

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benzylpenicillin sodium 3000 mg Powder for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 5,000,000 IU (equivalent to approximately 3 g) benzylpenicillin as sodium salt (= 8.42 mmol or 193 mg sodium).

3 PHARMACEUTICAL FORM

White to off-white powder for solution for injection/infusion

pH - value after reconstitution: 5.5 - 7.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Benzylpenicillin sodium is indicated for the treatment of the following infections in adults, adolescents, children, newborn infants and pre-term infants, caused by penicillin-sensitive pathogens (see section 5.1):

- septicaemia
- skin and wound infections
- diphtheria (in addition to antitoxin)
- community acquired pneumonia
- empyema
- erysipelas
- bacterial endocarditis
- peritonitis
- meningitis
- brain abscesses
- osteomyelitis
- infections of the genital tract caused by fusobacteria.

Benzylpenicillin sodium is also used for the treatment of the following specific infections:

- anthrax
- tetanus
- gas gangrene
- listeriosis
- pasteurellosis
- rat bite fever
- fusospirochaetosis
- actinomycosis.

Furthermore, Benzylpenicillin sodium is also used for complications in gonorrhoea and syphilis (e.g. gonorrhoeal endocarditis or arthritis, congenital syphilis). However, in uncomplicated cases, preference should be given to depot penicillins.

Benzylpenicillin sodium is not indicated for the treatment of syphilis during pregnancy.

Benzylpenicillin sodium is also used in Lyme borreliosis from the second stage of the disease onwards (meningopolyneuritis Garin-Bujadoux-Bannwarth, acrodermatitis chronica atrophicans, Lyme arthritis, Lyme carditis) if oral penicillin therapy is no longer indicated. During pregnancy, high-dose parenteral Benzylpenicillin sodium administration is recommended from the second stage of Lyme disease onwards to prevent diaplacental infections.

The generally acknowledged guidelines for the appropriate use of antibacterial agents should be considered when using Benzylpenicillin sodium.

4.2 Posology and method of administration

For international units (IU) and mass values, the following ratios apply:

1 mg benzylpenicillin sodium is equivalent to 1670 IU benzylpenicillin.

1 million IU benzylpenicillin is equivalent to 598.9 mg benzylpenicillin sodium.

In general, 600 mg benzylpenicillin sodium is considered to be equivalent to 1 million IU benzylpenicillin.

Benzylpenicillin has a wide dosage margin, which is guided by the method of administration, dose level and dosing interval according to pathogen type and susceptibility, severity of the infection and the patient's condition.

Posology

Adults and adolescents (aged 12 years and older):

Normal dosage (intramuscular or intravenous): 0.03 mega IU/kg/day, equivalent to approximately 1-5 mega IU per day, divided into 4-6 doses

High dosage (intravenous): 0.3 mega IU/kg/day, equivalent to about 10-40 mega IU per day, divided into 4-6 doses

Infants (aged one month and older) and children (up to 12 years of age):

Normal dosage (intramuscular or intravenous): 0.03-0.1 mega IU/kg/day, divided into 4-6 doses

High dosage (intravenous): 0.1-0.5 (-1.0) mega IU/kg/day, divided into 4-6 doses

Caution: Cerebral seizures and electrolyte imbalance may occur if infusions are too rapid. A rate of not more than 300mg/minute is recommended for intravenous doses above 1.2g.

Newborn infants (2-4 weeks of age):

Normal dosage (intramuscular or intravenous): 0.03-0.1 mega IU/kg/day, in 3-4 single doses

High dosage (intravenous): 0.2-0.5 (-1.0) mega IU/kg/day, in 3-4 single doses

Pre-term and newborn infants (up to 2 weeks of age):

Normal dosage (intramuscular or intravenous): 0.03-0.1 mega IU/kg/day, in 2 single doses

High dosage (intravenous): 0.2-0.5 (-1.0) mega IU/kg/day, in 2 single doses

In pre-term and newborn infants, the dosing interval must be no less than 12 hours due to immaturity and reduced excretion of benzylpenicillin (see section 5.2).

Elderly:

Elimination processes may be delayed with advanced age. The dosage must therefore be adjusted to renal function in each individual case (see section 5.2).

Renal impairment

If renal function is severely impaired, the degradation and excretion of penicillins may be delayed. This should be taken into account in the dosage. It is therefore recommended that the single doses and/or dosing intervals of Benzylpenicillin sodium be adjusted to the clearance values in each individual case:

Benzylpenicillin sodium dosage for adults and adolescents based on creatinine clearance				
Creatinine clearance in mL/min	100-60	50-40	30-10	<10
Serum creatinine in mg %	0.8-1.5	1.5-2.0	2-8	15
Benzylpenicillin sodium (daily dose)	<u>Below 60 years of age:</u> 40 (-60) mega IU; <u>Above 60 years of age:</u> 10-40 mega IU	10-20 mega IU	5-10 mega IU	2-5 mega IU
Dosing interval	in 3-6 single doses	in 3 single doses	in 2-3 single doses	in 1-2 single doses

Benzylpenicillin sodium dosage for infants (aged 1 month and older) and children (up to 12 years of age) based on creatinine clearance			
Creatinine clearance in mL/min	100-60	50-10	<10
Serum creatinine in mg %	0.8-1.5	1.5-8.0	15

Benzylpenicillin sodium (daily dose)	0.03-0.1 mega IU/kg	0.02-0.06 mega IU/kg	0.01-0.4 mega IU/kg
Dosing interval	in 4-6 single doses	in 2-3 single doses	in 2 single doses

Infants (aged 1 month and older) and children (up to 12 years of age): If renal function is moderately-to-severely impaired (glomerular filtration rate = 10–50 mL/minute/1.73 m²), the normal dose is administered every 8 – 12 hours. In very severe cases of impaired renal function or renal failure (glomerular filtration rate <10 mL/minute/1.73 m²), the normal dose is administered every 12 hours.

Pre-term and newborn infants (up to 4 weeks of age): Benzylpenicillin sodium is not suitable for the treatment of pre-term and newborn infants with impaired renal function.

Hepatic impairment:

No dose reduction is required provided that renal function is not impaired.

Special dosages

Bacterial endocarditis: Adults are given 10-80 mega IU/day intravenously in combination with aminoglycosides.

Meningitis: Due to increased seizure susceptibility and Jarisch-Herxheimer reactions, no more than 20-30 mega IU/day should be administered in adults and no more than 12 mega IU/day in children. Administration of the first dose should be protracted for very severe clinical forms - initially 1/4 of the individual single dose - to be given slowly under very strict surveillance.

Lyme borreliosis: In adults, 20-30 mega IU/day intravenously in 2-3 doses over 14 days and in children, 0.5 mega IU/kg/day intravenously in 2-3 doses over 14 days.

Special clinical situations: If required by the clinical situation, Benzylpenicillin sodium can also be administered as follows:

- Intrapleural instillation: up to 0.2 mega IU (5,000 IU/mL)
- Intra-articular injection: up to 0.1 mega IU (25,000 IU/mL)
- Intralumbar administration:

Adults, adolescents (aged 12 years and older): 10,000 up to a maximum of 20,000 IU

Children (aged 6-12 years): 8,000 IU

Infants (aged 1-6 years): 5,000 IU

Infants (aged 1 - 23 months): 2,500 IU.

After withdrawing a corresponding amount of cerebrospinal fluid, the sterile solution (no more than 1,000 IU/mL) must be injected slowly (1 mL/min) at body temperature. Local therapy should always be merely adjuvant to systemic treatment. For intralumbar instillations, the dosage for systemic treatment (IV, IM) must be reduced accordingly.

Method of administration

Benzylpenicillin sodium can be given **intravenously** (injection or short infusion at 10 mega IU/100 mL) or also **intramuscularly**.

Notes for IM injection:

Up to a maximum of 10 mega IU (= approximately 6 g) Benzylpenicillin sodium, dissolved in 6 - 10 mL water for injection, is applied up to twice daily as a deep intramuscular injection into the upper, outer quadrant of the gluteus maximus or Hochstetter's ventrogluteal field.

5 mL per injection site is to be regarded as the upper limit of tolerability. Repeated injections should be given on alternate sides. Higher doses can be given as an IV infusion.

Severe local reactions may occur with intramuscular administration, especially in infants. If possible, intravenous therapy should be performed.

Caution: Cerebral seizures and electrolyte imbalance may occur if the infusion is too rapid. A rate of not more than 300mg/minute is recommended for intravenous doses above 1.2g.

For further information on preparation, see section 6.6.

Duration of use

The usual duration of treatment is 10 – 14 days for most indications. However, the duration of treatment should be adjusted to the severity of infection, sensitivity of the pathogen(s) and the patient's clinical and bacteriological status.

It should be continued for at least 2-3 days after the resolution of clinical symptoms.

According to WHO recommendations, a treatment period of at least 10 days should be observed for streptococcal diseases.

4.3 Contraindications

- Hypersensitivity to the active substance
- History of hypersensitivity to penicillin
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. cephalosporin, carbapenem or monobactam)

4.4 Special warnings and precautions for use

In cases of cephalosporin hypersensitivity, a cross-allergy is possible (frequency according to the literature: 5-10%).

Prior to treatment, a hypersensitivity test should be carried out. Patients should be informed about the possible occurrence of a hypersensitivity reaction. Particular caution is required in patients with allergic diathesis or bronchial asthma. After administering the medication, patients should be observed for 30 minutes and an adrenaline solution should be ready for injection in the event of an emergency. If an allergic reaction occurs, treatment must be discontinued and, if necessary, symptomatic treatment instituted.

Caution should be exercised in patients with the following conditions:

- allergic diathesis (urticaria or hay fever) or asthma (increased risk of hypersensitivity reactions)
- severe heart conditions or severe electrolyte disturbances of any other origin (attention should be paid to electrolyte intake in this patient group, especially potassium intake);
- renal insufficiency (for dose adjustment, see section 4.2)
- liver damage (for dose adjustment, see section 4.2)
- epilepsy, cerebral oedema or meningitis (increased risk of seizures, especially with high-dose administration (> 20 mega IU) of Benzylpenicillin sodium; see section 4.8)
- existing mononucleosis (increased risk of skin rash)
- when treating co-infections in patients with acute lymphatic leukaemia (increased risk of skin reactions)
- dermatomycoses (para-allergic reactions are possible, as there may be common antigenicity between penicillins and metabolic products of dermatophytes; see section 4.8)

In rare cases, prolongation of the prothrombin time has been reported in patients receiving penicillins. Appropriate monitoring should be performed when anticoagulants are co-administered. Adjustment of the oral anticoagulant dose may be necessary to obtain the desired degree of anticoagulation (see sections 4.5 and 4.8).

It should be remembered that the absorption of Benzylpenicillin sodium is delayed after intramuscular administration in patients with diabetes (see section 5.2).

In venereal diseases, dark field examinations should be performed before the start of therapy if co-existing syphilis is suspected. Serological tests for monitoring purposes should also be performed for at least 4 months.

In long-term therapy, vigilance is required for the possible occurrence of an overgrowth of resistant organisms. If secondary infections occur, appropriate measures should be taken.

If severe, persistent diarrhoea occurs, antibiotic-associated pseudomembranous colitis should be considered (mucohaemorrhagic, watery diarrhoea, dull, diffuse to colicky abdominal pain, fever, occasionally tenesmus), which may be life-threatening. In these cases, Benzylpenicillin sodium must therefore be discontinued immediately and treatment based on the identification of the pathogen initiated. Preparations that inhibit peristalsis are contraindicated.

When treating Lyme borreliosis or syphilis, a Jarisch-Herxheimer reaction may occur as a result of the bactericidal action of penicillin on the pathogens, which is characterised by fever, chills, general symptoms and focal symptoms (mostly 2 to 12 hours after the initial dose). Patients should be informed that this is a usual transient sequela of antibiotic therapy. For the suppression or alleviation of a Jarisch-Herxheimer reaction (see section 4.8), appropriate therapy should be instituted.

For conditions such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, treatment with the water-soluble alkali salt of benzylpenicillin should be instituted.

If neurological involvement cannot be excluded in patients with congenital syphilis, forms of penicillin reaching a higher level in cerebrospinal fluid should be used.

Severe local reactions can occur with intramuscular administration to infants. If possible, intravenous therapy should be performed.

When intravenously administering very high doses (above 10 mega IU/day), the administration site should be alternated every other day to avoid superinfections and thrombophlebitis.

Due to possible electrolyte disturbances, Benzylpenicillin sodium should be administered slowly with infusions of more than 10 mega IU and, due to the possibility of seizure reactions, when administering more than 20 mega IU (see section 4.8).

In prolonged treatment (more than 5 days) with high penicillin doses, monitoring of the electrolyte balance, blood count monitoring and renal function tests are recommended.

Effect on diagnostic laboratory procedures:

- A positive direct Coombs' test often develops ($\geq 1\%$ to $< 10\%$) in patients receiving 10 million IU (equivalent to 6 g) benzylpenicillin or more per day. Upon discontinuation of the penicillin, the direct antiglobulin test may still remain positive for 6 to 8 weeks (see sections 4.5 and 4.8).
- Determination of urinary protein using precipitation techniques (sulphosalicylic acid, trichloroacetic acid), the Folin-Ciocalteu-Lowry method or the Biuret method may lead to false-positive results. Caution should therefore be exercised when interpreting the results of such tests in patients receiving Benzylpenicillin sodium. Protein determination with test strips is not affected.
- Equally, urinary amino acid determination using the ninhydrin method may lead to false-positive results.
- Penicillins bind to albumin. In electrophoresis methods to determine albumin, pseudobisalbuminaemia may thereby be simulated.
- During therapy with Benzylpenicillin sodium, non-enzymatic urinary glucose detection and urobilinogen detection may prove false-positive. Enzymatic urine glucose tests should be used in patients on therapy with Benzylpenicillin sodium, as these are not affected by this interaction.
- When determining 17-ketosteroids (using the Zimmermann reaction) in urine, increased values may occur during therapy with Benzylpenicillin sodium.

1 mega IU (= approximately 0.6 g) Benzylpenicillin sodium contains 1.68 mmol sodium; 10 mega IUs are therefore equivalent to a sodium exposure of 100 mL isotonic saline solution.

4.5 Interaction with other medicinal products and other forms of interactions

Concomitant administration of Benzylpenicillin sodium is not recommended with:

Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, Benzylpenicillin sodium should not be combined with bacteriostatic antibiotics.

Mixed injections or infusions: To avoid undesirable chemical reactions, administration of mixed injections or infusions or of admixtures with solutions that contain carbohydrates such as glucose, should be avoided (see section 6.2).

Caution is required when co-administering with:

Probenecid: Administration of probenecid leads to an inhibition of the tubular secretion of benzylpenicillin, resulting in an increase in serum concentration and prolongation of the elimination half-life. Furthermore probenecid inhibits the penicillin transport from the cerebrospinal fluid, so that the concomitant administration of probenecid reduces the penetration of benzyl penicillin into brain tissue even further.

Anti-inflammatories, antirheumatics and antipyretics: When co-administering Benzylpenicillin sodium with anti-inflammatories, antirheumatics or antipyretics (especially indomethacin, phenylbutazone, salicylates at high doses), it should be pointed out that excretion is competitively inhibited, resulting in an increase in serum concentration and prolongation of the elimination half-life.

Digoxin: In patients on digoxin treatment, Benzylpenicillin sodium should only be used with caution, as there is a risk of bradycardia as a result of interactions.

Methotrexate: When taken at the same time as Benzylpenicillin sodium, the excretion of methotrexate is reduced. This can lead to increased methotrexate toxicity. Concomitant use of methotrexate and penicillin should be avoided if possible. If concomitant use is unavoidable, a reduction in the methotrexate dose should be considered and methotrexate serum levels should be monitored. The patient should be monitored for possible additional adverse reactions of methotrexate, including leukopenia, thrombocytopenia and skin suppuration.

Oral anticoagulants: Oral anticoagulants and penicillin antibiotics have been used extensively in practice without interactions. However, in the literature, there are reports of an increased number of patients who experienced a bleeding event when they were prescribed acenocoumarol or warfarin at the same time as penicillin. If concomitant use is required, the prothrombin time or other suitable coagulation parameters should be carefully monitored upon co-administration or discontinuation of penicillin. Furthermore, an adjustment of the oral anticoagulant dose may be necessary (see sections 4.4 and 4.8).

Synergism between antibiotics:

Benzylpenicillin sodium should only be given in combination with other antibiotics if a synergistic or at least an additive effect is anticipated. In general, the individual components of a combination must be given at the full effective dose (exception: if synergism is proven, the dose of the more toxic combination partner can be reduced).

If duly indicated, it should, in particular, be remembered that Benzylpenicillin sodium can be combined with the following bactericidal antibiotics:

- isoxazolyl penicillins (e.g. flucloxacillin and other narrow-spectrum beta-lactams)
- aminopenicillins
- aminoglycosides

The above-mentioned penicillins are given by slow intravenous injection prior to the Benzylpenicillin sodium infusion. Wherever possible, aminoglycosides should be given separately via the intramuscular route.

4.6 Fertility, pregnancy and lactation

Pregnancy

Benzylpenicillin crosses the placenta. 1-2 hours after administration, concentrations corresponding to those in maternal serum are reached in foetal serum. Studies in animals have shown no indications of direct or indirect health effects with regard to reproductive toxicity.

Benzylpenicillin sodium may be used in pregnancy if duly indicated and after consideration of the benefits and risks.

Benzylpenicillin sodium is not indicated during pregnancy for the treatment of syphilis.

Breast-feeding

Small amounts of penicillins appear in breast milk.

Although no undesirable effects have been reported in breast-fed infants to date, the possibility of sensitisation or an adverse effect on the intestinal flora must nevertheless be considered.

In infants also fed on baby food, mothers should express and discard breast milk during treatment with Benzylpenicillin sodium. Breast-feeding can be resumed 24 hours after the cessation of treatment.

Fertility

No studies have been performed to investigate the effect of Benzylpenicillin sodium on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Due to the occurrence of possible serious undesirable effects (e.g. anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8), Benzylpenicillin sodium can have an influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects are ranked according to body system and frequency according to the following classification:

Very common ($\geq 1/10$)
Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)
Rare ($\geq 1/10,000$ to $< 1/1,000$)
Very rare ($< 1/10,000$)
Not known (cannot be estimated from the available data)

Blood and lymphatic system disorders*Very rare:*

Eosinophilia, leucopenia, neutropenia, granulocytopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, coagulation disorders

Not known:

Prolongation of the bleeding time and prothrombin time (see section 4.4)

Immune system disorders*Uncommon:*

Allergic reactions: urticaria, angioedema, erythema multiforme, exfoliative dermatitis, fever, arthralgia, anaphylaxis or anaphylactoid reactions (asthma, purpura, gastrointestinal symptoms). Para-allergic reactions may occur in patients with dermatomycoses, as there may be common antigenicity between penicillins and metabolic products of dermatophytes.

Not known:

Serum sickness, Jarisch-Herxheimer reaction in association with spirochete infections (syphilis and Lyme borreliosis)

Metabolism and nutrition disorders*Rare:*

Electrolyte imbalances may occur upon rapid infusion of more than 10 mega IU.

Nervous system disorders*Rare:*

Neuropathy. Convulsive reactions may occur upon infusion of high doses (in adults, more than 20 mega IU); this should be particularly borne in mind in patients with severely impaired renal function, epilepsy, meningitis, cerebral oedema or during cardiopulmonary bypass.

Gastrointestinal disorders*Uncommon:*

Stomatitis, glossitis, lingua villosa nigra, nausea, vomiting

If diarrhoea develops during treatment, the possibility of pseudomembranous colitis should be considered (see section 4.4).

Hepatobiliary disorders*Not known:*

Hepatitis, cholestasis

Skin and subcutaneous tissue disorders

Not known: pemphigoid.

Renal and urinary disorders*Rare:*

Nephropathy (after intravenous administration of more than 10 mega IU Benzylpenicillin sodium), albuminuria, cylindruria and haematuria

Oliguria or anuria, which can rarely occur during high-dose penicillin therapy, generally disappears within 48 hours upon discontinuation of treatment. Diuresis can also be stimulated with 10% mannitol solution.

General disorders and administration site conditions*Rare:*

Severe local reactions during intramuscular administration to infants.

Investigations*Common:*

- positive direct Coombs' test
- false-positive urinary protein determination using precipitation techniques (Folin-Ciocalteu-Lowry method, Biuret method)

- false-positive urinary amino acid determination (ninhydrin method)
- falsification of pseudobisalbuminaemia when using electrophoresis methods to determine albumin.
- false-positive non-enzymatic urinary glucose detection and urobilinogen detection
- increased values when determining 17-ketosteroids in urine (using the Zimmermann reaction) (see section 4.5)

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 national reporting system:

HPRa Pharmacovigilance

Website: www.hpra.ie

4.9 Overdose

Increased neuromuscular hyperexcitability or susceptibility to cerebral seizures can be anticipated in the event of an overdose. Countermeasures: discontinuation, clinical surveillance and symptomatic treatment, if required. Benzylpenicillin sodium can be hemodialysed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Benzylpenicillin (penicillin G) is a semi-synthetic, beta-lactamase-sensitive, beta-lactam antibiotic.

ATC code: J01CE01

Mechanism of action

For benzylpenicillin, the mechanism of action is based on inhibition of bacterial cell wall synthesis (during the growth phase) through a blockade of penicillin-binding proteins (PBPs) such as transpeptidases. This results in a bactericidal action.

Pharmacokinetic/pharmacodynamic relationship

Efficacy largely depends on the length of time that the active substance level remains above the pathogen's MIC.

Resistance mechanisms

Resistance to benzylpenicillin can be due to the following mechanisms:

- Inactivation by beta-lactamases: Benzylpenicillin is sensitive to beta-lactamase and is therefore inactive against beta-lactamase-producing bacteria (e.g. staphylococci or gonococci).
- Reduced affinity of PBPs for benzylpenicillin: The acquired resistance in pneumococci and a few other streptococci to benzylpenicillin is due to modifications of existing PBPs as a result of a mutation. However, the formation of an additional PBP with reduced affinity for benzylpenicillin is responsible for resistance in methicillin (oxacillin)-resistant staphylococci.
- In Gram-negative bacteria, inadequate penetration of benzylpenicillin through the outer cell wall can lead to an insufficient inhibition of PBPs.
- Benzylpenicillin can be actively transported from the cell by efflux pumps.
Benzylpenicillin is partially or completely cross-resistant to other penicillins and cephalosporins.

Breakpoints

Testing of benzylpenicillin is performed using the standard dilution series. Results are evaluated on the basis of breakpoints for benzylpenicillin. The following minimum inhibitory concentrations have been established for susceptible and resistant germs:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) breakpoints

Pathogen	Susceptible	Resistant
Staphylococcus spp.	≤ 0.12 mg/L	> 0.12 mg/L
Streptococcus spp. (Groups A, B, C, G)	≤ 0.25 mg/L	> 0.25 mg/L

Streptococcus pneumoniae	≤ 0.06 mg/L	> 2 mg/L
Streptococci of the "Viridans" group	≤ 0.25 mg/L	> 2 mg/L
Neisseria meningitidis	≤ 0.06 mg/L	> 0.25 mg/L
Neisseria gonorrhoeae	≤ 0.06 mg/L	> 1 mg/L
Gram-negative anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Gram-positive anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Non-species-specific breakpoints*	≤ 0.25 mg/L	> 2 mg/L

* Based mainly on serum pharmacokinetics

Prevalence of acquired resistance

The prevalence of acquired resistance in individual species may vary geographically and over time. Thus, local information on the resistance situation is required, particularly for the adequate treatment of severe infections. If, based on the local resistance situation, the efficacy of benzylpenicillin is questionable, expert therapeutic advice should be sought. Particularly in cases of serious infection or unsuccessful therapy, a microbiological diagnosis should be sought, with the detection of the pathogen and its susceptibility to benzylpenicillin.

Prevalence of acquired resistance based on data from the past 5 years from national resistance monitoring projects and studies (version: January 2015):

Commonly susceptible species
Aerobic Gram-positive micro-organisms
<i>Actinomyces israelii</i> °
<i>Corynebacterium diphtheriae</i> °
<i>Erysipelothrix rhusiopathiae</i> °
<i>Gardnerella vaginalis</i> °
<i>Streptococcus agalactiae</i>
<i>Streptococcus pneumoniae</i>
<i>Streptococcus pyogenes</i>
<i>Streptococcus dysgalactiae</i> subsp. <i>equisimilis</i> (Group C & G streptococci)
Streptococci of the "Viridans" group ° ^
Aerobic Gram-negative micro-organisms
<i>Borrelia burgdorferi</i> °
<i>Eikenella corrodens</i> ° \$
<i>Haemophilus influenzae</i> ° \$
<i>Neisseria meningitidis</i> °
Anaerobic micro-organisms
<i>Clostridium perfringens</i> °
<i>Clostridium tetani</i> °
<i>Fusobacterium</i> spp. °
<i>Peptoniphilus</i> spp. °
<i>Peptostreptococcus</i> spp. °
<i>Veillonella parvula</i> °
Other micro-organisms
<i>Treponema pallidum</i> °
Species in which acquired resistance may pose a problem during use
Aerobic Gram-positive micro-organisms
<i>Enterococcus faecalis</i> \$
<i>Staphylococcus aureus</i> +

<i>Staphylococcus epidermidis</i> ⁺
<i>Staphylococcus haemolyticus</i> ⁺
<i>Staphylococcus hominis</i> ⁺
Aerobic Gram-negative micro-organisms
<i>Neisseria gonorrhoeae</i> [§]
Naturally resistant species
Aerobic Gram-positive micro-organisms
<i>Enterococcus faecium</i>
<i>Nocardia asteroides</i>
Aerobic Gram-negative micro-organisms
All <i>Enterobacteriaceae</i> species
<i>Legionella pneumophila</i>
<i>Moraxella catarrhalis</i>
<i>Pseudomonas aeruginosa</i>
Anaerobic micro-organisms
<i>Bacteroides</i> spp.
Other micro-organisms
<i>Chlamydia</i> spp.
<i>Chlamydophila</i> spp.
<i>Mycoplasma</i> spp.

[°] At the time of the publishing of the table, no current data were available. Susceptibility is assumed in the primary literature, standard works and therapeutic recommendations.

[§] The natural susceptibility of most isolates is within the intermediate range.

⁺ In at least one region, the resistance rate is over 50%.

[^] Collective name for a heterogeneous group of streptococci species. The resistance rate can vary depending on the streptococci species present.

5.2 Pharmacokinetic properties

Absorption

Benzylpenicillin is not acid-stable and can therefore only be administered parenterally.

The alkali salts of benzylpenicillin are rapidly and completely absorbed after IM injection.

Peak plasma levels of 150-200 IU/mL are reached 15 - 30 min. after IM injection of 10 mega IU Benzylpenicillin sodium. After a short infusion (30 min.), peak levels of up to 500 IU/mL may be reached. About 55% of the administered dose is bound to plasma proteins.

Distribution

When administering high-dose penicillin therapy, therapeutically effective concentrations are reached even in poorly accessible tissues such as cardiac valves, bone, cerebrospinal fluid or empyema, etc.

Benzylpenicillin crosses the placenta. 10-30% of maternal plasma concentrations are found in the foetal circulation. High concentrations are also attained in the amniotic fluid. On the other hand, passage into breast milk is low. The volume of distribution is about 0.3-0.4 l/kg; in children, about 0.75 l/kg. Plasma protein binding is approximately 55%.

Biotransformation and elimination

Elimination occurs largely (50 - 80%) as unchanged substance via the kidneys (85 – 95%) and, to a lesser degree, in active form with the bile (approximately 5%).

The plasma half-life is approximately 30 min. in adults with healthy kidneys.

Kinetics of special patient groups

- *Diabetics*: Absorption from the intramuscular depot is likely to be delayed in diabetics.

- *Pre-term and newborn infants:* Due to the immaturity of the kidney and liver at this age, the serum half-life can be up to three hours (or more). The dosing interval should therefore be no less than 8 - 12 hours (depending on maturity).
- *Elderly:* Equally, elimination processes may be delayed with advanced age; the dosage should therefore be adjusted to renal function in each individual case.

5.3 Preclinical safety data

Reproduction studies in mice, rats and rabbits have shown no negative effects on fertility or on the foetus. There are no long-term studies available in laboratory animals with regard to carcinogenesis, mutagenesis or fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

The contents of the vial should only be used in a solution with water for injections, 5% glucose solution or 0.9% sodium chloride, in order to avoid incompatibilities.

In order to avoid undesirable chemical reactions or undesirable effects, the already dissolved vials should not be mixed with other mixed injections or infusions (e.g. Ringer's lactate solution etc.).

Oxidising and reducing substances, alcohol, glycerol, macrogols and other hydroxy compounds can inactivate benzylpenicillin.

Benzylpenicillin solutions are most stable in the pH range 6 – 7 (optimum pH 6.8).

Benzylpenicillin is incompatible in solution with the following:

- cimetidine
- cytarabine
- chlorpromazine HCl
- dopamine HCl
- heparin
- hydroxyzine HCl
- lactate
- lincomycin HCl
- metaraminol
- sodium hydrogen carbonate
- oxytetracycline
- pentobarbital
- tetracycline HCl
- thiopental Na
- vancomycin

Benzylpenicillin is not compatible with vitamin-B-complex and ascorbic acid in mixed solutions.

6.3 Shelf life

Unopened vial

5 years

Chemical and physical in-use stability of the reconstituted and diluted product is concentration and temperature dependent. The following in-use storage times have been demonstrated:

	2°C to 8°C	below 25°C
500,000 – 910,000 IU/ml	48 hours	8 hours

(this range includes the recommended concentration for IM injection)		
100,000 IU/ml	24 hours	4 hours
(the recommended concentration for IV injection/infusion)		

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°C to 8°C.

6.4 Special precautions for storage

Do not store above 25°C

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

6.5 Nature and contents of container

Vials of glass type III with halogenated butyl rubber stopper (infusion stoppers) with an aluminium bordered cap with crimp seal or alternatively with flip-off bordered cap.

Pack sizes:

1, 10, 25 and 50 vials (with nominal volume of 15 and 30 ml)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

In order to avoid hypersensitivity reactions caused by degradation products it is recommended to use the injection or infusion solution immediately after preparation. The administration should at least take place within the maximum recommended in-use shelf life (see section 6.3).

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

Preparation of a solution for IV injection or infusion:

A solution for intravenous use can be prepared with the following solvents:

- water for injections (WFI)
- 5% glucose solution
- 0.9% sodium chloride solution

The recommended concentration for intravenous use is 100,000 IU/ml.

An isotonic solution is obtained when using WFI as solvent (osmolarity of 100,000 IU/ml in WFI is 337 mOsmol/l). It should be taken in account that more concentrated solutions and solutions in 5% glucose or 0.9% sodium chloride are hypertonic and that the use of 0.9% sodium chloride leads to an additional supply of electrolytes.

For Benzylpenicillin sodium **500,000 IU** powder for solution for injection / infusion} a one-step reconstitution in the original vial suffices.

For Benzylpenicillin sodium **1,000,000 IU, 5,000,000 IU** and **10,000,000 IU** powder for solution for injection / infusion} a two-step preparation is required, i.e. reconstitution in the original vial followed by dilution of the concentrated solution in another container.

The reconstitution and dilution instructions in the table underneath result in an IV injection / infusion of 100,000 IU/ml.

Reconstitution and dilution instructions for IV injection / infusion		
	Reconstitution step	Dilution step

1 vial	<i>Recommended volume of solvent to be added for reconstitution</i>	<i>Resulting (concentrate for) solution for IV injection/infusion</i>	<i>Dilution until 10 mega IU/100 ml or 100,000 IU/ml)</i>	<i>Resulting solution for IV injection/infusion</i>
Benzylpenicillin sodium 500,000 IU powder for solution for injection / infusion (contains ± 0.3 gram powder)	4.8 ml	ready for use 5 ml = 500,000 IU (100,000 IU/ml)	not applicable	not applicable
Benzylpenicillin sodium 1,000,000 IU powder for solution for injection / infusion (contains ± 0.6 gram powder)	4.6 ml	concentrate to be diluted before use 5 ml = 1 Mega IU (200,000 IU/ml)	1 volume concentrate + 1 volume diluent e.g. add 5 ml concentrate to 5 ml diluent	ready for use 10 ml = 1 Mega IU (100,000 IU/ml)
Benzylpenicillin sodium 5,000,000 IU powder for solution for injection / infusion (contains ± 3 gram powder)	7.9 ml	concentrate to be diluted before use 10 ml = 5 Mega IU (500,000 IU/ml)	1 volume concentrate + 4 volumes diluent e.g. add 10 ml concentrate to 40 ml diluent	ready for use 50 ml = 5 Mega IU (100,000 IU/ml)
Benzylpenicillin sodium 10,000,000 IU powder for solution for injection / infusion (contains ± 6 gram powder)	15.8 ml	concentrate to be diluted before use 20 ml = 10 Mega IU (500,000 IU/ml)	1 volume concentrate + 4 volumes diluent e.g. add 20 ml concentrate to 80 ml diluent	ready for use 100 ml = 10 Mega IU (100,000 IU/ml)

Preparation of a solution for IM injection:

A solution for intramuscular use can be prepared with the following solvent:

- water for injections (WFI)

Due to the concentrated nature of a solution for intramuscular injection the recommended solvent is WFI in order to keep to tonicity as low as possible (any solution exceeding 100,000 IU/ml is hypertonic).

The maximum volume for intramuscular administration is 5 ml per injection site and the maximum intramuscular dose is 10,000,000 IU. Higher doses can be given as intravenous infusion (see section 4.2).

Instructions for the one-step reconstitution in the original vial in the minimum amounts of solvent is described in the table underneath. Further dilution is possible, but depends on the combination of intended dose and maximum injection volume of 5 ml per injection site.

Reconstitution instructions for IM injection		
<i>1 vial</i>	<i>Recommended volume of solvent to be added for reconstitution</i>	<i>Resulting solution for IM injection (maximum 5 ml per injection site)</i>
Benzylpenicillin sodium 500,000 IU powder for solution for injection / infusion <i>(contains ± 0.3 gram powder)</i>	0.3 - 0.6 ml	
	e.g. 0.3 ml	0.55 ml = 0.5 Mega IU (909,090 IU/ml)
	e.g. 0.6 ml	0.75 ml = 0.5 Mega IU (666,667 IU/ml)
Benzylpenicillin sodium 1,000,000 IU powder for solution for injection / infusion <i>(contains ± 0.6 gram powder)</i>	0.6 - 1 ml	
	e.g. 0.6 ml	1.1 ml = 1 Mega IU (909,090 IU/ml)
	e.g. 1 ml	1.5 ml = 1 Mega IU (666,667 IU/ml)
Benzylpenicillin sodium 5,000,000 IU powder for solution for injection / infusion <i>(contains ± 3 gram powder)</i>	3 - 5 ml	
	e.g. 3 ml	5.5 ml = 5 Mega IU (909,090 IU/ml)
	e.g. 5 ml	7.5 ml = 5 Mega IU (666,667 IU/ml)
Benzylpenicillin sodium 10,000,000 IU powder for solution for injection / infusion <i>(contains ± 6 gram powder)</i>	6-10 ml	
	e.g. 6 ml	11 ml = 10 Mega IU (909,090 IU/ml)
	e.g. 10 ml	15 ml = 10 Mega IU (666,667 IU/ml)

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/310/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 2021

10 DATE OF REVISION OF THE TEXT

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