SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Benzylpenicillin sodium for injection 1 million IU

2. Qualitative and quantitative composition

Each vial contains Benzylpenicillin sodium equivalent to 1 million IU Benzylpenicillin (0.6g). Each 0.6g of Benzylpenicillin sodium contains approximately 1.7mmol sodium.

3. Pharmaceutical form

Powder for solution injection.

4. Clinical particulars

4.1 Therapeutic indications

Benzylpenicillin sodium is indicated in varies infections caused by penicillin - sensitive pathogens such as abscess, bacteremia, pneumonia and endocarditis etc. It is the first line drug to treat the following infections:

Pharyngitis, tonsillitis, scarlatina, erysipelas, cellulitis and puerperal fever that caused by hemolytic streptococcus.
Pneumonia, tympanitis, meningitis and bacteremia that caused by streptococcus pneumonia.
Infections caused by non-penicillinase-producing staphylococcus.
Anthrax.
Tetanus and gas gangrene that caused by clostridia.
Syphilis (including congenital syphilis).
Leptospirosis.
Relapsing fever.
Diphtheria.
It can combine with aminoglycoside antibiotics to treat endocarditis that caused by streptococcus viridans.

Benzylpenicillin sodium can also be used to treatment:

Epidemic cerebrospinal meningitis;
Actinomycosis;
Gonorrhoea;
Vincent’s angina;
Lyme disease;
Rat-bite fever;
Listeriosis;
Other infections that caused by anaerobic bacteria except for bacteroides fragilis.
Many anaerobic infections other than Bacteroides fragilis. Benzylpenicillin can be used to prevent infective endocarditis before oral, dental, gastrointestinal or genitourinary tract surgery and operations for patients with rheumatic heart disease or congenital heart disease.

4.2 Administration and dosages

Benzylpenicillin Sodium for Injection may be administered both by intramuscular injection (i.m.) and intravenous injection (i.v.).

For adults: 0.8 to 2 million IU daily i.m, dosing in 3~4 times; 2 to 20 million IU daily i.v., dosing in 2~4 times.

Pregnancy or nursing mother: Animal procreation trial indicates that damage to embryo after administered with the product has not been found. This product should be used in pregnant women only when it is indeed necessary since the potential damage to embryo has not been eliminated because of no strict controlled trial being carried out in pregnant women.

Little of the product is excreted from latex, therefore women in lactation should stop lactation when administered with the product.

Pediatric use: This test has not been performed and no reliable reference literature is available.

Geriatric use: This test has not been performed and no reliable reference literature is available.

For children: 25,000 IU/kg of body weight i.m, dosing once every 12 hours; 50,000~200,000 IU/kg of body weight daily i.v., dosing in 2~4 times.

Newborn babies (mature: 50,000 IU/kg of body weight once i.v. or i.m.; for babies in the first week of birth, dosing in once every 12 hours; for babies for those over a week, dosing in every 8 hours and once every 6 hours for severe infections.

Premature babies: 30,000 IU/kg of body weight once; for babies in the first week, dosing in once every 12 hours; for babies in 2~4 weeks, dosing in once every 8 hours and then once every 6 hours.

Patients with kidney failure: For patients with slight or moderate renal impairment, it is not necessary to reduce the normal doses, but for those with severe renal impairment it is necessary to prolong intervals of administration or to adjust doses. When clearance rate of endogenous creatinine is within 10~50ml/ min, prolong the interval of administration from 8 hours to 8~12 hours or reduce the doses by 25% while administrated at normal intervals. When the endogenous creatinine clearance is less than 10ml/ min, prolong the intervals to 12~18 hours or reduce the doses by 25-50% while administrated at normal intervals.

For i.m., doses of 0.5 million IU of Benzylpenicillin sodium should be dissolved in 1 ml of sterile water for injection and doses of more than 0.5 million IU should be dissolved in 2 ml of sterile water for injection. Sodium chloride injection should not be used as solvent; the rate for i.v. drip should be controlled at less than 0.5 million IU/min to avoid toxicity to the central nervous system from occurring.

4.3 Contraindications

Benzylpenicillin Sodium is contraindicated in patients with allergy history to the drug or positive reaction in skin test of penicillin.

4.4 Special warnings and precautions for use

Before administering Benzylpenicillin Sodium, history of allergic reactions should be inquired in detail and skin test should be done. This product will be prohibited to use if positive reaction occurs 20 minutes after 0.05-0.1ml of solution containing 500 units/ml of benzylpenicillin is administered by intradermal injection. This product is only used in patients with negative reaction of skin test and emergency measures to allergic reactions should be taken at any moment if it is

necessary.

Patients allergic to one kind of benzylpenicillin may be allergic to other kinds of penicillin or penicillamine. This product should be used with caution in patients with anaphylactic diseases such as asthma, eczema, pollenosis, and urticaria, etc.

Freshly prepared solutions for injection of this product should be used immediately because aqueous solution of Benzylpenicillin sodium is unstable at room temperature. Potency of this product will reduce by 56% and assay of penicillenic acid will increase by 200 times if a solution of this product with concentration of 20 IU/ml is stored at 30℃ for 24 hours.

If large-dose penicillin is administered, blood electrolytes should be monitored periodically

Disturbance to diagnoses:

(1) During administered with penicillin, falsely positive results may appear when use copper sulfate method to determine urine sugar, but this phenomenon will not appear if glucose enzyme method is used.

(2) Blood sodium determined will increase when administering the product by intravenous infusion.

(3) The concentration of alanine aminotransferase and aspartic acid aminotransferase in serum will increase after administering this product.

Clinical medication data show that infants under 6 years old, parturients, and elderly people over 60 are prone to adverse reactions when using this product. This product should be used with caution when it is necessary to use this product, or use it in a reduced amount as prescribed by a doctor.

4.5 Interaction with other medicinal products

This product should not be combined with these drugs, such as chloramphenicol, erythromycin, tetracycline and sulfonamides, that can interfere with the activity of this product.

The half-life in serum will be prolonged since the secretion of this product through renal tubular can be reduced by probenecid, aspirin, indomethacin, butazolidin and sulfa. This product can strengthen anticoagulating action on warfarin.

This product is contraindicated with heavy metals, particularly with copper, zinc and mercury.

Benzyl intravenous infusion will turn turbid when Cefalotin, Lincomycin, Tetracycline, Vancomycin, Erythromycin Ethylsuccinate, Amphotericin B, Noradrenalin, m-hydroxylamine, Phenytoin sodium, Hydroxyzine Hydrochloride, Prochlorperazine, Phenergan, Vitamin B or Vitamin C are added in it.

This product cannot be instilled in the same container with aminoglycoside antibiotics, which may cause the antibacterial activity of the two to decrease, when placed in the same container.

4.6 Fertility, pregnancy and lactation

Preclinical studies and human experience with the penicillin during pregnancy has not shown any positive evidence of adverse effects on the foetus. There are, however, no well controlled studies in pregnant women showing conclusively that harmful effects of these drugs on the foetus can be excluded, the administration of this drug, this drug should be used during pregnancy only if clearly

needed.

Smallest quantities of benzylpenicillin are excreted in breast milk. The levels reach 2 – 15 % of serum concentration. This can be a reason of sensitization or changes of intestinal flora of child, even undesirable effects were not observed in breastfed infants whom mothers received Penicillin G sodium.

4.7 Effects on ability to drive and use machines

There no studies with Penicillin G sodium regarding influence on the ability to drive or use machines. However, higher dosage neurotoxic effects were reported (e.g. apathy) and they can influence the ability to drive or use machines

4.8 Undesirable effects

The frequency of adverse reactions caused by benzylpenicillin is given as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000 including isolated cases).

Blood and lymphatic system disorders

- rare: haemolytic anaemia, granulocytopenia (neutropenia), agranulocytosis, leukopenia, thrombocytopenia, have been reported, mainly after the administration of large doses of penicillin (e.g. treatment of bacterial endocarditis).

Immune system disorders

- very common: Patients undergoing treatment for syphilis or neurosyphilis with benzylpenicillin may develop a Jarisch-Herxheimer reaction.
- common: Penicillin is a substance of low toxicity but does have a significant index of sensitization. The following hypersensitivity reactions have been reported: transient eruptions, maculopapular eruptions, exfoliative dermatitis; urticaria, fever, and eosinophilia. These may be treated with antihistamine drugs.
- rare: anaphylactic reactions

Allergic reactions require the immediate discontinuance of treatment. Severe anaphylactic require immediate treatment with adrenaline, slow IV administration (0.1 to 0.3 mg diluted to 10 mL of normal saline solution, administered in 5-15 minutes. When necessary, oxygen, slow intravenous or corticosteroids, or infusion (250 to 500 mg of cortisone hemisuccinate); intubation or tracheotomy should also be administered as indicated.

- very rare: adenopathy and lupus syndrome

Nervous System Disorders

- rare: seizures and or epilepsy have been reported following the administration of large doses of 50,000,000 IU of benzylpenicillin or rapid injection of over 5,000,000 IU of benzylpenicillin.
- very rare: neurological and psychic disorders (polyneuropathy, peripheral neuropathy)may occur after administration of massive doses

Respiratory disorders

- very rare: clinical signs of acute pneumopathy associated with fever (Loeffler syndrome) have been reported, which required the discontinuance of treatment.

Gastrointestinal disorders

- rare: candidiasis
- very rare: glossitis, stomatitis, diarrhoea, pseudomembranous colitis

Hepatobiliary disorders

- rare: increase of transaminases.

Musculoskeletal and connective tissue disorders

- common: pain, nodules, tumefaction at injection site, in case of IM injections, phlebitis in case of IV injections
- very rare: joint and muscle pains has been reported following benzylpenicillin administration. In patients with renal insufficiency, myoclonia may occur after administering large doses of benzylpenicillin.

In children and neonates, after the IM administration of benzylpenicillin, muscular cramps may occur. *Renal and urinary disorders:*

- rare: interstitial nephropathy after IV administration of high doses (12g daily) of benzylpenicillin sodium.

4.9 Overdose

The main manifestation of drug overdose is the adverse reaction of the central nervous system. The drug should be suspended immediately, symptomatic and supportive treatment should be given. The product can be eliminated by hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Beta-lactamase Sensitive Penicillin
ATC code: J01CE01
Mechanism of action
Benzylpenicillin is natural penicillin obtained from a strain of Penicillinum chrysogenum.
Benzylpenicillin is a bactericidal against penicillin-susceptible microorganisms during the stage of active multiplication. It binds to specific protein binding penicillin (PBP) located on the inner membrane of the bactericidal cell wall. PBP-s (which include transpeptidases, carboxypeptidases, and endopeptidases) are enzymes that are involved in the terminal stage of assembling the bacterial cell wall and in reshaping the cell wall during growth and division. Penicillin bind to and inactivate PBP-s, resulting in the weakening of the bacterial cell wall and lysis. It is not active against the penicillinase-producing bacteria.

Mechanism of 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. Cross resistance can develop due to more than one resistance gene being present on a mobile section of DNA (e.g. plasmid, transposon etc.).

Breakpoints:

Organism	S ≤ (mg/L)	I (mg/L)	R ≥ (mg/L)
Streptococcus pneumoniae Neisseria gonorrhoeae	0.06	0.12-1.0	2.0
Neisseria meningitides	0.06	/	0.12
Haemolytic streptococci Staphylococci Moraxella catarrhalis	0.12	/	0.25

Haemophilus influenzae			
Rapidly growing anaerobes	1.0	/	2.0

S = Susceptible
I = Intermediate susceptibility
R = Resistant
Microorganisms susceptible to benzylpenicillin sodium
Aerobic Gram-positive micro-organisms
- Coagulase negative Staphylococcus
- Enterococcus Spp
- Staphylococcus aureus
Aerobic Gram-negative microorganisms
- Acinetobacter
- Bordetella pertussis
- Brucella spp.
- Enterobacteriaceae (including Escherichia coli, Salmonella, Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter)
- Haemophilus influenza
- Pseudomonas
Anaerobic microorganisms

- Bacteroides fragilis

5.2 Pharmacokinetic properties

Absorption
Benzylpenicillin sodium rapidly appears in the blood following intramuscular injection: plasma concentration of 12 µl/mL are usually reached in 30 minutes, following IM injection of 1,000,000 IU of benzylpenicillin.
Distribution
50 – 60 % is bound to plasmatic proteins.
Benzylpenicillin crosses the placenta.
It is distributed into the breast milk. Milk/serum ratio is about 0.1.
Distribution into the cerebrospinal fluid (CSF) is low in subjects with non-inflamed meninges, but in meningitis it may reach 5 % of the peak plasma concentration.
Penicillin G is distributed to most areas of the body including tissues, serosae, joints, being actively secreted into the bile.
The half-life is about 30 minutes.
Elimination
It is metabolized in penicillin acid by penicillinase in liver. Benzylpenicillin elimination is renal and biliary. In kidney: 60-90 per cent of the total dose within 24 hours, 20 per cent by glomerular filtration, 80 per cent by tubular secretion. Probenicid inhibits tubular secretion. In liver: following IM injection of 600 mg, 0.08 % undergoes biliary elimination within 12 hours as penicillin acid and phenaceturic acid (30 to 60 %). Elimination by haemodialysis is negligible and by peritoneal dialysis is null.

5.3 Preclinical safety data

There are no conclusive studies on the mutagenic potential of penicillin but bacterial tests *in vitro* and *in vivo* showed no mutagenic potential.

Benzylpenicillin passes through placental barrier. Both preclinical and human studies have shown no teratogenic potential.

6. Pharmaceutical particulars

6.1 List of excipients

None

6.2 Incompatibilities

Benzylpenicillin is not stable in the presence of acids, bases, oxidants, alcohols, heavy metals, and at high temperatures. Benzylpenicillin is incompatible with solutions for infusion having an acid or basic pH (pH < 5, and pH > 8).
Benzylpenicillin is incompatible with: chlorpromazine hydrochloride, heparin sodium, hydroxyzine hydrochloride, lincomycin hydrochloride, oxytetracycline hydrochloride, prochlorperazine mesylate, tetracycline hydrochloride, and thiopental sodium.
Benzylpenicillin is not compatible with the B vitamin complex, or with ascorbic acid solutions.

Benzylpenicillin should not be mixed in the same syringe with metaraminol tartrate, pentobarbital, bicarbonate solutions or lactate solutions.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Airtight, preserve from light, store in a dry place not exceeding 30℃.

6.5 Commercial presentation

Benzylpenicillin sodium for injection 1 million IU: Antibiotic vials, 10vials/box.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

CSPC Zhongnuo Pharmaceutical (Shijiazhuang) Co., Ltd.

Address: No. 88, Yangzi Road, High-tech industry Zone of Shijiazhuang, China

8. Date of first authorization/renewal of the authorization

Dec. 12, 2020

9. Date of revision of the text