1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal product

Benzylpenicillin sodium for injection 1mega

2. Qualitative and quantitative composition

Each vial contains Benzylpenicillin sodium 0.6g (1 000 000 I.U.)

3. Pharmaceutical form

Powder for injection

White crystalline, water-soluble sterile powder.

4. Clinical particulars

4.1 Therapeutic indications

Benzylpenicillin is indicated for most wound infections, pyogenic infections of the skin, soft tissue infections and infections of the nose, throat, nasal sinuses, respiratory tract and middle ear, etc.

It is also indicated for the following infections caused by penicillin-sensitive microorganisms: Generalised infections, septicaemia and pyaemia from susceptible bacteria. Acute and chronic osteomyelitis, sub-acute bacterial endocarditis and meningitis caused by susceptible organisms. Suspected meningococcal disease. Gas gangrene, tetanus, actinomycosis, anthrax, leptospirosis, rat-bite fever, listeriosis, severe Lyme disease, and prevention of neonatal group B streptococcal infections. 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

4.2 Posology and method of administration

Route of administration:

Intramuscular, intravenous.

Preparation of solutions:

Pharmaceutical preparation

Only freshly prepared solutions should be used. Reconstituted solutions of benzylpenicillin sodium are intended for immediate administration.

600 mg vial

Intramuscular injection: 600 mg (1 mega unit) is usually dissolved in 1.6 to 2.0 ml of Water for Injections BP.

600 mg

Intravenous Injection: A suitable concentration is 600 mg (1 mega unit) dissolved in 4 to 10 ml of Water for Injections BP or Sodium Chloride

Injection BP

Intravenous Infusion: It is recommended that 600 mg (1 mega unit) should be dissolved in at least 10 ml of Sodium Chloride Injection BP or Water for Injections BP

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.

Dosage and administration:

The following dosages apply to both intramuscular and intravenous injection.

Alternate sites should be used for repeated injections.

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.

Doses up to 43.2 g (72 mega units) per day may be necessary for patients with rapidly spreading gas gangrene.

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 may result in hypernatraemia and hypokalaemia unless the sodium content is taken into account.

For the prevention of Group B Streptococcal disease of the newborn, a 3 g (5 mega units) loading dose should be given to the mother initially, followed by 1.5 g (2.5 mega units) every 4 hours until delivery.

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

Suspected meningococcal disease

If meningococcal disease is suspected general practitioners should give a single dose of benzylpenicillin sodium, before transferring the patient to hospital, as follows:

Adults and children over 10 years:	1,200 mg IV (or IM)
Children 1-9 years:	600 mg IV (or IM)
Children under 1 year:	300 mg IV (or IM)

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 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.

4.3 Contraindications

Allergy to penicillins. Hypersensitivity to any ingredient of the preparation.

Cross allergy to other beta-lactams such as cephalosporins should be taken into account.

4.4 Special warnings and precautions for use

600 mg benzylpenicillin contains 1.68 mmol of sodium. Massive doses of Benzylpenicillin Sodium can cause hypokalaemia and sometimes hypernatraemia. 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 sensitisation may occur in persons handling the antibiotic and care should be taken to avoid contact with the substance.

It should be recognised 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.

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 superinfections.

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.

4.5 Interaction with other medicinal products and other forms of interaction

The efficacy of oral contraceptives may be impaired under concomitant administration of benzylpenicillin sodium, 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.

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

Penicillins 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

Benzylpenicillin sodium 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 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. It can be administered during breast feeding, nevertheless, breast feeding (or medicine) suspended in case of diarrhea, candidiasis and rash appear to the baby.

4.7 Effects on ability to drive and use machines

None

4.8 Undesirable 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 (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%-.01%)

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 at doses of more than 12 g per day.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 Overdose

Excessive blood levels of benzylpenicillin sodium can be corrected by haemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase sensitive penicillins.

ATC code: J01 CE01.

General Properties:

Benzylpenicillin sodium 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 are as follows:

Organism	S ≤ (mg/L)	I (mg/L)	R ≥ (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 influenzae	0.12		0.25
Rapidly growing anaerobes	1.0		2.0

S = Susceptible, I = Intermediate susceptibility, R = Resistant

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 or not.

Susceptible and intermediately susceptible microorganisms		
Type of Microorganism	Microorganism	Range of acquired resistance
Aerobic Gram-positive microorganisms	• Bacillus anthracis	0%**
	• Corynebacterium 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 meningitidis	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 microorganisms	• Borrelia bugdorferi	Usually sensitive
	• Capnocytophaga canimorosus	Usually sensitive
	• Leptospirae	Usually sensitive
	• Streptobacillus moniliformis and spirrillum 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	• Coagulase negative Staphylococcus	71-81%*

microorganisms		
	• 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 influenzae	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.

5.2 Pharmacokinetic properties

Benzylpenicillin sodium 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 accounts for only a minor fraction of the dose.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to the prescriber.

6. Pharmaceutical particulars

6.1 List of excipients

None.

6.2 Incompatibilities

Benzylpenicillin sodium 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.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products

6.3 Shelf life

Unopened 36 months.

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 to 8 ℃, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30 ℃.

6.5 Nature and contents of container

7ml USP type II glass, mould vial sealed with butyl rubber stopper and Flip off cap. This product is supplied in vials containing 600 mg of powder in boxes containing 10, 25, 50, and 100 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After contact with skin, wash immediately with water. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice if discomfort persists.

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

7. Marketing authorisation holder

DERM PHARMACEUTICAL LIMITED.

19, Alhaji Salami Street, Aguda Surulere, Lagos, Nigeria