SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

BENPEN 1 MU, 1 000 000 IU, Powder for solution for injection

BENPEN 5 MU, 5 000 000 IU, Powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each BENPEN 1 MU vial contains benzylpenicillin sodium equivalent to benzylpenicillin 1 000 000 IU

Each BENPEN 5 MU vial contains benzylpenicillin sodium equivalent to benzylpenicillin 5 000 000 IU

Sugar free

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for injection.

A white or almost white, crystalline powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment:

- Infections caused by benzylpenicillin sensitive microorganisms when rapid and high penicillinemia is

required.

Therapy should be guided by bacteriological studies (including sensitivity tests) and by clinical response.

Prophylactic use:

- Prevention of recurrence of rheumatic fever.
- Infective endocarditis in patients with valvular heart disease undergoing surgical procedures.

4.2 Posology and method of administration

Posology

Prophylaxis

Prevention of recurrence of rheumatic fever:

- 200 000 units intramuscularlry twice daily.

Patients with valvular heart disease undergoing surgery:

Adults:

- 2 million units intravenously or intramuscularly 30 to 60 minutes preoperatively and 1 million units six hours later.

Treatment

Adults:

500 000 – 20 million units daily preferably in divided doses.

Severe infections such as memingitis, endocarditis and peritonitis: 20 million units daily.

Paediatric population

Prophylaxis

Patients with valvular heart disease undergoing surgery:

- Children: 50 000 units per kg body mass 30 to 60 minutes preoperatively and 25 000 units per kg body mass six hours later.

Treatment

- Children: 10 000 – 50 000 units per kg body mass per 24-hour period, divided in 4 doses.

  Severe infections: 300 000 – 400 000 units/kg/day.

- Neonates: 50 000 units per kg body mass per day in divided doses.

  Severe infections: 50 000 – 200 000 units/kg/day.

In the treatment of beta-haemolytic streptococcal infections a therapeutic dose must be administered for at least 10 days.

Method of administration

Intramuscularly or intravenously.

Where doses of 2 million units or more are required, these should be administered by slow intravenous infusion at a rate of less than 500 000 units per minute, or by intermittent piggy-bag infusion.

See section 6.6 for dilution of BENPEN.

4.3 Contraindications

- Known allergy to penicillin or other beta-lactams such as cephalosporins. Cases of cross sensitivity have been reported.
- Babies born to allergic mothers in the neonatal period.

4.4 Special warnings and precautions for use

When administered to a patient with penicillin sensitivity, anaphylactic shock may occur. Adrenaline, corticosteroids and antihistamines should be used to treat anaphylaxis.

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

Use with caution in patients with known history of allergy.

Any patient with a history of allergy, especially to medicine, is more likely to develop a hypersensitivity reaction to penicillin. Patients should be observed for 30 minutes after administration and if an allergic reaction occurs the medicine should be withdrawn, and appropriate treatment given.

Skin sensitisation may occur in persons handling the antibiotic and care should be taken to avoid contact with the substance.

Care should be taken when high doses are given to patients with renal impairment (because of the risk of neurotoxicity) or congestive heart failure.

In the presence of impaired renal function, large doses of penicillin can cause cerebral irritation, convulsions and coma.

Renal and haematological systems should be monitored during prolonged and high dose therapy.

Care should be taken when treating patients with syphilis, as the Jarisch-Herxheimer reaction may occur shortly

after starting treatment. This reaction, manifesting as fever, chills, headache and reactions at the site of the lesion, can be dangerous in cardiovascular syphilis or where there is a serious risk of increased local damage such as with optic atrophy.

Intrathecal administration of penicillin's is not recommended because it is a potent convulsant when given by this route.

Disturbances of blood electrolytes may follow the administration of large doses.
High doses of BENPEN can cause hypokalaemia and sometimes hypernatremia. Use of a potassium-sparing diuretic may be helpful. In patients undergoing high-dose treatment for more than 5 days, electrolyte balance, blood counts and renal functions should be monitored.

Delayed absorption from the intramuscular depot may occur in diabetics.

Prolonged use of BENPEN may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for superinfections.

Pseudomembranous colitis should be considered in patients who develop severe and persistent diarrhoea during or after receiving BENPEN. In this situation, even if *Clostridium difficile* is only suspected, administration of BENPEN should be discontinued and appropriate treatment given.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalised exanthematous pustulosis (AGEP) have been reported in association with beta-lactam antibiotics (including penicillins) treatment.

BENPEN is contraindicated in patients who are hypersensitive to penicillins (see section 4.3). Patients who have a history of hypersensitivity to other beta-lactam antibacterials may also be hypersensitive to BENPEN. BENPEN should be used with caution in patients with a history of non-severe hypersensitivity reactions to any other beta-lactam antibiotics (e.g., carbapenems) and not at all in patients with history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with BENPEN, treatment with BENPEN should be discontinued and appropriate measures taken.

BENPEN contains sodium

Each 1 MU BENPEN vial contains 38,66 mg sodium (main component of cooking/table salt) in each 1 MU BENPEN vial. This is equivalent to 1,93 % of the recommended maximum daily dietary intake of sodium for an adult. 10 dosage units (6 g) reflects the lowest number of dosage units for which the threshold of 17 mmol (391 mg) of sodium is reached. This should be particularly taken into account for those on a low salt (sodium) diet.

Each 5 MU BENPEN vial contains 193,2 mg sodium (main component of cooking/table salt) in each 5 MU BENPEN vial. This is equivalent to 9,66 % of the recommended maximum daily dietary intake of sodium for an adult. 2 dosage units (6 g) reflects the lowest number of dosage units for which the threshold of 17 mmol (391 mg) of sodium is reached. This should be particularly taken into account for those on a low salt (sodium) diet.

4.5 Interaction with other medicines and other forms of interaction

There is reduced excretion of methotrexate (and therefore increased risk of methotrexate toxicity) when used with benzylpenicillin sodium as in BENPEN.

Probenecid inhibits tubular secretion of benzylpenicillin sodium as in BENPEN and so may be given to increase the plasma concentrations.

Penicillins as contained in BENPEN may interfere with:

- Urinary glucose test
- Coomb's tests
- Tests for urinary or serum proteins
- Tests which use bacteria e.g., Guthrie test.

4.6 Fertility, pregnancy and lactation

Fertility

No known data available.

Pregnancy

Benzylpenicillin sodium (e.g., BENPEN) has been taken by a large number of pregnant women and women of childbearing age without an increase in malformations or other direct or indirect harmful effects on the foetus having been observed.

Breastfeeding

Although it is not known if BENPEN may be excreted into the breast milk of nursing mothers, it is actively transported from the blood to milk in animals and trace amounts of other penicillins in human milk have been detected.

4.7 Effects on ability to drive and use machines

BENPEN has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

MedDRA	***Frequency***	**Undesirable Effects**

System Organ Class		
Infections and infestations	*Frequency unknown*	Superinfection by resistant species, such as *Pseudomonas* or *Candida*, which do not respond to penicillin therapy, may occur. A sore mouth or tongue and a black hairy tongue have been reported.
Blood and lymphatic system disorders	*Less frequent*	Granulocytopenia (neutropenia), agranulocytosis and leukopenia have been reported in patients receiving prolonged high doses of BENPEN (e.g., subacute bacterial endocarditis). Diarrhoea caused by *Clostridium difficile.*
	Frequency unknown	Anaemia, thrombocytopenia. Prolongation of bleeding time and defective platelet function have been observed usually following high intravenous doses.
Immune system disorders	*Frequent*	Patients undergoing treatment for syphilis or neurosyphilis with BENPEN may develop a Jarisch-Herxheimer reaction. Hypersensitivity to penicillin in the form of rashes (all types), fever, and serum sickness may occur.
	Less frequent	Anaphylactic reactions
	Frequency unknown	Angioedema, exfoliative dermatitis, vasculitis A generalised sensitivity reaction with urticaria, joint pains and eosinophilia can develop within a few hours to several weeks after starting treatment.

Nervous system disorders	*Less frequent*	Central nervous system toxicity, including convulsions, has been reported with large doses over 60 g per day and in patients with severe renal impairment.
	Frequency unknown	Metabolic encephalopathy
Cardiac disorders	*Frequency unknown*	Kounis syndrome
Gastrointestinal disorders	*Frequency unknown*	Diarrhoea, nausea, heartburn
Hepato-biliary disorders	*Frequency unknown*	Increases in liver enzyme values have been reported.
Skin and subcutaneous tissue disorders	*Frequency unknown*	Acute Generalised Exanthematous Pustulosis (AGEP), pruritus, maculo-papular rash, rash morbilliform, erythema. Severe Cutaneous Adverse Reactions SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms) have been reported with beta-lactam antibiotics, including penicillins (see section 4.4). Linear IgA disease.
Renal and urinary disorders	*Less frequent*	Interstitial nephritis has been reported after intravenous BENPEN at doses of more than 12 g per day.

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. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Treatment is symptomatic and supportive.

Excessive blood levels of BENPEN can be corrected by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Beta-lactamase sensitive penicillins. ATC code: J01CE01

Benzylpenicillin sodium is a beta-lactam antibiotic. It is bactericidal by inhibiting bacterial cell wall biosynthesis.

Benzylpenicillin is highly effective *in-vitro* against:

Many Gram+ and Gram- cocci, including non-penicillinase-producing gonococci and streptococci (not enterococci) as well most meningococci and pneumococci, *Treponema pallidum* and *Borrelia burgdorferi* (Lyme disease).

Other organisms sensitive to benzylpenicillin *in vitro* are:

The majority of *Corynebacterium diphtheria* and *Bacillus anthracis* strains. *Clostridia, Actinomyces israeli, Streptobacillus moniliformis, Pasteurella multocida* and *Listeria monocytogenes*. *Leptospira*. Many *E.coli* and *Proteus mirabilis* strains are susceptible to high concentrations.

The meningococcal carrier state is not eliminated.

In-Vitro sensitivity does not necessarily imply *in-vivo* efficacy.

5.2 Pharmacokinetic properties

Distribution

Benzylpenicillin is widely distributed throughout the body. Significant amounts appear in the liver, bile, semen, joint fluid, lymph and intestines.

Elimination

The half-life of benzylpenicillin is only 30 minutes. Administration of probenecid significantly increases half-life.

It becomes reversibly bound to plasma proteins and is normally rapidly eliminated from the body, mainly by the kidneys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer

than 24 hours at 2 °C to 8 °C.

6.4 Special precautions for storage

Store at or below 30 ºC (dry powder).

BENPEN should be used immediately after dilution with water for injection (see section 6.3).

For storage conditions after dilution of the BENPEN, see section 6.3.

6.5 Nature and contents of container

BENPEN 1 MU: 7 mL mould vial, closed with butyl rubber stoppers, flip-off cap and adhesive vials label.

Pack size: 50 vials/tray/box, 20 boxes per carton.

BENPEN 5 MU: 20 mL mould vial, closed with butyl rubber stoppers, flip-off cap and adhesive vials label.

Pack size: 50 vials/tray/box, 12 boxes per carton.

6.6 Special precautions for disposal and other handling

To be dissolved in water for injection.

Dilution Table 600 mg (1 MU) Vial – addition of sterile water

Concentration	**Amount of sterile water to add**
200 000 units per mL	4,6 mL
500 000 units per mL	3,6 mL
1 million units per 2 mL	1,6 mL
1 million units per 5 mL	4,6 mL

Dilution Table 3 g (5 MU) Vial – addition of sterile water

Concentration	**Amount of sterile water to add**
250 000 units per mL	17,8 mL
500 000 units per mL	7,8 mL
2 million units per 5 mL	10,4 mL
5 million units per 10 mL	7,8 mL

Any unused BENPEN or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ando Pharma (Pty) Ltd.

73 Keurboom Crescent

Plattekloof

Cape Town

7500

8. REGISTRATION NUMBER(S)

To be allocated by SAHPRA upon registration.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by SAHPRA upon registration.

10. DATE OF REVISION OF THE TEXT

To be allocated