AUSTRALIAN PRODUCT INFORMATION – BENPEN™ benzylpenicillin (as benzylpenicillin sodium), powder for injection

1 NAME OF THE MEDICINE

Benzylpenicillin (as benzylpenicillin sodium)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

BENPEN™ (benzylpenicillin sodium) is the sodium salt of (2*S*,5*R*,6*R*)-3,3-dimethyl-7-oxo-6-[(phenylacetyl) amino]-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

BENPEN™ contains no antiseptic or buffering agent nor are there any excipients. Each 600 mg dose of BENPEN™ contains 41.4 mg of sodium.

3 PHARMACEUTICAL FORM

BENPEN™ is a fine white to off-white homogenous powder, which is soluble in water. The injection is prepared by the addition of the appropriate volume of Water for Injections to give the desired concentration of benzylpenicillin.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the treatment of infections caused by benzylpenicillin sensitive organisms. These include *Streptococcus pyogenes* and most other Gram-positive organisms. It is also indicated for the treatment of syphilis. BENPEN™ may also be used for the prevention of bacterial endocarditis in dental and upper respiratory tract procedures and prevention of wound infections and sepsis in surgical procedures where Streptococci are the likely pathogens.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The initial dose of BENPEN™ should be sufficient to achieve a bactericidal concentration in the blood as rapidly as possible in order to prevent the emergence of resistant strains.

Precise dosage levels cannot be stated. The nature of the infection and the patients' response to therapy should determine the dose of BENPEN™ and its frequency of administration. Benzylpenicillin may be given by intramuscular or intravenous injection.

The minimum dosage should be:

Age	Minimum dose
Adults and Children > 10 years	300 mg 6 hourly
Children 3 - 10 years	150 to 300 mg 6 hourly
Children < 3 years	60 mg 6 hourly
Premature babies and neonates	30 to 60 mg 12 hourly

A reduced dosage is necessary in neonatal infants as the renal clearance of penicillin is less than that of older children.

For severe infections or where more resistant organisms are involved, the dose may be increased in amount and frequency of administration. For some severe infections, 4 to 24 g may need to be given daily.

Special dosage recommendations

Meningeal Infections

The initial dose of benzylpenicillin for children in the treatment of meningococcal meningitis is 600 mg followed by 300 mg intramuscularly every 4 to 6 hours; for pneumococcal meningitis at least 300 mg should be given every 4 hours for 14 days and then every 6 hours for 7 days.

Renal failure

In patients with severe renal damage up to 6 g daily should be well tolerated, but massive doses e.g. 20 g or more given intravenously may lead to convulsions and coma. If it is desired to give large doses to these patients, it is necessary to assess the daily maintenance dose of benzylpenicillin to achieve the desired serum-penicillin concentration. A suitable method of assessment is based on the endogenous creatine clearance as follows:

Clearance of benzylpenicillin (mL/min): = 35.5 + 3.35 x creatine clearance (mL/min).
The maintenance dose of benzylpenicillin (grams/24 hrs) = Clearance of benzylpenicillin (mL/min) x desired serum penicillin concentration (µg/mL) x 0.00138.

This is equally applicable to continuous and intermittent intravenous infusion.

Subacute bacterial endocarditis

Prolonged treatment is required with not less than 1.2 g daily in divided doses. Up to 24 g daily may be needed when the infecting organism is relatively resistant. Treatment must be continued for 4 to 6 weeks, e.g. patients with highly sensitive *Strep. viridans* or similar organisms should be given intravenous BENPEN™ for 4 to 6 weeks in doses of 6 to 12 g daily.

Antimicrobial Prophylaxis for Surgery

Where the likely pathogens are Streptococci, 600 mg BENPEN™ should be given intravenously immediately prior to surgery. For prolonged operations the same dose may be given 4 to 8 hourly for the duration of the procedure.

Clostridial infections

In conditions where infection with *Clostridium perfringens* is present, the dose of BENPEN™ should be 1.2 g given intravenously 6 hourly for 48 hours, in addition to standard surgical procedures.

Method of administration

BENPEN™ should be reconstituted with Water for Injections. To achieve a particular concentration, Water for Injections should be added to the vial according to **Table 1** below.

Table 1: Reconstitution Volumes

BENPEN™ Product Presentation Dose	**Volume (mL) of Water for Injections to be added to the vial for a concentration of:**		
	150 mg/mL	**200 mg/mL**	**300 mg/mL***
600 mg	3.6	2.6	1.6
1.2 g	7.2	5.2	3.2
3 g	-	13	8

***Please note** for intravenous use the recommended concentration is 600 mg in 10 mL or 60 mg/mL. To achieve this final concentration reconstitute the product to 300 mg/mL and then perform a further 1 in 5 dilution with Water for Injections.

When BENPEN™ is reconstituted with Water for Injections, it must be used immediately to reduce microbiological hazard. BENPEN™ is for one dose in one patient only. Discard any remaining contents.

Benzylpenicillin may be given by intramuscular or intravenous injection. The intravenous route is preferred in cases of shock as blood levels following intramuscular injection are unreliable in shocked patients.

Intramuscular Administration

For intramuscular administration, doses of 600 mg should be dissolved in 1.6 mL of Water for Injections and larger doses in the volume of Water for Injections indicated in **Table 1** above to give 300 mg per mL.

Intravenous Administration

Intravenous administration may be by intermittent injections or by injection into an infusion line. **It should not be added to an intravenous infusion bottle as benzylpenicillin is unstable at room temperature and may form highly allergenic derivatives.**

Reconstitute and dilute each 600 mg of BENPEN™ in a sufficient volume of Water for Injection to achieve a final concentration of 600 mg per 10 mL. This quantitative ratio produces an approximately isotonic solution with the recommended osmolarity for I.V. injection/infusion. Ringer's solution or other sodium containing solutions should not be used for reconstitution due to their additional electrolytic content.

Normal saline 0.9% and glucose 5% infusion line solutions have been shown to be compatible with reconstituted BENPEN™ product.

4.3 CONTRAINDICATIONS

History of hypersensitivity reactions to beta-lactam antibiotics.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious, and occasionally fatal, hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. Before commencing therapy with any beta-lactam antibiotic, careful enquires should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If a hypersensitivity reaction occurs, appropriate therapy should be instituted and BENPEN™ therapy discontinued.

Serious anaphylactoid reactions require emergency treatment with adrenaline. Oxygen, intravenous steroids and airway management including intubation, should also be administered as indicated.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including benzylpenicillin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases, appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil) may prolong and/or worsen the condition and should not be used.

Caution should be exercised in the treatment of patients with an allergic diathesis.

Disturbances of blood electrolytes may follow the administration of large doses of sodium salts of benzylpenicillin. Each 1 gram dose of BENPEN™ contains 3.0 mmol of sodium. In prolonged therapy with benzylpenicillin and particularly with high dosage schedules, periodic evaluation of the electrolyte balance, renal and haematopoietic systems is recommended.

Prolonged use of antibiotics may promote overgrowth of susceptible organisms including fungi. Should superinfection occur, appropriate measures should be taken.

When BENPEN™ is reconstituted with Water for Injections, it must be used immediately.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCAR), such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in patients taking beta-lactam antibiotics. When SCAR is suspected, benzylpenicillin should be discontinued immediately and an alternative treatment should be considered.

Use in the elderly

The renal elimination of penicillin is often reduced in elderly patients. If very high doses are required, the blood levels of penicillin should be monitored.

Paediatric use

See **4.2 DOSE AND METHOD OF ADMINISTRATION** for the recommended paediatric dosage.

Effects on Laboratory Tests

As administration of BENPEN™ will result in high benzylpenicillin concentrations in the urine, false positive reactions may be elicited when testing the urine for glucose with Clinitest, Benedict's solution or Fehling's solution. Tests based on enzymatic glucose oxidase reactions such as Testape or Clinistix should be used instead.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Probenecid decreases the renal tubular secretion of benzylpenicillin. Concurrent use with BENPEN™ may result in increased and prolonged blood levels of benzylpenicillin.

Intravenous solutions of benzylpenicillin are physically incompatible with many other substances including certain antihistamines, some other antibiotics, metaraminol tartrate, noradrenaline acid tartrate, thiopentone sodium and phenytoin sodium.

Tetracyclines, erythromycin and chloramphenicol antagonise the action of benzylpenicillin.

Gentamicin should not be mixed with benzylpenicillin when both drugs are given parenterally as inactivation occurs.

In common with other antibiotics, patients should be warned that benzylpenicillin may reduce the effectiveness of oral contraceptives.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy – Pregnancy Category A

Benzylpenicillin diffuses across the placenta into the foetal circulation. Animal studies with benzylpenicillin have shown no teratogenic effects. Benzylpenicillin has been in clinical use for over 50 years and the limited number of reported cases of use in human pregnancy have shown no evidence of untoward effect. The use of BENPEN™ in pregnancy should be reserved for cases considered essential by the clinician.

Use in lactation

Benzylpenicillin is excreted in breast milk. An alternative feeding method is recommended to avoid any possible sensitisation of the newborn.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of this medicine on person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

As with all penicillins, the possibility of hypersensitivity reactions must always be considered. Reactions are more likely to occur in those with an allergic diathesis. Anaphylactic shock is most likely to occur with injected penicillins (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

The following adverse reactions have been reported in association with the use of benzylpenicillin:

HYPERSENSITIVITY REACTIONS

Dermatological reactions are the most common hypersensitivity reactions, and include rash, pruritus, bullous eruptions and exfoliative dermatitis. Oedema and bronchospasm have also been reported, along with reports of anaphylactic shock, hypotension, syncope and other anaphylactoid reactions.

When benzylpenicillin is used in the treatment of syphilis, the Jarisch-Herzheimer reaction, consisting of malaise, fever, chills, sore throat, myalgia, headache and tachycardia may occur in 50% of those treated for syphilis. A similar reaction may occur following the treatment of leptospirosis with penicillin.

GASTROINTESTINAL

Gastrointestinal reactions to benzylpenicillin include abdominal pain, nausea, vomiting and diarrhoea. Pseudomembraneous colitis has been reported (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

HEPATIC

As with other beta-lactam antibiotics, hepatitis and cholestatic jaundice have been reported.

RENAL

Isolated cases of abnormal renal function have been reported.

HAEMATOLOGICAL

Reactions such as agranulocytosis, anaemia, neutropenia, eosinophilia and coagulation disorders have been reported.

CENTRAL NERVOUS SYSTEM
Adverse events have been reported. These include confusion, convulsions and encephalopathy. Encephalopathy can occur following doses of over 60 g I.V. (See **4.9 OVERDOSE**). As the blood brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower doses of penicillin in patients with meningitis.

OTHER
Fever has been reported following the use of benzylpenicillin; vaginal or oral moniliasis may follow the use of antibiotics.

INJECTION SITE
Pain may be experienced at the site of intramuscular injection and phlebitis at the site of intravenous injection.

Amongst the adverse events spontaneously reported to the Therapeutic Goods Administration (TGA), 69% were due to hypersensitivity and 75% of these were cutaneous reactions. Other reactions included gastrointestinal (12%), hepatic (7%), haematological (5%) and CNS (3%).

SKIN AND OTHER SUBCUTANEOUS TISSUE DISORDERS
Severe cutaneous adverse reactions (SCAR), including Stevens-Johnson syndrome (SIS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in beta-lactam antibiotics.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Encephalopathy can occur following doses of over 60 g I.V. and with lower doses in patients with renal impairment. As the blood brain barrier becomes more permeable in patients with meningitis, toxic symptoms may be precipitated by smaller doses of penicillin. This can result in drowsiness, hyper-reflexia, myoclonic twitches, convulsions and coma. Nephropathy has also been demonstrated in patients receiving 12 to 36 g of benzylpenicillin for several days.

There is no specific treatment for benzylpenicillin overdosage. Penicillin is removed by haemodialysis. Patients usually recover as the penicillin blood level decreases.

For information on the management of overdose, contact the Poisons Information Centre on 131 126 (Australia).

5 Pharmacological properties

5.1 Pharmacodynamic properties

Mechanism of action

BENPEN™ is bactericidal and is active against many Gram-positive organisms such as *Streptococcus pyogenes*. BENPEN™ is active against most Gram-positive bacilli and spirochaetes such as *Treponema pallidum*. Many strains of *Streptococcus pneumoniae* and *Strep. viridans* are also sensitive. BENPEN™ is active against most non-beta-lactamase producing Staphylococci and some Gram-negative cocci such as gonococci and meningococci. It acts by inhibiting cell wall synthesis. It is inactivated by bacterial beta-lactamases.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

An intramuscular injection of 600 mg of benzylpenicillin produces blood levels of 12 mg/L after 30 minutes. Effective concentrations last for 4-6 hours. When given intravenously, a blood level of 20 mg/L can be attained by the administration of 1.2 g of benzylpenicillin every 2 hours or 1.8 g 3 hourly.

In patients with impaired renal function, the benzylpenicllin serum half-life increases as renal function deteriorates, but the drug still disappears from the blood at a significant but reduced rate in anuric patients. Elderly subjects also have a diminished renal tubular secretory ability and are liable to benzylpenicillin neurotoxicity if large doses are given I.V.

If renal function is normal, over 70% of a dose of benzylpenicillin is excreted within 6 hours, 10% by glomerular filtration and the remainder by tubular secretion. Approximately 4.5% of a dose is excreted in the bile and the remainder (less than 30%) is inactivated in the liver with the formation of penicilloic acid. Up to 60% of a single intramuscular dose may appear in the urine within one hour and 95% within 4 hours. The renal tubular secretion of benzylpenicillin can be partly blocked by probenecid.

There is very poor penetration by benzylpenicillin into the cerebrospinal fluid through intact healthy meninges. Although benzylpenicillin is mainly excreted through the kidneys, effective elimination occurs in all but severe degrees of renal impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

6.2 INCOMPATIBILITIES

Refer to Section **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

The dry powder should be stored in a dry place, below 25°C and protected from light. After reconstitution, BENPEN™ injection should be used immediately. Any unused portion must be discarded.

6.5 NATURE AND CONTENTS OF CONTAINER

BENPEN™ powder for injection is available in vials containing 600 mg, 1.2 g and 3 g of benzylpenicillin (as benzylpenicillin sodium).

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

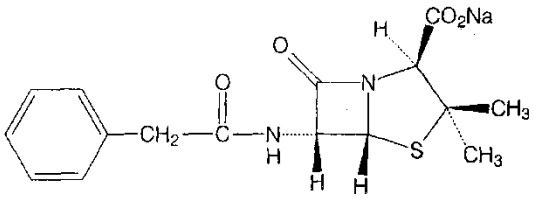
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements

6.7 PHYSICOCHEMICAL PROPERTIES

Benzylpenicillin sodium has a molecular weight of 356.4.

Chemical structure

Benzylpenicillin sodium has the following structure:



$C_{16}H_{17}N_2NaO_4S$

CAS number

69-57-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

04 November 1991

10 DATE OF REVISION

26 June 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
N/A	Product information reformatted as per the current TGA Form for Providing Product Information (March 2018).
4.4	Additional warning statement to include information regarding severe cutaneous adverse reactions (SCAR).
4.8	Additional warning statement to include information regarding severe cutaneous adverse reactions (SCAR). Change reference of ADRAC to the Therapeutic Goods Administration (TGA)
8	Inclusion of Australia to Sponsor Address

BENPEN™ is a trademark of CSL Limited.