# Benzylpenicillin sodium 1200mg Powder for Injection

Summary of Product Characteristics Updated 13-Sep-2021 | Genus Pharmaceuticals

## 1. Name of the medicinal product

Benzylpenicillin sodium 1200mg Powder for Injection

## 2. Qualitative and quantitative composition

Each vial contains Benzylpenicillin sodium 1200 mg

## 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.

1200 mg vials

*Intravenous Injection*: 1200 mg (2 mega units) dissolved in at least 8 ml of Sodium Chloride Injection BP or Water for Injections BP.

*Intravenous Infusion*: It is recommended that 1200 mg (2 mega units) should be dissolved in at least 20 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<br>or<br>1.8 | 2<br>or<br>3 | 2<br><br>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 | 0.5 | 6 |

| | | | |
|---|---|---|---|
| | or<br>0.6 | or<br>1.0 | 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**

1200 mg benzylpenicillin contains 77.4mg (3.36 mmol) of sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 3.86% of the recommended maximum daily dietary intake of sodium for an adult. 5 dosage units (6g) reflects the lowest number of dosage units for which the threshold of 17mmol (391mg) of sodium is reached. This should be particularly taken into account for those on a low salt (sodium) diet.

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.

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.

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

**4.5 Interaction with other medicinal products and other forms of interaction**

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.

**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%)*

Granulocytopenia (neutropenia), agranulocytosis and leucopenia have been reported in patients receiving prolonged high doses of benzylpenicillin sodium (eg. Subacute bacterial endocarditis). Diarrhoea caused by Clostridium difficile.

*Not known*

Anaemia, thrombocytopenia.

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).

*Not known*

Angioedema.

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.

*Not known*

Metabolic encephalopathy.

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.

Skin and subcutaneous tissue disorders

*Not known*

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, acute generalised exanthematous pustulosis) have been reported with beta-lactam antibiotics, including penicillins (see section 4.4).

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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

**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<br>Neisseria gonorrhoeae | 0.06 | 0.12-1.0 | 2.0 |
| Neisseria meningitides | 0.06 | | 0.12 |
| Haemolytic streptococci<br>Staphylococci<br>Moraxella catarrhalis<br>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 microorganisms | • 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 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 which are additional to that already included in other sections of the SmPC.

## 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°C, unless dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

Store below 25°C.

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

### 6.5 Nature and contents of container

Tubular type III glass vials sealed with bromobutyl rubber plugs with aluminium overseals or plastic 'flip-top' caps. This product is supplied in vials 1200 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

Genus Pharmaceuticals

Linthwaite

Huddersfield

HD7 5QH

UK

## 8. Marketing authorisation number(s)

PL 06831/0284

## 9. Date of first authorisation/renewal of the authorisation

08/09/2016

## 10. Date of revision of the text

10/09/2021

## Company Contact Details

Genus Pharmaceuticals

**Address**

Linthwaite, Huddersfield, West Yorkshire, HD7 5QH, UK

**Telephone**

+44 (0)1484842217

**Medical Information Direct Line**

**Fax**
+44 (0)1484847301

**Medical Information e-mail**
thorntonross@medinformation.co.uk

**Medical Information Fax**
+44 (0)1484 848164

**Customer Care direct line**
+44 (0)1484 848200

**Out of Hours Telephone**
+44 (0)1484 848164