

## BENPEN™

### Benzylpenicillin (as benzylpenicillin sodium) Powder for Injection

600mg

AUST R 10329

1.2g

AUST R 10326

3g

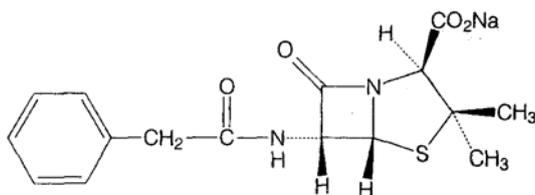
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## PRODUCT INFORMATION

### DESCRIPTION

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



Benzylpenicillin sodium has a molecular weight of 356.4 and a CAS registry number, 69-57-8.

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

### PHARMACOLOGY

#### Microbiology

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.

#### Pharmacokinetics

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

In patients with impaired renal function, the benzylpenicillin 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.

## 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.

## CONTRAINDICATIONS

History of hypersensitivity reactions to beta-lactam antibiotics.

## PRECAUTIONS

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, eg. 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 3.0mmol 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.

### Use in 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.

## Interactions with Other Drugs

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.

## 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.

## ADVERSE REACTIONS

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 **PRECAUTIONS**).

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. Pseudomembranous colitis has been reported (See **PRECAUTIONS**).

**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 60g IV (See **OVERDOSAGE**). 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 ADRAC, 69% were due to hypersensitivity and 75% of these were cutaneous reactions. Other reactions included gastrointestinal (12%), hepatic (7%), haematological (5%) and CNS (3%).

## **DOSAGE AND 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:

<b>Age</b>	<b>(Minimum dose)</b>
Adults and Children > 10 years	300 mg 6 hourly
Children 3 - 10 years	150 to 300mg 6 hourly
Children < 3 years	60mg 6 hourly
Premature babies and neonates	30 to 60mg 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 24g may need to be given daily.

### **Elderly patients**

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.

### ***Special dosage recommendations***

**Meningeal Infections:** The initial dose of benzylpenicillin for children in the treatment of meningococcal meningitis is 600mg followed by 300mg intramuscularly every 4 to 6 hours; for pneumococcal meningitis at least 300mg 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 6g daily should be well tolerated, but massive doses eg 20g 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): =  $35.5 + 3.35 \times \text{creatinine clearance (mL/min)}$ .

The maintenance dose of benzylpenicillin (grams/24 hrs) = Clearance of benzylpenicillin (mL/min) x desired serum penicillin concentration ( $\mu\text{g/mL}$ ) x 0.00138.

This is equally applicable to continuous and intermittent intravenous infusion.

**Subacute bacterial endocarditis:** Prolonged treatment is required with not less than 1.2g daily in divided doses. Up to 24g 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 12g daily.

**Antimicrobial Prophylaxis for Surgery:** Where the likely pathogens are Streptococci, 600mg 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 1.2g given intravenously 6 hourly for 48 hours, in addition to standard surgical procedures.

### **Administration**

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

**Table 1** Reconstitution Volumes

<b>BENPEN™ Product Presentation Dose</b>	<b>Volume (mL) of Water for Injection BP to be added to the vial for a concentration of:</b>		
	<b>150 mg/mL</b>	<b>200 mg/mL</b>	<b>300 mg/mL*</b>
<b>600 mg</b>	3.6	2.6	1.6
<b>1.2 g</b>	7.2	5.2	3.2
<b>3 g</b>	-	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 600mg 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 300mg 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 600mg of BENPEN™ in a sufficient volume of Water for Injection BP to achieve a final concentration of 600mg per 10 mL. This quantitative ratio produces an approximately isotonic solution with the recommended osmolarity for iv 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.

### **OVERDOSAGE**

Encephalopathy can occur following doses of over 60g IV 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 overdose. Penicillin is removed by haemodialysis. Patients usually recover as the penicillin blood level decreases.

Contact the Poisons Information Centre on 131 126 for further advice on overdose management.

## **PRESENTATION**

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

## **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.

## **SPONSOR**

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**Date of most recent amendment:** 01 December 2006

BENPEN™ is a trademark of CSL Limited.