Proposed Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BETAPEN 125 mg GRANULES

BETAPEN 250 mg GRANULES

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BETAPEN 125 mg GRANULES:

After reconstitution each 5 ml suspension contains phenoxymethylpenicillin potassium equivalent to 125 mg phenoxymethylpenicillin.

Sugar 2,5 g

BETAPEN 250 mg GRANULES:

After reconstitution each 5 ml suspension contains phenoxymethylpenicillin potassium equivalent to 250 mg phenoxymethylpenicillin.

Sugar 2,3 g

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Granules

Granules (125 mg/5 ml and 250 mg/5 ml)

White to light pink granules.

Reconstituted Elixir (125 mg/5 ml and 250 mg/5 ml)

Clear red syrupy solution with a cherry odour and almost sweet taste.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by penicillin sensitive microorganisms including sore throat due to Group A beta haemolytic streptococci. Rheumatic fever prophylaxis.

4.2 Posology and method of administration

(1) **Streptococcal infections:**

Adults: 125 to 250 mg every 4 hours

Children: up to 1 year 60 mg every 6 hours.

1 to 5 years: 125 mg every 6 hours.

6 to 12 years: 250 mg every 6 hours.

(2) **Rheumatic fever prophylaxis:** 125 mg every 12 hours.

FOR BETAPEN 125 mg GRANULES:

DIRECTIONS FOR RECONSTITUTING 100 ml GRANULES FOR SUSPENSION

Add 69 ml of water in divided amounts shaking after each addition.

DIRECTIONS FOR RECONSTITUTING 60 ml GRANULES FOR SUSPENSION

Add 41,5 ml of water in divided amounts shaking after each addition.

FOR BETAPEN 250 mg GRANULES:

DIRECTIONS FOR RECONSTITUTING 100 ml GRANULES FOR SUSPENSION

Add 68 ml of water in divided amounts shaking after each addition.

Method of Administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6

4.3 Contraindications

Dysentry and typhus, and other infections caused by penicillin resistant microbes such as Brucella and E. coli. Hypersensitivity to penicillin.

For treatment of trivial disorders.

4.4 Special warnings and precautions for use

Penicillin should be used with caution in individuals with histories of significant allergies and/or asthma.

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 doses.

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.

BETAPEN GRANULES contains sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take **BETAPEN GRANULES.**

As with all beta-lactam antibiotics, serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous reactions) have been reported in patients on penicillin therapy (see sections 4.3 and 4.8).

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8).

4.5 Interaction with other medicines and other forms of interaction

Aminoglycosides: Neomycin is reported to reduce the absorption of phenoxymethylpenicillin.

Anticoagulants: Penicillins may interfere with anticoagulant control.

Bacteriostatic antibiotics: Certain bacteriostatic antibiotics such as Chloramphenicol, Erythromycin and Tetracyclines have been reported to antagonise the bactericidal activity of penicillins and concomitant use is not recommended.

Guar gum: Reduced absorption of phenoxymethylpenicillin

Methotrexate: Use of Phenoxymethylpenicillin while taking methotrexate can cause reduced excretion of methotrexate thereby increasing the risk of toxicity.

Probenecid: Reduced excretion of phenoxymethylpenicillin by competing with it for renal tubular secretion.

Sulfinpyrazone: Excretion of penicillins reduced by sulfinpyrazone.

Typhoid vaccine (oral): Penicillins may inactivate oral typhoid vaccine if ingested concomitantly.

4.6 Fertility, pregnancy and lactation

Pregnancy:

There are no or a limited amount of data from the use of Phenoxymethylpenicillin in pregnant women. As a precautionary measure, it is preferable to avoid the use of Phenoxymethylpenicillin during pregnancy.

Lactation:

Phenoxymethylpenicillin metabolites are excreted in human milk to such an extent that effects on breastfed newborns are likely.

4.7 Effects on ability to drive and use machines

This medicine should not affect your ability to drive or to use machinery.

4.8 Undesirable effects

The most common reactions to oral penicillin are gastrointestinal effects and hypersensitivity reactions. Although hypersensitivity 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.

System Class	Frequent	Less Frequent	Frequency Unknown
Infections and infestations			Pseudomembranous colitis
Blood and lymphatic Disorders		Changes in blood counts, including, thrombocytopenia, neutropenia, leucopenia, eosinophilia and haemolytic anaemia.	Coagulation disorders (including prolongation of bleeding time and defective platelet function)
Cardiac disorders			Kounis syndrome
Gastrointestinal disorders	Nausea, vomiting, abdominal pain, diarrhoea		Sore mouth and black hairy tongue (discolouration of tongue)
Hepatobiliary disorders		Hepatitis and cholestatic jaundice	

Immune disorders	Allergic Reactions (typically manifest as skin reactions (See Skin and subcutaneous disorders).	Severe allergic reactions causing angioedema, laryngeal oedema and anaphylaxis	Serum sickness-like reactions characterised by fever, chills and oedema and anaphylaxis
Nervous system disorders			Central nervous system toxicity including convulsions (especially with high doses or insevere renal impairment); paraesthesia mayoccur with prolonged use, Neuropathy (usually Associated with high doses of parenteral penicillin)
Renal and urinary disorders		Interstitial nephritis	

		Nephropathy (usually associated with high doses of parenteral penicillin)	
Skin and subcutaneous Disorders	Urticarial, erythematous or mobilliform rashand pruritus	Exfoliative dermatitis	Linear IgA disease

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 Suspected adverse reactions can also be reported directly to the Holder of Certificate of Registration via email: pharmacovigilance.africasme@sunpharma.com or tel: +27(0) 12 643 2000

4.9 Overdose

Any form of actual toxicity of phenoxymethylpencillin is rare and doses of 8 g have been well tolerated.

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 overdosage, particularly for patients with renal insufficiency.
Management: 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

Category and class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Beta lactamase sensitive natural penicillins

ATC Code: J01C E02.

Mechanism of action

Phenoxymethylpenicillin is a narrow spectrum antibiotic inhibited by penicillinase.

Phenoxymethylpenicillin acts through interference with the final stage of synthesis of the bacterial cell wall. The action depends on its ability to bind certain membrane-bound proteins, (penicillin-binding proteins or PBPs) that are located beneath the cell wall. These proteins are involved in maintaining cell wall structure, in cell wall synthesis and in cell division, and appear to possess transpeptidase and carboxypeptidase activity.

PK/PD relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for phenoxymethylpenicillin.

Mechanism(s) of Resistance:

Phenoxymethylpenicillin is inhibited by penicillinase and other betalactamases that are produced by certain micro-organisms. The incidence of beta-lactamase producing organisms is increasing.

Mechanisms of resistance

The two main mechanisms of resistance to phenoxymethylpenicillin are:

• Inactivation by bacterial penicillinases and other beta-lactamases

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance.

EUCAST clinical MIC breakpoints to separate susceptible (S) pathogens from resistant (R) pathogens (version 1.022.11.210) are:

The susceptibility of streptococci Groups A, C and G and S. pneumoniae to phenoxymethylpenicillin is inferred from thesusceptibility to benzylpenicillin

EUCAST Species-related breakpoints (Susceptible≤/Resistant>) Units:	
Mg/L	
Staphylococcus	≤ 0,12/>0,12
Streptococcus A, C, G	≤ 0,25/>0,25
S. pneumoniae	≤ 0,06/>2

Staphylococci: Most staphylococci are penicillinase-producers. Penicillinase producing strains are resistant. The benzylpenicillin breakpoint (shown) will mostly, but not unequivocally, separate beta-lactamase producers from nonproducers.

Streptococcus pneumoniae: For phenoxymethylpenicillin, report S. pneumoniae with benzylpenicillin MICs above 0,06mg/L resistant.

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. Expert advice should be sought as necessary when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

Commonly susceptible species
Streptococcus A, ***B**, C, G
Species for which acquired resistance may be a problem
Staphylococcus aureus
Streptococcus pneumonia
Staphylococcus epidermidis

*** Not applicable for 125 mg.**

5.2 Pharmacokinetic properties

Absorption

Rapidly but incompletely absorbed after oral administration (about 60 % of an oral dose is absorbed). Calcium and potassium salts are better absorbed 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 125 mg, peak serum concentrations of 200 to 700 ng/ml are attained in 2 hours. After an oral dose of 500 mg, peak serum concentrations reach 3 to 5 micrograms /ml in 30 to 60 minutes.

Half-life: Biological half-life is about 30 minutes, increased to about 4 hours in severe renal impairment.

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).

Biotransformation: It is metabolised in the liver; several metabolites have been identified, including penicilloic acid.

Elimination: Unchanged drug and metabolites are excreted rapidly in the urine. (20 % to 35 % of an oral dose is excreted in the urine in 24 hours).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Granules (125 mg/5 ml)

- Col Red Rasberry H1277
- Trusil Cherry F 1496
- Saccharin Sodium
- Sucrose

Granules (250 mg/5 ml)

- Col Red Rasberry H1277
- Ess. Fl. Cherry DM 6040
- Saccharin Sodium
- Sucrose

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Granules: Store well-closed in a cool, dry place, at or below

25 ºC.

Reconstituted suspension: Must be used within 14 days if stored in a refrigerator and used with 7 days if stored at or below 25 ºC.

6.5 Nature and contents of container

BETAPEN 125 mg GRANULES:

Containers of granules for 60 ml and 100 ml suspension.

BETAPEN 250 mg GRANULES:

Containers of granules for 100 ml suspension.

6.6 Special precautions for disposal and other handling

DIRECTIONS FOR RECONSTITUTING 100 ml GRANULES FOR SUSPENSION

Add 69 ml of water in divided amounts shaking after each addition.

DIRECTIONS FOR RECONSTITUTING 60 ml GRANULES FOR SUSPENSION

Add 41,5 ml of water in divided amounts shaking after each addition.

FOR BETAPEN 250 mg GRANULES:

DIRECTIONS FOR RECONSTITUTING 100 ml

GRANULES FOR SUSPENSION

Add 68 ml of water in divided amounts shaking after each addition.

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7 HOLDER OF CERTIFICATE OF REGISTRATION

RANBAXY PHARMACEUTICALS (PTY) LTD

14 LAUTRE ROAD

STORMILL, EXT.1

ROODEPOORT

1724

SOUTH AFRICA

Telephone: +27(0) 11 495 0100

8 REGISTRATION NUMBER(S)

BETAPEN 125 mg GRANULES:

B/20.1.2/90 (125 mg/5ml) (South Africa)

S2 BOT 0901558 (Botswana) (125 mg/5 ml) 100 ml
NS2 90/20.1.2/00369 (125 mg/5 ml) (Namibia) 100 ml

BETAPEN 250 mg GRANULES:

B/20.1.2/203 (250 mg/5 ml) (South Africa)

NS2 90/20.1.2/00370 (250 mg /5 ml) Namibia)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

The date on the registration certificate of the medicine:

BETAPEN 125 mg GRANULES: 9 January 1970

BETAPEN 250 mg GRANULES: 11 August 1970

10 DATE OF REVISON OF THE TEXT