SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Phenoxymethylpenicillin, 250mg, Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet

White, circular, biconvex film coated tablets with break line on one side and 'I 04' on the other.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Phenoxymethylpenicillin is indicated in the treatment or prophylaxis of mild to moderately severe infections caused by penicillin sensitive organisms, i.e. those microorganisms whose susceptibility to phenoxymethylpenicillin is within the range of serum levels attained.

Phenoxymethylpenicillin is indicated in the treatment of the following Infections (See Section 5.1):

Streptococcal infections:
Pharyngitis
Scarlet fever
Skin and soft tissue infections (e.g. erysipelas)

Pneumococcal infections:
Pneumonia
Otitis media

Vincent's gingivitis and pharyngitis

Phenoxymethylpenicillin is also indicated for (see Section 5.1):

Prophylaxis of rheumatic fever and/or chorea Prophylaxis of pneumococcal infection (e.g. in asplenia and in patients with sickle cell disease).

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

4.2 Posology and method of administration

Phenoxymethylpenicillin 250 mg is approximately equivalent to 400,000 units.

Method of administration

Phenoxymethylpenicillin 250 mg Film-Coated Tablets are for oral use.

Each tablet should be swallowed whole with water, at least 30 minutes before food, as ingestion of phenoxymethylpenicillin with meals slightly reduces the absorption of the drug.

The **usual dosage recommendations** are as follows:

Adults: 250-500 mg every six hours.
Children 1-5 years: 125 mg every six hours
6-12 years: 250 mg every six hours

Elderly: The dosage is as for adults. The dosage should be reduced if renal function is markedly impaired.

Prophylactic Use

Prophylaxis of rheumatic fever/ chorea: 250 mg twice daily on a continuing basis
Prophylaxis of pneumococcal infection (e.g. in asplenia and in sickle cell disease):
Adults and children over 12 years: 500mg every 12 hours.
Children 6-12 years: 250mg every 12 hours.
Children below 5 years: 125mg every 12 hours.

In children younger than 5 years of age tablets are not usually administered. The more appropriate formulation for this age group should be used. Sometimes older children may have difficulties swallowing tablets.

To avoid late complications (rheumatic fever), infections with β-haemolytic streptococci should be treated for 10 days.

The treatment of acute otitis media with Phenoxymethylpenicillin should be limited to 5 days. However, 5-10 days treatment may be recommended in patients with potential for complications.

Renal impairment

The dosage should be reduced if renal function is markedly impaired.

Hepatic impairment

Dosage adjustment may be necessary in patients with impaired liver function when they also have renal failure. In this situation the liver may be a major excretion route.

4.3 Contraindications

Phenoxymethylpenicillin is contraindicated in patients with known penicillin hypersensitivity.

Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics e.g. cephalosporins. Severe acute infections should not be treated with phenoxymethylpenicillin.

4.4 Special warnings and precautions for use

Phenoxymethylpenicillin should be given with caution to patients with a history of allergy, especially to other drugs. Phenoxymethylpenicillin should also be given cautiously to cephalosporin-sensitive patients, as there is some evidence of partial cross-allergenicity between the cephalosporins and penicillins. Patients have had severe reactions (including anaphylaxis) to both drugs. If the patient experiences an allergic reaction phenoxymethylpenicillin should be discontinued and treatment with

the appropriate agents initiated (e.g. adrenaline and other pressor amines, antihistamines and other corticosteroids).

Particular caution should be exercised in prescribing phenoxymethylpenicillin to patients with an allergic diathesis or with bronchial asthma.

Oral Penicillins are not indicated in patients with severe illness or with a gastrointestinal disease that causes persistent nausea, vomiting, gastric dilation, cardiospasm, intestinal hyper motility or diarrhoea, because absorption may be reduced. Occasionally, patients do not absorb therapeutic amounts of orally administered penicillin.

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.

In patients undergoing long-term phenoxymethylpenicillin treatment the complete and differential blood count, as well as the liver and kidney function, should be monitored.

During long-term treatment attention should also be paid to the potential overgrowth of resistant organisms including Pseudomonas or Candida. If super-infection occurs, appropriate measures should be taken.

Caution should be used when treating patients with a history of antibiotic associated colitis.

Sustained severe diarrhoea should prompt suspicion of pseudomembranous colitis. As this condition may be life-threatening phenoxymethylpenicillin should be withdrawn immediately and treatment guided by bacteriologic studies. Each tablet contains 28 mg of potassium, which may be harmful to people on low potassium diets and may cause stomach upset, diarrhoea and hyperkalaemia. High doses should be used with caution in patients receiving potassium-containing drugs or potassium sparing-diuretics.

In renal impairment the safe dosage may be lower than usually recommended.

During treatment with phenoxymethylpenicillin non-enzymatic glucose tests may be false-positive.

4.5 Interaction with other medicinal products and other forms of interaction

As penicillins like phenoxymethylpenicillin are only active against proliferating microorganisms, phenoxymethylpenicillin should not be combined with bacteriostatic antibiotics such as tetracycline, erythromycin, chloramphenicol and sulphonamides.

Concomitant use of uricosuric drugs (e.g. probenecid and sulfinpyrazone) reduces the excretion of phenoxymethylpenicillin resulting in increased plasma levels and thus prolongs its action.

Phenoxymethylpenicillin may reduce the excretion of methotrexate causing an increased risk of toxicity.

Like other antibiotics, phenoxymethylpenicillin may reduce the effectiveness of oral contraceptives. Patients should be advised to use additional forms of contraceptive precautions while taking phenoxymethylpenicillin.

During treatment with phenoxymethylpenicillin non-enzymatic urinary glucose tests may be false-positive.

Guar gum may slow the speed of absorption of Phenoxymethylpenicillin.

Phenoxymethylpenicillin has the following interaction information:

Neomycin reduces the absorption of phenoxymethylpenicillin.

Combined use of phenoxymethylpenicillin and oral anticoagulants (e.g. warfarin) may prolong prothrombin time.

Coumarin - Common experience in anticoagulant clinics is that INR can be altered by a course of broad-spectrum penicillins such as ampicillin, although studies have failed to demonstrate an interaction with coumarins.

Phenindione - Common experience in anticoagulant clinics is that INR can be altered by a course of broad-spectrum penicillins such as ampicillin, although studies have failed to demonstrate an interaction with phenindione.

Typhoid Vaccines - Antibacterials inactive oral typhoid vaccine.

Concurrent use of phenoxymethylpenicillin with potassium sparing diuretics (e.g Amiloride and Spironolactone) may cause hyperkalaemia, which can be life-threatening.

4.6 Fertility, Pregnancy and lactation

Pregnancy

Animal studies with phenoxymethylpenicillin have shown no teratogenic effects.

Phenoxymethylpenicillin has been in extensive clinical use and suitability in human pregnancy has been well documented in clinical trials. However, as with other drugs, caution should be exercised when prescribing to pregnant patients.

Lactation

Breast feeding is not contraindicated with phenoxymethylpenicillin. Trace quantities of phenoxymethylpenicillin can be detected in breast milk. While adverse effects are apparently rare, two potential problems exist for nursing infant:

- modification of bowel flora

- direct effects on the infant such as allergy/sensitisation

Caution should therefore be exercised when prescribing for the nursing mother.

4.7 Effects on ability to drive and use machines

Not Known.

4.8 Undesirable effects

Hypersensitivity

Potential allergic reactions include urticaria, angioneurotic oedema, erythema multiforme, exfoliative dermatitis, fever, joint pain, serum sickness-like reactions, haemolytic anaemia, interstitial nephritis or anaphylactic shock (which could be fatal) with collapse and anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms). Although these are less common, and take a milder course, in oral treatment than during parenteral penicillin treatment, it should be remembered that all degrees of hypersensitivity, including fatal anaphylaxis, have been observed with oral penicillin.

Gastro-intestinal tract

Phenoxymethylpenicillin potassium is generally well tolerated. Occasionally soft stools occur and they do not require the interruption of the treatment.

Nausea, diarrhoea, vomiting, stomatitis and glossitis are sometimes seen.

Sustained severe diarrhoea should prompt suspicion of pseudomembranous colitis. As this condition may be life-threatening phenoxymethylpenicillin should be withdrawn immediately and treatment guided by bacteriologic studies with appropriate antibiotherapy (i.e. vancomycin).

Blood

Eosinophilia, haemolytic anaemia, leukopenia, thrombocytopenia and agranulocytosis are extremely rare. Other possible effects on the blood composition include: neutropenia, haemolytic anaemia and coagulation disorders.

Central nervous system

Central nervous system toxicity, including convulsions, has been reported, especially following high doses or in severe renal impairment. Paraesthesia has been reported with prolonged use.

As with other broad-spectrum antibiotics prolonged use may result in the overgrowth of non-susceptible organisms, e.g. candida. This may present a vulvo-vaginitis.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

4.9 Overdose

A large overdose may cause nausea, vomiting and diarrhoea. Rarely major motor seizures may occur. There is no known antidote. Symptomatic and supportive therapy is recommended. It is advisable to monitor blood levels in patients with renal malfunction. Phenoxymethylpenicillin may be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General properties

ATC classification: Pharmacotherapeutic Group: Beta lactamase sensitive penicillins
ATC Code: J01CE02.

Mode of action

Phenoxymethylpenicillin exerts a bactericidal action against penicillin-susceptible bacteria by inhibition of biosynthesis of cell wall mucopeptides.

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

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

PK/PD relationship

Efficacy correlates with the time that plasma levels exceed the MIC of the pathogen under treatment.

Resistance

Resistance to phenoxymethylpenicillin is usually mediated by one or both of:
Bacterial production of β-lactamases: This family of enzymes can inactivate Phenoxymethylpenicillin by hydrolyzing the β-lactam ring.

The occurrence of modified penicillin-binding proteins resulting in impaired binding of phenoxymethylpenicillin.

EUCAST recommendations for susceptibility testing:

Staphylococcus spp: Isolates positive for β- lactamase are resistant to phenoxymethylpenicillin. Isolates negative for β- lactamase and susceptible to methicillin can be reported susceptible to phenoxymethylpenicillin. Isolates resistant to methicillin are resistant to phenoxymethylpenicillin.

Streptococcus groups A, B, C and G: The β-lactam susceptibility of β-haemolytic Streptococcus groups A, B, C and G is inferred from the penicillin susceptibility.

Streptococcus pneumoniae: Isolates fully susceptible to benzylpenicillin (MIC≤ 0.064 mg/ml, susceptible by Oxacillin disk screen, Screen for β- lactam resistance with the Oxacillin 1µg disk – isolates categorized as susceptible can be reported as susceptible to phenoxymethylpenicillin irrespective of the clinical condition. Isolates categorized as Oxacillin resistant can be reported to phenoxymethylpenicillin in meningitis) can be reported susceptible to phenoxymethylpenicillin, otherwise reported as phenoxymethylpenicillin resistant without further testing.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent is at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organism
Streptococcus A,B,C,G
Species for which acquired resistance may be a problem
Staphylococcus aureus
Streptococcus pneumoniae

5.2 Pharmacokinetic properties

Absorption

Phenoxymethylpenicillin is stable under acidic conditions so it can be administered by oral route.

Phenoxymethylpenicillin is rapidly, but incompletely absorbed after oral administration and the absorption level is around 60%. The simultaneous administration of food slightly decreases the peak plasma concentration of phenoxymethylpenicillin, but does not appear to affect the extent of absorption. Peak plasma concentrations are reached in about 45 minutes. The peak plasma concentration increases approximately in proportion with increased doses. Peak serum concentrations of 3-6 μg per ml have been seen following dosage of 250 mg to 500 mg by mouth.

Distribution

Phenoxymethylpenicillin is widely distributed round the body tissues and fluids (volume of distribution about 0.21 kg-1 of body weight) and more readily penetrates inflamed tissues. It also diffuses across the placenta into foetal circulation and small amounts appear in the milk of nursing mothers. Eighty per cent is reported to be protein bound.

Biotransformation

Phenoxymethylpenicillin is partially metabolised to inactive penicilloic acid by hydrolysis of the lactam ring. This metabolism occurs in the liver.

Elimination

The plasma half-life of phenoxymethylpenicillin is about 45 minutes which may increase to four hours in renal failure.

Excretion is by tubular secretion into urine. About 40% of the dose is eliminated in the urine either as under unchanged or as penicilloic acid in the first 10 hours after oral administration. Small excretion occurs in bile. Impaired absorption is seen in patients with coeliac disease.

5.3 Preclinical safety data

No data of clinical relevance

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium Hydrogen Phosphate Dihydrate
Maize Starch
Cellulose, Microcrystalline E460
Magnesium Stearate E572
Basic Butylated Methacrylate

Macrogol 6000
Sodium Laurilsulfate E487
Stearic Acid E570
Titanium Dioxide E171

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25º C.

6.5 Nature and contents of container

Al /PVC blister. Pack sizes of 14, 28, 42, 56, 70, 140 tablets are available
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

7. MARKETING AUTHORISATION HOLDER

Brown & Burk UK Ltd
5, Marryat Close, Hounslow west,
Middlesex TW4 5DQ,
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 25298/0106

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/04/2012

10. DATE OF REVISION OF THE TEXT

05/2015