

# Penicillin G Sodium injection

***Benzylpenicillin Sodium Ph Eur, powder for injection, 1 million IU, 5 million IU and 10 million IU***

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## Presentation

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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.

The three presentations of Penicillin G Sodium injection are: a 5 ml vial containing 1 million IU (equivalent to approximately 0.6 g benzylpenicillin sodium or Penicillin G Sodium); a 15 ml vial containing 5 million IU (equivalent to approximately 3 g benzylpenicillin sodium or Penicillin G Sodium); a 30 ml vial containing 10 million IU (equivalent to approximately 6 g benzylpenicillin sodium or Penicillin G Sodium).

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## Uses

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### Actions

#### 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*, *Bifidobacterium*, *Borrelia*, *Clostridium perfringens*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, *Fusobacterium* spp., *Gaffkya anaerobius*, *Gardnerella vaginalis*, *Lactobacillus* spp., *Listeria monocytogenes*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *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*.

## **Pharmacokinetics**

### **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 groups**

#### *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.

## **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.

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## Dosage and administration

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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.

## **Administration**

### **Preparation of solutions for IV injection or infusion**

Reconstitute each 1 million IU (600 mg) of Penicillin G Sodium Injection in a sufficient volume of a suitable diluent to give a final concentration of 1 million IU per 10 ml (refer to [Pharmaceutical precautions](#)). This quantitative ratio produces an approximately isotonic solution with the recommended osmolarity for IV injection/infusion. To avoid electrolyte imbalances, do not use Ringer's lactate or other solutions containing sodium ions.

### **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.

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## Contraindications

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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.

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## Warnings and precautions

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### 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 Adverse 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 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-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 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 meningovascular 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.

### **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.

### **Effects on ability to drive and use machines**

This medicine is presumed to be safe or unlikely to produce an effect.

### **Other**

#### **Preclinical safety data**

##### *Carcinogenesis, mutagenesis, 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.

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## **Adverse effects**

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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 Warnings and precautions).

### **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.

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## **Interactions**

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### **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.

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## **Overdosage**

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### ***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.

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## **Pharmaceutical precautions**

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### ***Instructions for use/handling***

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

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.

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.

### ***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.

### ***Special precautions for storage***

Store at or below 25°C.

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## **Medicine classification**

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Prescription Medicine.

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## **Package quantities**

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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.

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## **Further information**

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### ***List of excipients***

Nil.

### ***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.

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## **Name and address**

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## **Date of preparation**

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14 December 2009