BEPEN INJECTION
Benzylpenicillin for Injection BP

Product Name
BEPEN INJECTION 1.0 MU
BEPEN INJECTION 5.0 MU

Product Description
A white crystalline powder in glass vials. Pale yellow solution after reconstitution.

Composition
BEPEN INJECTION 1.0 MU
Each vial contains Benzylpenicillin Sodium BP 600 mg.

BEPEN INJECTION 5.0 MU
Each vial contains Benzylpenicillin Sodium BP 3 g.

Pharmacodynamics
General Properties:
Benzylpenicillin sodium BP is a beta-lactam antibiotic. It is bactericidal by inhibiting bacterial cell wall biosynthesis.

Breakpoints:
The tentative breakpoints (British Society for Antimicrobial Chemotherapy, BSAC) for Benzylpenicillin sodium BP are as follows:

Organism	Susceptibility ≤ (mg/L)	Intermediate susceptibility (mg/L)	Resistant ≥ (mg/L)
Streptococcus pneumoniae *Neisseria gonorrhoeae*	0.06	0.12 – 1.0	2.0
Neisseria meningitides	0.06		0.12
Haemolytic streptococci *Staphylococci* *Moraxella catarrhalis* *Haemophilus influenza*	0.12		0.25
Rapidly growing anaerobes	1.0		2.0

Susceptibility:
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. The following table gives only approximate guidance on probabilities whether microorganisms will be susceptible to Benzylpenicillin sodium BP or not.

Susceptible and intermediately susceptible microorganisms		
Type of Microorganism	**Microorganism**	**Range of acquired resistance**
Aerobic Gram-positive microorganism	*Bacillus anthracis*	0%**
	Cornybacterium diphtheriae	0%*
	Haemolytic streptococci (including *Streptococcus pyogenes*)	0%* - 3%**
	Listeria monocytogenes	0%**
	Streptococcus pneumoniae	4%* - 40%**
	Streptococcus viridans	3 – 32%*
Aerobic Gram-negative microorganisms	*Neisseria gonorrhoeae*	9 – 10%*
	Neisseria meningtidis	18%*
	Pasteurella multocida	0%***
Anaerobic microorganisms	*Actinomyces israelii*	8%**
	Fusobacterium nucleatum and	Usually sensitive

	Fusobacterium necrophorum	
	Gram-positive sporing bacilli (including *Clostridium tetani* and *Clostridium perfringens [welchii*])	14%**
	Gram-positive cocci (including peptostreptococcus)	7%*
Other microorganism	*Borrelia bugdorferi*	Usually sensitive
	Capnocytophaga canimorosus	Usually sensitive
	Leptospirae	Usually sensitive
	Streptobacillus moniliformis and *Spirillum minus*	Usually sensitive
	Treponema pallidum	0%**

* UK data; ** European data, ***Global data

Insusceptible microorganisms		
Type of Microorganism	**Microorganism**	**Range of acquired resistance**
Aerobic Gram-positive microorganism	Coagulase negative Staphylococcus	71 – 81%*
	Enterococcus Spp	Resistant
	Staphylococcus aureus	79 – 87%*
Aerobic Gram-negative microorganisms	*Acinetobacter*	Resistant
	Bordetella pertussis	Generally resistant
	Brucella spp.	Resistant
	Enterobacteriaceae (including *Escherichia coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter*)	Generally resistant
	Haemophilus influenza	Resistant
	Pseudomonas	Resistant
Anaerobic microorganisms	*Bacteroides fragilis*	100%***

* UK data; ** European data, ***Global data

Other Information:
Known Resistance Mechanisms and Cross-resistance
Penicillin resistance can be mediated by alteration of penicillin binding proteins or development of beta-lactamases.

Resistance to penicillin may be associated with cross-resistance to a variety of other beta lactam antibiotics either due to a shared target site that is altered, or due to a beta-lactamase with a broad range of substrate molecules. In addition to this, cross resistance to unrelated antibiotics can develop due to more than one resistance gene being present on a mobile section of DNA (e.g. plasmid, transposon etc) resulting in two or more resistance mechanisms being transferred to a new organism at the same time.

Pharmacokinetics
Benzylpenicillin sodium BP rapidly appears in the blood following intramuscular injection of water-soluble salts and maximum concentrations are usually reached in 15-30 minutes. Peak plasma concentrations of about 12 mcg/mL have been reported after doses of 600 mg with therapeutic plasma concentrations for most susceptible organisms detectable for about 5 hours. Approximately 60% of the dose injected is reversibly bound to plasma protein.

In adults with normal renal function the plasma half-life is about 30 minutes. Most of the dose (60-90%) undergoes renal elimination, 10% by glomerular filtration and 90% by tubular secretion. Tubular secretion is inhibited by probenecid, which is sometimes given to increase plasma penicillin concentrations. Biliary elimination of Benzylpenicillin sodium BP accounts for only a minor fraction of the dose.

Indication
Benzylpenicillin is indicated for most wound infections, pyogenic infections of the skin, soft tissue infections and infections of the respiratory tract.
It is also indicated for the following infections caused by penicillin-sensitive microorganisms:
Generalised infections and septicaemia from susceptible bacteria.

Acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms.
Tetanus, actinomycosis, anthrax, rat-bite fever, listeriosis and severe Lyme disease.
Complications secondary to gonorrhoea and syphilis (e.g. gonococcal arthritis or endocarditis, congenital syphilis and neurosyphilis).
Diphtheria, brain abscesses and pasteurellosis.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.

Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Recommended Dosage

Route of administration:
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.

Preparation of solution:
Pharmaceutical preparation
BEPEN Injection 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 the Table below.

BEPEN product presentation dose	**Volume (mL) of Water for Injections BP 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 – 2.0
3 g	-	13	8.0 – 10.0

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

Intramuscular Injection:
600 mg vial:
Dissolve 600 mg (1 mega unit) in 1.6 to 2.0 mL of Water for Injections BP.

3g vial:
Dissolve 3g (5 mega unit) in 8.0 to 10.0 mL of Water for Injections BP as indicated in the above Table to give 300 mg/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 BEPEN 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.

Sodium overload and/or heart failure may occur if benzylpenicillin sodium is administered in sodium-containing solvents to patients who suffer from renal failure and/or heart failure. Therefore, for such patients, benzylpenicillin

sodium should not be reconstituted in sodium-containing liquids such as Sodium Chloride Injection BP or Ringer's solution due to their additional electrolytic content.

Dosage and administration:

Adults

600 to 3,600 mg (1 to 6 mega units) daily, divided into 4 to 6 doses, depending on the indication. Higher doses (up to 14.4 g/day (24 mega units) in divided doses) may be given in serious infections such as adult meningitis by the intravenous route.

In bacterial endocarditis, 7.2 to 12 g (12 to 20 mega units) or more may be given daily in divided doses by the intravenous route, often by infusion.

High doses should be administered by intravenous injection or infusion, with intravenous doses in excess of 1.2g (2 mega units) being given slowly, taking at least one minute for each 300 mg (0.5 mega unit) to avoid high levels causing irritation of the central nervous system and/or electrolyte imbalance.

High dosage of Benzylpenicillin sodium BP may result in hypernatraemia and hypokalaemia unless the sodium content is taken into account.

Children aged 1 month to 12 years

100 mg/kg/day in 4 divided doses; not exceeding 4 g/day.

Infants 1-4 weeks

75 mg/kg/day in 3 divided doses.

Newborn Infants

50 mg/kg/day in 2 divided doses.

Meningococcal disease

Children 1 month to 12 years: 180-300 mg/kg/day in 4-6 divided doses, not exceeding 12 g/day.
Infants 1-4 weeks: 150 mg/kg/day in 3 divided doses.
Newborn infants: 100 mg/kg/day in 2 divided doses.
Adults and children over 12 years: 2.4 g every 4 hours

Premature babies and neonates

Dosing should not be more frequent than every 8 or 12 hours in this age group, since renal clearance is reduced at this age and the mean half-life of Benzylpenicillin may be as long as 3 hours.
Since infants have been found to develop severe local reactions to intramuscular injections, intravenous treatment should preferably be used.

Patients with renal insufficiency

For doses of 0.6-1.2 g (1-2 mega units) the dosing interval should be no more frequent than every 8-10 hours.
For high doses e.g. 14.4 g (24 mega units) required for the treatment of serious infections such as meningitis, the dosage and dose interval of Benzylpenicillin sodium BP should be adjusted in accordance with the following schedule:

Creatinine clearance (mL per minute)	**Dose (g)**	**Dose (mega units)**	**Dosing interval (hours)**
125	1.2 or 1.8	2 or 3	2 3
60	1.2	2	4
40	0.9	1.5	4
20	0.6	1.0	4
10	0.6	1.0	6
Nil	0.3 or 0.6	0.5 or 1.0	6 8

The dose in the above table should be further reduced to 300 mg (0.5 mega units) 8 hourly if advanced liver disease is associated with severe renal failure.
If haemodialysis is required, an additional dose of 300 mg (0.5 mega units) should be given 6 hourly during the procedure.

Elderly patients
Elimination may be delayed in elderly patients and dose reduction may be necessary.

Incompatibility
Benzylpenicillin sodium BP and solutions that contain metal ions should be administered separately.

Benzylpenicillin sodium should not be administered in the same syringe / giving set as amphotericin B, cimetidine, cytarabine, flucloxacillin, hydroxyzine, methylprednisolone, or promethazine since it is incompatible with these drugs.

Contraindication
Benzylpenicillin is contraindicated in individuals with a history of allergy to penicillins.
Hypersensitivity to any ingredient of the preparation.
Cross allergy to other beta-lactams such as cephalosporins should be taken into account.

Warnings and Precautions
BEPEN 1.0 MU INJECTION contains 41.6 mg of sodium/vial
BEPEN 5.0 MU INJECTION contains 208 mg of sodium/vial

Massive doses of Benzylpenicillin Sodium BP 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.

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

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

It should be recognized that any patient with a history of allergy, especially to drugs, 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 drug should be withdrawn and appropriate treatment given.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with BEPEN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillin, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, BEPEN must be discontinued immediately and appropriate alternative therapy instituted.

Delayed absorption from the intramuscular depot may occur in diabetics.
Prolonged use of Benzylpenicillin may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for super infections.

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

Interactions with Other Medicaments
The efficacy of oral contraceptives may be impaired under concomitant administration of Benzylpenicillin sodium BP, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.

There is reduced excretion of methotrexate (and therefore increased risk of methotrexate toxicity) when used with Benzylpenicillin sodium BP.

Probenecid inhibits tubular secretion of Benzylpenicillin sodium BP and so may be given to increase the plasma concentrations.

Penicillins may interfere with:
• Urinary glucose tests
• Coomb's tests
• Tests for urinary or serum proteins
• Tests which use bacteria e.g. Guthrie test

Pregnancy and Lactation
Benzylpenicillin sodium BP 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.

Although it is not known if Benzylpenicillin sodium BP 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.

Side Effects
Blood and Lymphatic System Disorders
Rare (0.01% - 0.1%)
Haemolytic anaemia and granulocytopenia (neutropenia), agranulocytosis, leucopenia and thrombocytopenia, have been reported in patients receiving prolonged high doses of benzylpenicillin sodium BP (eg. Subacute bacterial endocarditis).

Immune System Disorders
Very Common >10%)
Patients undergoing treatment for syphilis or neurosyphilis with Benzylpenicillin may develop a Jarisch-Herxheimer reaction.

Common (1-10%)
Hypersensitivity to penicillin in the form of rashes (all types), fever, and serum sickness may occur (1-10% treated patients). These may be treated with antihistamine drugs.

Rare (0.01%-0.1%)
More rarely, anaphylactic reactions have been reported (<0.05% treated patients).

Nervous System Disorders
Rare (0.01%-0.1%)
Central nervous system toxicity, including convulsions, has been reported with massive doses over 60 g per day and in patients with severe renal impairment.

Renal and Urinary Disorders
Rare (0.01%-0.1%)
Interstitial nephritis has been reported after intravenous Benzylpenicillin sodium BP at doses of more than 12 g per day.

Symptoms and Treatment ofOverdose
Symptoms of overdosage includes convulsion and neurological adverse reactions. In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. In patients with renal function impairment, ampicillin-class antibiotics can be removed by haemodialysis but not by peritoneal dialysis.

Presentation
One folded paper box contains 10 vials or 50 vials.

Storage Condition
Store below 30°C.

Shelf Life
Unopened vials: 36 months from the date of manufacture if kept as recommended.
Reconstituted solution: Freshly prepared solutions should be used immediately.

Registration number
BEPEN INJECTION 1.0 MU- MAL07031151AZ
BEPEN INJECTION 1.0 MU- BRU22023178P
BEPEN INJECTION 5.0 MU- MAL07031152AZ
Name and Address of Manufacturer
KARNATAKA ANTIBIOTICS & PHARMACEUTICALS LIMITED
Plot No. 14, II Phase, Peenya Industrial Area,
Bengaluru – 560058, INDIA
Tel: 091 (080) 28395 186/187/188
Fax: 091 (080) 28392606/28396475

Product Registration Holder
Averroes Pharmaceutical Sdn. Bhd.
03-08-01 & 03-09-01, Block 3, Presint Alami
Worldwide Business Center II
Persiaran Akuatik, Seksyen 13
40100 Shah Alam, Selangor
Malaysia
Tel: +603 5511 1433
Fax: +603 5511 1431

Date of revision of package insert
25th January 2024

BEPEN INJECTION 1.0 MU & 5.0 MU - Malaysia Pack Insert
Open Length 340 (L) x 240(H) mm
57 GSM White Print Paper, Colour Black
Ref. specification No.FD/LT/3OT9306/003/0124

Prepared by	Checked by	Reviewed by		Approved by
AM (RNG)	E / IC - Production	E / IC - FD	DGM (RPS)	AGM (NCM)

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Penicillins may interfere with:
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Although it is not known if Benzylpenicillin sodium BP 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.

Side Effects
Blood and Lymphatic System Disorders
Rare (0.01% - 0.1%)
Hemolytic anaemia and granulocytopenia (neutropenia), agranulocytosis, leucopenia and thrombocytopenia, have been reported in patients receiving prolonged high doses of benzylpenicillin sodium BP (eg. Subacute bacterial endocarditis).

Immune System Disorders
Very Common >10%)
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Common (1-10%)
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Rare (0.01%-0.1%)
More rarely, anaphylactic reactions have been reported (<0.05% treated patients).

Nervous System Disorders
Rare (0.01%-0.1%)
Central nervous system toxicity, including convulsions, has been reported with massive doses over 60 g per day and in patients with severe renal impairment.

Renal and Urinary Disorders
Rare (0.01%-0.1%)
Interstitial nephritis has been reported after intravenous Benzylpenicillin sodium BP at doses of more than 12 g per day.

Symptoms and Treatment of Overdose
Symptoms of overdosage includes convulsion and neurological adverse reactions. In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. In patients with renal function impairment, ampicillin-class antibiotics can be removed by hemodialysis but not by peritoneal dialysis.

Presentation
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Store below 30°C.

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Unopened vials: 36 months from the date of manufacture if kept as recommended.
Reconstituted solution: Freshly prepared solutions should be used immediately.

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BEPEN INJECTION 5.0 MU

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Composition
BEPEN INJECTION 1.0 MU
Each vial contains Benzylpenicillin Sodium BP 600 mg.

BEPEN INJECTION 5.0 MU
Each vial contains Benzylpenicillin Sodium BP 3 g.

Pharmacodynamics
General Properties:
Benzylpenicillin sodium BP is a beta-lactam antibiotic. It is bacteriocidal by inhibiting bacterial cell wall biosynthesis.

Breakpoints:
The tentative breakpoints (British Society for Antimicrobial Chemotherapy, BSAC) for Benzylpenicillin sodium BP are as follows:

Organism	Susceptibility < (mg/L)	Intermediate susceptibility (mg/L)	Resistant ≥ (mg/L)
Streptococcus pneumoniae Neisseria gonorrhoeae	0.06	0.12 – 1.0	2.0
Neisseria meningitides	0.06		0.12
Haemolytic streptococci *Staphylococci Moraxella catarrhalis Haemophilus influenza*	0.12		0.25
Rapidly growing anaerobes	1.0		2.0

Susceptibility:
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. The following table gives only approximate guidance on probabilities whether microorganisms will be susceptible to Benzylpenicillin sodium BP or not.

Susceptible and intermediately susceptible microorganisms

Type of Microorganism	Microorganism	Range of acquired resistance
Aerobic Gram-positive microorganism	*Bacillus anthracis*	0%**
	Cornybacterium diphtheriae	0%*
	Haemolytic streptococci (including *Streptococcus pyogenes*)	0%* - 3%**
	Listeria monocytogenes	0%**
	Streptococcus pneumoniae	4%* - 40%**
	Streptococcus viridans	3 – 32%*
Aerobic Gram-negative microorganisms	*Neisseria gonorrhoeae*	9 – 10%*
	Neisseria meningtidis	18%*
	Pasteurella multocida	0%***
Anaerobic microorganisms	*Actinomyces israelii*	8%**
	Fusobacterium nucleatum and *Fusobacterium necrophorum*	Usually sensitive
	Gram-positive sporing bacilli (including Clostridium tetani and Clostridium perfringens [welchii])	14%**
	Gram-positive cocci (including peptostreptococcus)	7%*
Other microorganism	*Borrelia bugdorferi*	Usually sensitive
	Capnocytophaga canimorsus	Usually sensitive
	Leptospirae	Usually sensitive
	Streptobacillus moniliformis and *Spirillum minus*	Usually sensitive
	Treponema pallidum	0%**

* UK data; ** European data, ***Global data

Insusceptible microorganisms

Type of Microorganism	Microorganism	Range of acquired resistance
Aerobic Gram-positive microorganism	Coagulase negative Staphylococcus	71 – 81%*
	Enterococcus Spp	Resistant
	Staphylococcus aureus	79 – 87%*
Aerobic Gram-negative microorganisms	*Acinetobacter*	Resistant
	Bordetella pertussis	Generally resistant
	Brucella spp.	Resistant
	Enterobacteriaceae (including *Escherichia coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter*)	Generally resistant
	Haemophilus influenza	Resistant
	Pseudomonas	Resistant
Anaerobic microorganisms	*Bacteroides fragilis*	100%***

* UK data; ** European data, ***Global data

Other Information:
Known Resistance Mechanisms and Cross-resistance
Penicillin resistance can be mediated by alteration of penicillin binding proteins or development of beta-lactamases.

Resistance to penicillin may be associated with cross-resistance to a variety of other beta lactam antibiotics either due to a shared target site that is altered, or due to a beta-lactamase with a broad range of substrate molecules. In addition to this, cross resistance to unrelated antibiotics can develop due to more than one resistance gene being present on a mobile section of DNA (e.g. plasmid, transposon etc) resulting in two or more resistance mechanisms being transferred to a new organism at the same time.

Pharmacokinetics
Benzylpenicillin sodium BP rapidly appears in the blood following intramuscular injection of water-soluble salts and maximum concentrations are usually reached in 15-30 minutes. Peak plasma concentrations of about 12 mcg/mL have been reported after doses of 600 mg with therapeutic plasma concentrations for most susceptible organisms detectable for about 5 hours. Approximately 60% of the dose injected is reversibly bound to plasma protein.

In adults with normal renal function the plasma half-life is about 30 minutes. Most of the dose (60-90%) undergoes renal elimination, 10% by glomerular filtration and 90% by tubular secretion. Tubular secretion is inhibited by probenecid, which is sometimes given to increase plasma penicillin concentrations. Biliary elimination of Benzylpenicillin sodium BP accounts for only a minor fraction of the dose.

Indication
Benzylpenicillin is indicated for most wound infections, pyogenic infections of the skin, soft tissue infections and infections of the respiratory tract.
It is also indicated for the following infections caused by penicillin-sensitive microorganisms:

- Generalized infections and septicaemia from susceptible bacteria.
- Acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms.
- Tetanus, actinomycosis, anthrax, rat-bite fever, listeriosis and severe Lyme disease.
- Complications secondary to gonorrhoea and syphilis (e.g. gonococcal arthritis or endocarditis, congenital syphilis and neurosyphilis).
- Diphtheria, brain abscesses and pasteurellosis.

Consideration should be given to official local guidance (e.g. national recommendations) on the appropriate use of antibacterial agents.
Susceptibility of the causative organism to the treatment should be tested (if possible), although therapy may be initiated before the results are available.

Recommended Dosage

Route of administration:
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.

Preparation of solution:
Pharmaceutical preparation
BEPEN Injection 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 the Table below.

BEPEN product presentation dose	Volume (mL) of Water for Injections BP 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 – 2.0
3 g	-	13	8.0 – 10.0

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

Intramuscular Injection:
600 mg vial:
Dissolve 600 mg (1 mega unit) in 1.6 to 2.0 mL of Water for Injections BP.

3g vial:
Dissolve 3g (5 mega unit) in 8.0 to 10.0 mL of Water for Injections BP as indicated in the above Table to give 300 mg/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 BEPEN 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.

Sodium overload and/or heart failure may occur if benzylpenicillin sodium is administered in sodium-containing solvents to patients who suffer from renal failure and/or heart failure. Therefore, for such patients, benzylpenicillin sodium should not be reconstituted in sodium-containing liquids such as Sodium Chloride Injection BP or Ringer's solution due to their additional electrolytic content.

Dosage and administration:
Adults
600 to 3,600 mg (1 to 6 mega units) daily, divided into 4 to 6 doses, depending on the indication. Higher doses (up to 14.4 g/day (24 mega units) in divided doses) may be given in serious infections such as adult meningitis by the intravenous route.

In bacterial endocarditis, 7.2 to 12 g (12 to 20 mega units) or more may be given daily in divided doses by the intravenous route, often by infusion.

High doses should be administered by intravenous injection or infusion, with intravenous doses in excess of 1.2g (2 mega units) being given slowly, taking at least one minute for each 300 mg (0.5 mega unit) to avoid high levels causing irritation of the central nervous system and/or electrolyte imbalance.

High dosage of Benzylpenicillin sodium BP may result in hypernatremia and hypokalemia unless the sodium content is taken into account.

Children aged 1 month to 12 years
100 mg/kg/day in 4 divided doses; not exceeding 4 g/day.

Infants 1-4 weeks
75 mg/kg/day in 3 divided doses.

Newborn Infants
50 mg/kg/day in 2 divided doses.

Meningococcal disease
Children 1 month to 12 years: 180-300 mg/kg/day in 4-6 divided doses, not exceeding 12 g/day.
Infants 1-4 weeks: 150 mg/kg/day in 3 divided doses.
Newborn infants: 100 mg/kg/day in 2 divided doses.
Adults and children over 12 years: 2.4 g every 4 hours

Premature babies and neonates
Dosing should not be more frequent than every 8 or 12 hours in this age group, since renal clearance is reduced at this age and the mean half-life of Benzylpenicillin may be as long as 3 hours.
Since infants have been found to develop severe local reactions to intramuscular injections, intravenous treatment should preferably be used.

Patients with renal insufficiency
For doses of 0.6-1.2 g (1-2 mega units) the dosing interval should be no more frequent than every 8-10 hours.
For high doses e.g. 14.4 g (24 mega units) required for the treatment of serious infections such as meningitis, the dosage and dose interval of Benzylpenicillin sodium BP should be adjusted in accordance with the following schedule:

Creatinine clearance (mL per minute)	Dose (g)	Dose (mega units)	Dosing interval (hours)
125	1.2 or 1.8	2 or 3	2 3
60	1.2	2	4
40	0.9	1.5	4
20	0.6	1.0	4
10	0.6	1.0	6
Nil	0.3 or 0.6	0.5 or 1.0	6 8

The dose in the above table should be further reduced to 300 mg (0.5 mega units) 8 hourly if advanced liver disease is associated with severe renal failure.
If haemodialysis is required, an additional dose of 300 mg (0.5 mega units) should be given 6 hourly during the procedure.

Elderly patients
Elimination may be delayed in elderly patients and dose reduction may be necessary.

Incompatibility
Benzylpenicillin sodium BP and solutions that contain metal ions should be administered separately.

Benzylpenicillin sodium should not be administered in the same syringe / giving set as amphotericin B, cimetidine, cytarabine, flucloxacillin, hydroxyzine, methylprednisolone, or promethazine since it is incompatible with these drugs.

Contraindication
Benzylpenicillin is contraindicated in individuals with a history of allergy to penicillins.
Hypersensitivity to any ingredient of the preparation.
Cross allergy to other beta-lactams such as cephalosporins should be taken into account.

Warnings and Precautions
BEPEN 1.0 MU INJECTION contains 41.6 mg of sodium/vial
BEPEN 5.0 MU INJECTION contains 208 mg of sodium/vial
Massive doses of Benzylpenicillin Sodium BP 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.

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

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

It should be recognized that any patient with a history of allergy, especially to drugs, 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 drug should be withdrawn and appropriate treatment given.

Serious and occasionally fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions) have been reported in patients receiving therapy with beta-lactams. Before initiating therapy with BEPEN, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, carbapenems or other beta-lactam agents. If an allergic reaction occurs, BEPEN must be discontinued immediately and appropriate alternative therapy instituted.

Delayed absorption from the intramuscular depot may occur in diabetics.
Prolonged use of Benzylpenicillin may occasionally result in an overgrowth of non-susceptible organisms or yeast and patients should be observed carefully for super infections.

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

Interactions with Other Medicaments
The efficacy of oral contraceptives may be impaired under concomitant administration of Benzylpenicillin sodium BP, which may result in unwanted pregnancy. Women taking oral contraceptives should be aware of this and should be informed about alternative methods of contraception.