

NEW ZEALAND DATA SHEET

PENICILLIN G SODIUM (BENZYL PENICILLIN SODIUM)

1. PRODUCT NAME

PENICILLIN G SODIUM INJECTION 1 million IU, 5 million IU and 10 million IU

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 million IU (equivalent to approximately 0.6 g benzylpenicillin sodium or Penicillin G Sodium),

5 million IU (equivalent to approximately 3 g benzylpenicillin sodium or Penicillin G Sodium)

10 million IU (equivalent to approximately 6 g benzylpenicillin sodium or Penicillin G Sodium).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Powder for injection.

Penicillin G Sodium injection is a white to whitish crystalline, water soluble powder aseptically filled into glass vials. Reconstitution yields a clear solution of Benzylpenicillin Injection BP.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Penicillin G Sodium is indicated in the following infections caused by penicillin-sensitive pathogens: septicaemia; skin and wound infections; diphtheria (in addition to antitoxin); pneumonia; empyema; erysipela; pericarditis; bacterial endocarditis; mediastinitis; peritonitis; meningitis; brain abscesses; arthritis; osteomyelitis; infections of the genital tract caused by fusobacteria. Sensitivity should be tested wherever possible.

Specific infections

Penicillin G Sodium is effective in infections such as anthrax, clostridial infections including tetanus, listeriosis, pasteurilosis, rat bite fever, fusospirochaetosis, actinomycosis. In addition, it has a place in the treatment of complications secondary to gonorrhoea and syphilis (e.g. gonorrhoeal endocarditis or arthritis, and congenital syphilis). If uncomplicated, gonorrhoea and syphilis should preferably be treated with long-acting penicillins.

Penicillin G Sodium is also beneficial in patients with Lyme borreliosis after the first stage of the disease (meningopolyneuritis Garin-Bujadoux-Bannwarth, acrodermatitis chronica atrophicans, Lyme arthritis, Lyme carditis), if oral penicillin is no longer indicated. During pregnancy parenteral Penicillin G Sodium at high doses is recommended after the first stage of Lyme disease to prevent diaplacental infections.

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

Penicillin G Sodium injection may be administered intravenously both by injection or short infusion and intramuscularly. In general, 30,000 IU/kg body weight daily, divided into 2 to 3 doses, are administered. In general, the following dosage schedule should be followed:

Average benzylpenicillin doses

Adults

High dose: 10 to 40 million IU daily IV

Normal dose: 1 to 5 million IU daily IM or IV

Infants

Body weight, up to 10 kg and children up to age 12 years.

High dose: 0.1 to 0.5 (to 1.0) million IU/kg daily IV

Normal dose: 0.03 to 0.1 million IU/kg daily IM or IV

Neonates and premature infants

Body weight approximately 3.5 kg.

High dose: 0.2 to 0.5 million IU/kg daily IV

Normal dose: 0.03 to 0.1 million IU/kg daily IM or IV

Special dosage recommendations

Sepsis

Sepsis induced by Gram-negative bacilli (*E. coli*, *E. aerogenes*, *A. faecalis*, salmonellae, shigellae and *P. mirabilis*): In the presence of sensitive organisms adults receive 20 to 80 million IU daily.

Bacterial endocarditis

Adults are given 10 to 80 million IU daily IV in combination with aminoglycosides.

Meningitis

To prevent convulsions and Jarisch-Herxheimer reactions, daily doses should not exceed 20 to 30 million IU in adults and 12 million IU in children. In extremely severe clinical conditions the first dose should be protracted, starting with 1 quarter of the individual single dose level, and administered slowly under careful observation of the patient.

Death cap (*Amanita phalloides*) poisoning

In general, 0.5 to 1.0 million IU/kg daily.

Lyme borreliosis

20 to 30 million IU daily IV in 2 to 3 doses for 14 days in adults and 0.5 million IU/kg IV in 2 to 3 doses for 14 days in children.

According to WHO recommendations, treatment of streptococcal infections should be continued for at least 10 days.

If necessitated by the patient's clinical condition, Penicillin G Sodium may also be administered by intrapleural instillation at a dose of up to 0.2 million IU (5,000 IU/ml), by intra-articular injection at a dose of up to 0.1 million IU (25,000 IU/ml) or by intrathecal instillation.

Intrathecal dosing rapidly produces reliable bactericidal CSF concentrations. Doses should not exceed 10,000 to 20,000 IU for adults, 8,000 IU for children between age 6 and 12 years, 5,000 IU for children between age 1 and 6 years and 2,500 IU for infants. After withdrawing a corresponding amount of CSF, the sterile solution (no more than 1,000 IU/ml) should be injected slowly (1 ml/min) at body temperature. Local dosing should invariably be adjuvant to systemic treatment. For intrathecal instillations the dosage level designed for systemic treatment (IV, IM) should be reduced accordingly.

Dosage guidelines for patients with renal insufficiency

In patients with severely reduced renal function, single doses and dosage intervals of Penicillin G Sodium should be adjusted to the clearance levels.

Adult daily doses of Penicillin G Sodium by creatinine clearances

Creatinine clearance 100 to 60 ml/min (serum creatinine 0.8 to 1.5 mg%): adults aged under 60 years 40 to 60 million IU; adults aged over 60 years 10 to 40 million IU. May be divided into 3 to 6 single doses.

Creatinine clearance 50 to 40 ml/min (serum creatinine 1.5 to 2.0 mg%): 10 to 20 million IU divided into 3 single doses.

Creatinine clearance 30 to 10 ml/min (serum creatinine 2 to 8 mg%): 5 to 10 million IU divided into 2 to 3 single doses.

Creatinine clearance <10 ml/min (serum creatinine 15 mg%): 2 to 5 million IU divided into 1 to 2 single doses.

In children with renal insufficiency the dose should be adjusted accordingly relative to the patient's body weight.

Extremely severe renal and hepatic functional impairment may delay penicillin metabolism and elimination. This should be remembered for dosing.

4.3. CONTRAINDICATIONS

History of penicillin hypersensitivity. Cross allergenicity to cephalosporins, with a reported incidence, of 5 to 10%, is possible, and should be considered when treating patients known to be hypersensitive to these medicines.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Warnings

1 million IU is approximately equivalent to 600 mg of Penicillin G Sodium and contains 1.68 mmol of sodium. 10 million IU correspond to the sodium load from 100 ml of isotonic saline solution. To prevent potential electrolyte imbalances IV infusions of more than 10 million IU should be administered slowly. This also applies to doses of more than 20 million IU to avoid potential convulsions (refer to Section 4.8 Undesirable effects).

A hypersensitivity test should be carried out before treatment. Patients should be alerted to the potential occurrence of allergic reactions and instructed to report them. They should be observed for 30 minutes after medicine administration and adrenaline or epinephrine should be made immediately available for injection. For serious anaphylactoid reactions, oxygen, intravenous steroids and airway management including intubation, should also be administered

as indicated. If allergic reactions occur, the medicine must be withdrawn and symptomatic treatment initiated, if necessary.

In diabetics delayed absorption from the IM depot should be kept in mind.

If high-dose penicillin treatment is continued for more than 5 days, electrolyte balance, blood counts and renal function should be monitored.

The potential overgrowth of resistant organisms should be considered during long-term treatment. Patients developing secondary infections should be treated accordingly.

As infants have been found to develop severe local reactions to intramuscular injections, treatment should preferably be intravenous.

In patients receiving very high intravenous doses (more than 10 million IU daily) injection sites should be alternated every 2 days to prevent superinfections and thrombophlebitis.

Local application of benzylpenicillin to the skin or mucous membranes or by aerosol is contraindicated.

For patients presenting sexually transmitted diseases who are suspected of having co-existent syphilis, dark-field examinations should be ordered prior to treatment and serologic tests should be obtained for at least 4 months thereafter. To suppress or mitigate Jarisch-Herxheimer reactions (refer to Section 4.8 Undesirable effects) prednisolone 50 mg, or an equivalent steroid may be administered at the time of the first antibiotic dose. In patients with cardiovascular or meningovascular syphilis Jarisch-Herxheimer reactions can be prevented by prednisolone, 50 mg daily, or an equivalent steroid, for 1 to 2 weeks.

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 may prolong and/or worsen the condition and should not be used.

Precautions

Particular caution should be exercised when treating patients with an allergic diathesis such as urticaria or hay fever or with bronchial asthma.

Caution is also necessary when treating newborns, patients with severe cardiopathies and other serious heart disease, hypovolaemia, epilepsy and renal or hepatic damage.

Caution is required when treating concurrent infections in patients presenting mononucleosis and acute lymphatic leukaemia due to the increased risk of skin reactions.

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

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 Section 4.2 Dose and method of administration for the recommended paediatric dosage.

Effects on laboratory tests

Benzylpenicillin can simulate falsely positive results in diagnostic urinary sugar tests.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Medicines and other pharmacologically active substances

As penicillins are only active against proliferating micro-organisms, Penicillin G Sodium should not be combined with bacteriostatic antibiotics. Combinations with other antibiotics should only be considered if their effects can be expected to be synergistic or at least additive. In general, each component in the combination should be given at the individually effective dose for monotherapy. However for combinations with proven synergistic action, the dose of the more toxic component in the combination may be reduced.)

If indicated, bactericidal antibiotic candidates for combination with Penicillin G Sodium include isoxazolyl penicillins such as flucloxacillin and other narrow-spectrum beta-lactam antibiotics, aminopenicillins, aminoglycosides. These should be administered by slow IV injection prior to Penicillin G Sodium infusions. Wherever possible, aminoglycosides should be administered separately by IM injection.

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.

Competitive inhibition of drug elimination rates should be considered whenever anti-inflammatories, anti-rheumatics, antipyretics (particularly indomethacin, phenylbutazone and salicylates in high doses) or probenecid are concomitantly used.

In common with other antibiotics, Penicillin G Sodium may occasionally reduce the efficacy of oral contraceptives.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data available.

Use in pregnancy

Category A

Although benzylpenicillin diffuses across the placenta, there is currently no evidence suggesting that penicillins, if administered during pregnancy, have an embryotoxic, teratogenic or mutagenic effect. 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.

Use in lactation

Residual benzylpenicillin may be present in breast milk at levels corresponding to approximately 0.8% of the maternal dose. Penicillins are considered to be compatible with breastfeeding although there are theoretical risks of alterations to infant bowel flora and allergic sensitisation.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of this medicine on a person's ability to drive and use machines were not assessed as part of its registration. This medicine is presumed to be safe or unlikely to produce an effect.

4.8. UNDESIRABLE EFFECTS

Undesirable effects are classified systematically and by frequency according to the following convention: very common (above 1 in 10); common (from 1 in 100 to 1 in 10); uncommon (from 1 in 1000 to 1 in 100); rare (from 1 in 10,000 to 1 in 1,000); very rare (below 1 in 10,000 including isolated reports).

Systemic adverse effects

Blood and lymphatic system disorders

Very rare

Eosinophilia, leucopenia, neutropenia, granulocytopenia, thrombocytopenia, agranulocytosis, pancytopenia. In addition, haemolytic anaemia, blood clotting disorders and a positive direct Coombs' test can occur.

Immune system disorders

Rare

Allergic reactions: urticaria, pruritus, bullous eruptions, angioneurotic oedema, erythema multiforme, exfoliative dermatitis, fever, joint pain, anaphylaxis, anaphylactic shock, hypotension, syncope or anaphylactoid reactions (asthma, bronchospasm, purpura, gastrointestinal symptoms).

Nervous system disorders

Rare

Patients receiving high doses by IV infusion (i.e. more than 20 million IU in adults) may become confused and convulsive, particularly in the presence of severely reduced renal function, epilepsy, meningitis or cerebral oedema or during cardiopulmonary bypass procedures. Encephalopathy can occur following high doses of benzylpenicillin. As the blood

brain barrier becomes more permeable in meningitis, toxic symptoms may be precipitated by lower doses of penicillin in patients with meningitis.

Metabolism and nutritional disorders

Rare

Electrolyte imbalance can occur on rapid infusion of more than 10 million IU.

Gastrointestinal disorders

Uncommon

Stomatitis, glossitis, lingua villosa nigra (black, hairy tongue), nausea, vomiting. If diarrhoea develops during treatment, the possibility of pseudomembranous colitis should be excluded (refer to Section 4.4 Special warnings and precautions for use).

Hepatobiliary disorders

Isolated cases

Hepatitis, cholestatic jaundice.

Renal and urinary disorders

Rare

Nephropathy has been reported to occur sporadically after IV doses of more than 10 million IU. Rarely patients with pre-existent kidney disease may develop albuminuria, cylindruria and haematuria. Oliguria and anuria occur rarely during high-dose penicillin therapy and usually disappear within 48 hours after discontinuing treatment. Diuresis can also be stimulated with 10% mannitol solution.

General disorders and administration site conditions

Rare

Severe local reactions on intramuscular administration to infants.

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

Patients receiving treatment for syphilis may show Jarisch-Herxheimer reactions secondary to bacteriolysis. These are characterised by fever, shivering, general and focal symptoms.

Skin and other subcutaneous tissue disorders

Severe cutaneous adverse reactions (SCAR), including 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 beta-lactam antibiotics.

Other adverse effects

There have been rare reports of paraesthesia following long term administration.

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. OVERDOSE

Signs and symptoms

An overdose of benzylpenicillin may decrease the seizure threshold. Overdosage by the intrathecal route can cause convulsions, paralysis and may be fatal.

Management

Initiate symptomatic treatment, if necessary. Excessive blood levels of benzylpenicillin can be corrected by haemodialysis. In the event of overdosage by the intrathecal route, CSF lavage to reduce the toxic concentration of benzylpenicillin may be considered

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group

J01CE01 - Beta-lactamase sensitive penicillins; benzylpenicillin.

Mechanism of action

Beta-lactam antibiotic.

Pharmacodynamic effects

Inhibition of bacterial cell wall synthesis.

Antibiotic class

Penicillin G Sodium is a water-soluble benzylpenicillin.

Antibiotic nature and mode of action

In adequate concentrations penicillin is bactericidal for susceptible, proliferating micro-organisms by inhibiting cell wall biosynthesis.

Susceptibility data

Using break points according to EUCAST, micro-organisms (staphylococci, streptococci, *M. catarrhalis*, *H. influenzae*) with a MIC of 0.12 mcg/ml and above are regarded as susceptible. Resistance increases as the MIC approaches 0.25 mcg/ml.

Susceptible

Actinomyces spp., *Arachnia propionica*, *Bacillus anthracis*, *Bifidiobacterium*, *Borrelia*, *Clostridium perfringens*, *Corynebacterium diptheriae*, *Erysipelothrix rhusiopathiae*, *Fusobacterium* spp., *Gaffkya anaerobius*, *Gardnerella vaginalis*, *Lactobacillus* spp., *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitides*, *Pasteurella multocida*,

Peptococcus spp., Peptostreptococcus spp., Propionibacterium spp., Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococci Group C and G, Viridans group streptococci, Treponema pallidum, Veillonella parvula.

Moderately susceptible

Staphylococcus aureus, Staphylococcus epidermidis, Leptospira spp., Enterococcus faecalis, Enterococcus faecium, Bacteroides melanogenicus, Eikenella corrodens, Actinobacillus actinomycetem-comitans.

Resistant

Bacteroides spp., Brucella, Chlamydia, Enterobacteriaceae (Enterobacter, E. coli, Klebsiella etc.), Haemophilus influenzae, Legionella, Mycoplasmas, Nocardia, Pseudomonas spp., Vibriones.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Benzylpenicillin is acid labile and can therefore only be given parenterally. The alkali salts of benzylpenicillin are rapidly and completely absorbed after IM injection. Peak plasma levels of 150 to 200 IU/ml are attained 15 to 30 minutes after IM injections of 10 million IU of Penicillin G Sodium. Following short infusions (30 minutes) levels may peak at up to 500 IU/ml.

Distribution

Even in poorly accessible tissues, e.g. cardiac valves, bone, CSF and empyema, etc., high dose penicillin therapy produces therapeutically active concentrations. It appears in pleural, pericardial, peritoneal, and synovial fluids but diffuses less readily into the eye and only to a small extent into abscess cavities and avascular areas. Inflamed tissue is more readily penetrated. Benzylpenicillin diffuses across the placenta into the foetal circulation at levels 10 to 30% of those found in maternal plasma. High concentrations are also attained in the amniotic fluid. Conversely, levels in breast milk are relatively low and very little passes into the CSF unless the meninges are inflamed. The volume of distribution is about 0.3 to 0.4 l/kg in adults and approaches 0.75 l/kg in children. Plasma protein binding is approximately 55%.

Elimination

In adults with normal kidney function plasma half-life is approximately 30 minutes. Most of the administered dose (50 to 80%) is eliminated along renal pathways in an unchanged form (85 to 95%). Tubular excretion is inhibited by probenecid which is sometimes given to increase plasma-penicillin concentrations. Biliary elimination of the active medicine accounts for only a minor fraction (about 5% of the dose).

Special patient considerations

Prematures and neonates

As kidney and liver functions are still immature in this age group, the plasma half-life can approach 3 hours or longer. Therefore, the dosage interval should not be less than 8 to 12 hours (depending on the degree of organ maturity).

Elderly patients

Elimination may also be delayed in patients of advanced age. Dosing should, therefore be guided by the kidney function. Penicillin G Sodium may be used alone or in combination with other antibiotics (for details, refer to Interactions). To extend the dosage intervals it may also be combined with depot preparations of penicillin.

Other

Absorption from the intramuscular depot is likely to be delayed in diabetics

5.3. PRECLINICAL SAFETY DATA

Carcinogenicity, mutagenicity and impairment of fertility

Reproduction studies in mice, rats and rabbits have not produced evidence of any negative effects on fertility or the foetus. Long-term pre-clinical studies to examine the carcinogenic or mutagenic potential or fertility impairment in laboratory animal models have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

None.

6.2. INCOMPATIBILITIES

Benzylpenicillin solutions are most stable in the pH range 6 to 7 and optimally at pH 6.8. To preclude undesirable chemical reactions, avoid mixed-content injections or infusions as well as solutions containing glucose or dextrose.

Penicillin G sodium is incompatible with metal ions, particularly those of copper, zinc, mercury and zinc compounds that may be present in the rubber stoppers of infusion bottles. Oxidising and reducing substances, alcohol, glycerol, macrogols and other hydroxylated compounds may also inactivate it. In slightly alkaline solutions benzylpenicillin is rapidly inactivated by cysteine and other aminothiols compounds.

Specifically, benzylpenicillin is incompatible in solution with the following substances: cimetidine; cytarabine; chlorpromazine hydrochloride; dopamine hydrochloride and other sympathomimetic amines; heparin; hydroxyzine hydrochloride; lactate; lincomycin hydrochloride; metaraminol; sodium hydrogen carbonate; oxytetracycline; pentobarbital; tetracycline hydrochloride; thiopental sodium; vancomycin. Benzylpenicillin is also incompatible with vitamin B complex and ascorbic acid in mixed solution.

6.3. SHELF LIFE

5 years

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials:

Store at or below 25°C.

If properly stored, non-reconstituted Penicillin G Sodium Injection retains its full potency to the date of expiry shown on the pack.

Reconstituted solution:

Freshly prepared solutions for injection or infusion should be used immediately, because even at refrigerator temperatures aqueous solutions of benzylpenicillin rapidly disintegrate to form degradation and conversion products.

6.5. NATURE AND CONTENTS OF CONTAINER

1 million IU (5 ml vials): packs of 10 and 100 vials.

5 million IU (15 ml vials): packs of single, 5 and 10 vials.

10 million IU (30 ml vials): packs of single, 5 and 10 vials.

Not all pack sizes and/or strengths may be currently marketed.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Reconstitution/Preparation Administration:

Preparation of solutions for IV injection or infusion

It is recommended that solutions for IV injection or infusion are prepared by reconstitution of the vial contents in water for injections at the ratio of 10 ml per one million IU. If this ratio is observed, an approximately isotonic solution is obtained. Ringer's or other sodium-containing solutions will increase the electrolyte concentration beyond physiological levels and are not recommended as diluents.

Notes on IM injections

Administer up to, but no more than 10 million IU (= approximately 6 g) of Penicillin G Sodium dissolved in 6 to 10 ml of water for injections up to twice daily by deep IM injection into the upper, outer quadrant of the buttock or Hochstetter's ventrogluteal field.

Up to 5 ml of injectable solution per injection site will be tolerated. Alternate injection sites for repeated injections. Higher doses may be administered by IV infusion.

To prevent hypersensitivity reactions caused by degradation products, solutions should be injected immediately after their preparation.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

1 million IU: 01 Jan 1962

5 million IU and 10 million IU: 18 Oct 2007

10. DATE OF REVISION OF THE TEXT

20 March 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Change in sponsor details