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.

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, pasteurellosis, 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).

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 adrenalin or epinephrine should be made immediately available for injection. 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-exsistent 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 Adverse effects) prednisolone 50 mg, or an equivalent steroid may be administered at the time of the first antibiotic dose. In patients with cardiovascular or meningo-vascular syphilis Jarisch-Herxheimer reactions can be prevented by prednisolone, 50 mg daily, or an equivalent steroid, for 1 to 2 weeks.

Persistent and severe diarrhoea should prompt suspicion of antibiotic-associated pseudomembranous colitis manifesting as blood-streaked, mucoid, watery diarrhoea; dull, diffuse to colicky abdominal pain, fever and occasionally also tenesmus. As this condition may be life-threatening, Penicillin G Sodium should be withdrawn immediately and treatment appropriate to the pathogen initiated. Drugs that inhibit peristalsis are contraindicated.

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.

4.5 Interation with other medicines and other forms of interaction

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.

Competitive inhibition of drug elimination rates should be considered whenever antiinflammatories, antirheumatics, 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.

Abnormal laboratory test results

Benzylpenicillin can simulate falsely positive results in diagnostic urinary sugar tests.
4.6 Fertility, pregnancy and lactation

Use in pregnancy

Assigned Category A by the Australian Drug Evaluation Committee. This category includes medicines which have been taken by a large number of pregnant women and women of childbearing age without any proven increase in the frequency of malformations or other direct or indirect harmful effects on the foetus having been observed. 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.

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

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, angioneurotic oedema, erythema multiforme, exfoliative dermatitis, fever, joint pain, anaphylaxis or anaphylactoid reactions (asthma, 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 convulsive, particularly in the presence of severely reduced renal function, epilepsy, meningitis or cerebral oedema or during cardiopulmonary bypass procedures.

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).

Hepatobiliary disorders

*Isolated cases*

Hepatitis, cholestasis.

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.

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

Other adverse effects

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

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.

Contact the Poisons Information Centre on (telephone 0800 POISON or 0800 764766) for advice on management of overdose.

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 microorganisms 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**


**Moderately susceptible**


**Resistant**

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

**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 aminothiol 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 handling, reconstitution and 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 Medicine.

8 SPONSOR

Novartis New Zealand Limited
PO Box 99102, Newmarket,
**NEW ZEALAND DATA SHEET**

Auckland 1149  
Telephone: 0800 354 335

**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**
08 Mar 2017

**SUMMARY TABLE OF CHANGES**

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<tr>
<th>Section changed</th>
<th>Summary of new information</th>
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<tr>
<td>All</td>
<td>Minor editorial changes in accordance to Medsafe new template for data sheet.</td>
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| 6.6             | Deleted redundant statement:  
*Displacement volume*  
*Penicillin G Sodium 1 million IU (600 mg) is packaged in a 5 ml vial Reconstitution with diluent displaces the expected volume by approximately 0.4 ml.* |