
Adults and Children over 5 years: 125 or 250 mg every four to six hours. The usual total daily dose is 500 to 1500 mg in divided doses.
Children 1-5 years: 125mg every six hours. The usual total daily dosage is 500mg in divided doses.
Infants (up to 1 year): 62.5 mg every six hours.
Elderly: As for adults.
Prophylactic use: 250 mg twice daily is recommended for long term prophylaxis of rheumatic fever.
Your doctor may sometimes prescribe a different dose to that stated above and if this applies to you, discuss it with your doctor if you have not already done so. You should always follow your doctor's instructions as to how and when to take your medicine.

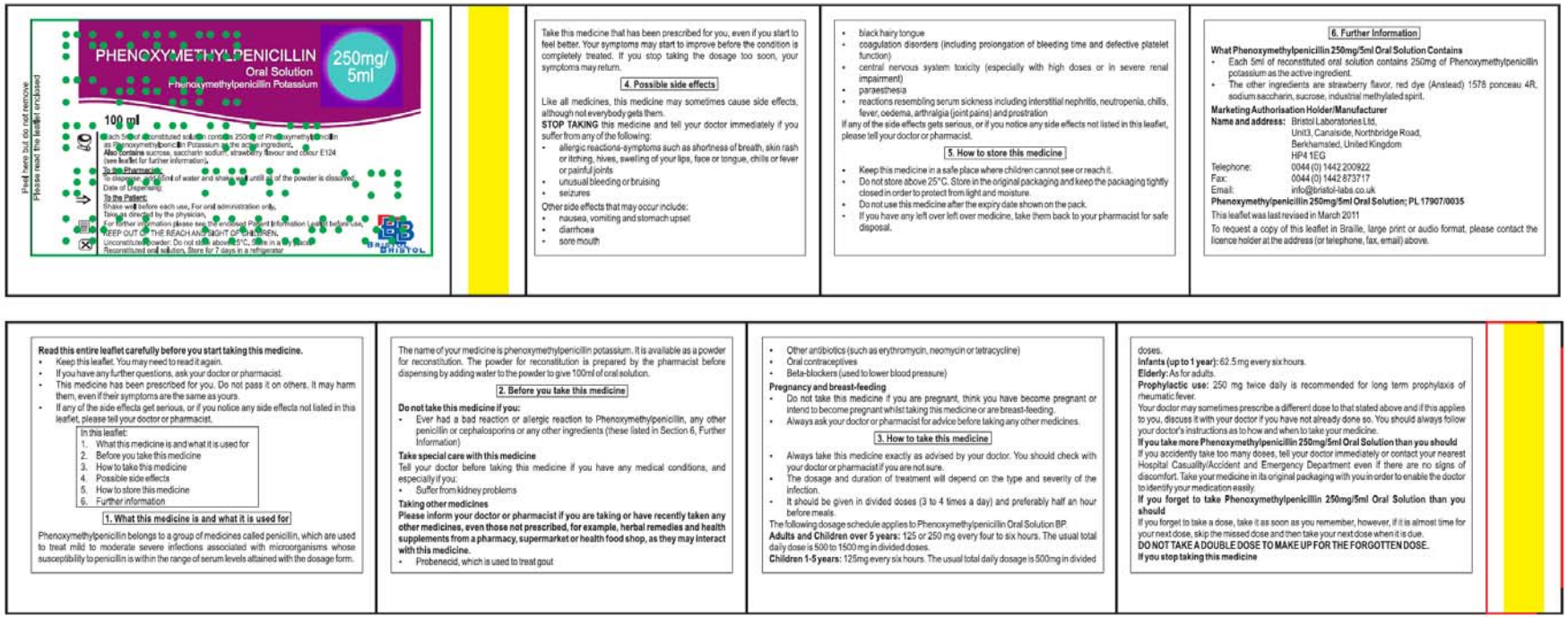
If you take more Phenoxymethylpenicillin 125mg/5ml Oral Solution than you should

If you accidently take too many doses, tell your doctor immediately or contact your nearest Hospital Casualty/Accident and Emergency Department even if there are no signs of discomfort. Take your medicine in its original packaging with you in order to enable the doctor to identify your medication easily.

If you forget to take Phenoxymethylpenicillin 125mg/5ml Oral Solution than you should

If you forget to take a dose, take it as soon as you remember, however, if it is almost time for your next dose, skip the missed dose and then take your next dose when it is due.
DO NOT TAKE A DOUBLE DOSE TO MAKE UP FOR THE FORGOTTEN DOSE.

If you stop taking this medicine



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6. Further Information

What Phenoxymethylpenicillin 250mg/5ml Oral Solution Contains

- Each 5ml of reconstituted oral solution contains 250mg of Phenoxymethylpenicillin potassium as the active ingredient.
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