Summary of Product Characteristics for Pharmaceutical Products

1. Name of the finished pharmaceutical product

Benzylpenicillin for Injection 1mega

2. Qualitative and quantitative composition

Each vial contains 600 mg Benzylpenicillin as sodium salt.

Each vial contains 38.6 mg of sodium.

3. Pharmaceutical form

Powder for injection

White or almost white, crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Benzylpenicillin Sodium for Injection is indicated for the treatment of the following infections in adults, adolescents, children, newborn infants and pre-term infants, caused by penicillin-sensitive pathogens:

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 fusobacterial

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

Anthrax

Tetanus

Gas gangrene

listeriotic

Pasteurellosis

rat bite fever

fusospirochaetosis

Actinomycosis

Furthermore, Benzylpenicillin Sodium for Injection is also used for complications in gonorrhea and syphilis (e.g. gonorrheal endocarditis or arthritis, congenital syphilis), provided that the isolate of Neisseria gonorrhea is documented to have sensitivity to penicillin. However, in uncomplicated cases, preference should be given to depot penicillins. Benzylpenicillin Sodium for Injection is not indicated for the treatment of syphilis during pregnancy.

Benzylpenicillin Sodium for Injection 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 for Injection 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 for Injection.

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 0.018 g/kg/day 18mg/kg/day, equivalent to approximately 1-5 mega IU per day 0.6-3 g per day 600-3000 mg per day, divided into 4-6 doses.

High dosage (intravenous):

0.3 mega IU/kg/day 0.18 g/kg/day 180 mg/kg/day, equivalent to about 10-40 mega IU per day 6-24 g per day 6000-24000 mg 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 0.018-0.06 g/kg/day18-60 mg/kg/day, divided into 4-6 doses.

High dosage (intravenous):

0.1-0.5 (-1.0) mega IU/kg/day 0.06-0.3 (-0.6) g/kg/day 60-300 (-600)mg/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 500,000 IU/minute 0.3 g/minute 300 mg/minute is recommended for intravenous doses above 2,000,000 IU 1.2 g 1200 mg.

Newborn infants (2-4 weeks of age):

Normal dosage (intramuscular or intravenous): 0.03-0.1 mega IU/kg/day 0.018-0.06 g/kg/day18-60 mg/kg/day, in 3-4 single doses

High dosage (intravenous): 0.2-0.5 (-1.0) mega IU/kg/day 0.12-0.3 g (-0.6 g)/kg/day 120-300 mg(-600 mg)/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 0.018-0.06 g/kg/day18-60 mg/kg/day, in 2 single doses.

High dosage (intravenous): 0.2-0.5 (-1.0) mega IU/kg/day 0.12-0.3 g (-0.6 g)/kg/day 120-300 mg(-600 mg)/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 for injection be adjusted to the clearance values in each individual case:

Benzylpenicillin for injection dosage for adults and adolescents based on creatinine clearance

CAVE: related to a normalized dosage of 40 mega IU per day 6-24 g per day 6000-24000mg per day in patients with normal renal function

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 for injection(daily dose)	Below 60 years of age:40 (-60) mega IU; 24 (-36 g)24000 (-36000mg);Above 60 years of age:10-40 mega IU 6-24g 6000-24000 mg	10-20 mega IU6-12 g 6000-12000 mg	5-10 mega IU3-6 g 3000-6000mg	2-5 mega IU1.2-3 g 1200-3000 mg

Dosing interval	in 3-6 single doses	in 3 single doses	in 2-3 single doses in 1-2 single doses

Benzylpenicillin for injection 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 for injection (daily dose)	0.03-0.1 mega IU/kg 0.018-0.06g/kg 18-60 mg/kg	0.02-0.06 mega IU/kg 0.012-0.036 g/kg 12-36 mg/kg	0.01-0.04 mega IU/kg 0.006-0.024 g/kg 6-24 mg/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 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 6-48 g/day 6000-48000 mg/day intravenously in combination with aminoglycosides.

Meningitis: Due to increased seizure susceptibility and Jarisch-Herxheimer reactions, no more than 20-30 mega IU/day 12-18 g/day 12000-18000 mg/day should be administered in adults and no more than 12 mega IU/day 7.2 g/day 7200 mg/day in children.

Lyme borreliosis: In adults, 20-30 mega IU/day 12-18 g/day 12000-18000 mg/day intravenously in 2-3 doses over 14 days and in children, 0.5 mega IU/kg/day 0.3 g/kg/day 300 mg/kg/day intravenously in 2-3 doses over 14 days.

Method of administration

Benzylpenicillin for injection can be given intravenously ((injection or short infusion at 10 mega IU/100mL 6 g/100mL 6000 mg/100mL) or also intramuscularly.

Notes for IM injection:

Up to a maximum of 10 mega IU (= approximately 6 g) 6 g 6000 mg [Benzylpenicillin for injection], 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.

5mL 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 infusions are too rapid. A rate of not more than 500,000 IU/minute 0.3 g/minute 300 mg/minute is recommended for intravenous doses above 2,000,000 IU 1.2 g 1200 mg.

For further information on preparation, see section 6.6.

Duration of use

The duration of treatment with [Benzylpenicillin for injection] may vary with the specific indication and should follow the recommendations of the latest updated guidelines from national authorities.

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 inpatients 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.
Severe cutaneous adverse reactions (SCAR), including Stevens Johnson syndrome (SJS),toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms(DRESS) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with beta-lactam antibiotics (including penicillins) treatment (see section 4.8).
Benzylpenicillin is contraindicated in patients who are hypersensitive to penicillins. Patients who have a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to benzylpenicillin (see section 4.3).

Benzylpenicillin should be used with caution in patients with a history of non-severe hypersensitivity reactions to any other beta-lactam antibiotics (e.g. cephalosporins orcarbapenems) and not at all in patients with history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with benzylpenicillin, treatment with the medicinal product should be discontinued and appropriate measures taken.

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 12 g 12000 mg) of [Benzylpenicillin for injection]; see section 4.8)

---existing mononucleosis (increased risk of skin rash)

---when treating co-infections in patients with acute lymphatic leukaemia (increased riskof skin reactions)

---dermatomycoses (para-allergic reactions are possible, as there may be common antigenicity between penicillins and metabolic products of dermatophytes; see section4.8)

In rare cases, prolongation of the prothrombin time has been reported in patients receiving penicillins. Appropriate monitoring should be performed when anticoagulants are coadministered. 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 for injection] 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, [Nationally completed name] 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 6 g/day 6000mg/day), the administration site should be alternated every other day to avoid superinfections and thrombophlebitis.
Due to possible electrolyte disturbances, [Benzylpenicillin for injection] should be administered slowly with infusions of more than 10 mega IU 6 g 6000 mg and,

due to the possibility of seizure reactions, when administering more than 20 mega IU 12 g 12000 mg (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 (≥ 1% to < 10%) in patients receiving10 million IU (equivalent to 6 g) 6 g 6000 mg 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 for injection]. 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 for injection], non-enzymatic urinary glucosedetection and urobilinogen detection may prove false-positive. Enzymatic urine glucosetests should be used in patients on therapy with [Benzylpenicillin for injection], 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 for injection].

[Benzylpenicillin for injection] contains sodium

[500,000 IU powder for solution for injection / infusion] This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

[1,000,000 IU powder for solution for injection / infusion] This medicinal product contains 38.6 mg sodium per vial, equivalent to 1.9 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
[5,000,000 IU powder for solution for injection / infusion] This medicinal product contains 193 mg sodium per vial, equivalent to 9.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
[10,000,000 IU powder for solution for injection / infusion] This medicinal product contains 386 mg sodium per vial, equivalent to 19.3 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant administration of [Benzylpenicillin for injection] is not recommended with:
Based on the general principle not to combine bactericidal and bacteriostatic antibiotics, [Benzylpenicillin for injection] 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 for injection] 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 for injection] 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 for injection], 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 for injection] 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 for injection] 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 for injection] 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 fetal serum. Studies in animals have shown no indications of direct or indirect health effects with regard to reproductive toxicity.

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

Benzylpenicillin 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 sensitization 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. Breast-feeding can be resumed 24 hours after the cessation of treatment.

Fertility

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

4.7 Effects on ability to drive and use machines

Generally, [Benzylpenicillin for injection] has no influence on the ability to concentrate and react.

Due to the occurrence of possible serious undesirable effects (e.g. anaphylactic shock with collapse and anaphylactoid reactions, see also section 4.8),

[Benzylpenicillin for injection] 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 (≥ 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)

Not known (cannot be estimated from the available data)

System Organ Class (MedDRA)	**Common**	**Uncommon**	**Rare**	**Very rare**	**Not known**
Blood and lymphatic system disorders				Eosinophilia, leucopenia, neutropenia, granulocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, coagulation disorders	Prolongation of the bleeding time and prothrombin time (see section 4.4), thrombocytopenia

Immune system disorders	Allergic reactions: urticaria, 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		Serum sickness, Jarisch-Herxheimer reaction in association with spirochete infections (syphilis and Lyme borreliosis), angioedema

	dermatophytes.		
Metabolism and nutrition disorders		Electrolyte imbalances may occur upon rapid infusion of more than 6000 mg.	
Nervous system disorders		Neuropathy. Convulsive reactions may occur upon infusion of high doses (in adults, more than 12000 mg); this should be particularly borne in mind in patients with severely impaired renal function, epilepsy, meningitis, cerebral oedema or during cardiopulmonary bypass.	Metabolic encephalopathy
Gastrointestinal disorders	Stomatitis, glossitis, lingua villosa nigra, nausea, vomiting If diarrhoea develops during treatment, the possibility of	Diarrhoea caused by *Clostridium difficile*	

	pseudomembranous colitis should be considered (see section 4.4).		
Hepatobiliary disorders			Hepatitis, cholestasis
Skin and subcutaneous tissue disorders			Pemphigoid, acute generalised exanthematous pustulosis (AGEP), pruritus, maculopapular rash, rash morbilliform, erythema.
Renal and urinary disorders		Nephropathy(after intravenous administration of more than10 mega IU 6 g6000 mg[Benzylpenicillin for injection]),albuminuria,c	

		ylindruria and hematuria Oliguria or anuria, which can rarely occur during high dose penicillin therapy, generally disappears within48 hours upon discontinuation of treatment. Diuresis can also be stimulated with10% mannitol solution.
General disorders and administration site conditions		Severe local reactions during intramuscular administration to infants.
Investigations	• 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)

Description of selected adverse reactions

Severe cutaneous adverse reactions SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalised exanthematous pustulosis) have been reported with beta-lactam antibiotics, including penicillins (see section 4.4).

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.

4.9 Overdose

Increased neuromuscular hyper excitability or susceptibility to cerebral seizures can be anticipated in the event of an overdose. Countermeasures: discontinuation, clinical surveillance and symptomatic treatment, if required. Benzylpenicillin for injection 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 (version 10.0)

PATHOGEN	**SUSCEPTIBLE**	**RESISTANT**
Staphylococcus *aureus*	≤ 0.125 mg/L	> 0.125 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

(indications other than meningitis)		
Streptococcus pneumoniae (meningitis)	≤ 0.06 mg/L	> 0.06 mg/L
Streptococci of the " Viridans" group	≤ 0.25 mg/L	> 2 mg/L
Neisseria gonorrhoeae	≤ 0.06 mg/L	> 1 mg/L
Neisseria meningitidis	≤ 0.06 mg/L	> 0.25 mg/L
Gram-positive anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Gram-negative anaerobes	≤ 0.25 mg/L	> 0.5 mg/L
Listeria monocytogenes	≤ 1 mg/L	> 1 mg/L
Pasteurella multocida	≤ 0.5 mg/L	> 0.5 mg/L
***Corynebacterium* spp.**	≤ 0.125 mg/L	> 0.125 mg/L
Aerococcus sanguinicola and urinae	≤ 0.125 mg/L	> 0.125 mg/L
Kingella kingae	≤ 0.03 mg/L	> 0.03 mg/L
PK/PD (Non-species-related)breakpoints*	≤ 0.25 mg/L	> 2 mg/L

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: April 2019):

Commonly susceptible species

Aerobic Gram-positive micro-organisms

Actinomyces israelii °

Corynebacterium diphtheriae °

Erysipelothrix rhusiopathiae °

Gardnerella vaginalis °

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Streptococcus dysgalactiae subsp. *equisimilis*

(Group C & G streptococci)

Streptococci of the " Viridans" group ° ^

Aerobic Gram-negative micro-organisms

Borrelia burgdorferi °

Eikenella corrodens ° $

Haemophilus influenzae ° $

Neisseria meningitidis °

Anaerobic micro-organisms

Clostridium perfringens °

Clostridium tetani °

Fusobacterium spp. °

Peptoniphilus spp. °

Peptostreptococcus spp. °

Veillonella parvula °

Other micro-organisms

Treponema pallidum °

Species in which acquired resistance may pose a problem during use

Aerobic Gram-positive micro-organisms

Enterococcus faecalis $

Staphylococcus aureus +

Staphylococcus epidermidis +

Staphylococcus haemolyticus +

Staphylococcus hominis +

Aerobic Gram-negative micro-organisms

Neisseria gonorrhoeae $

Naturally resistant species

Aerobic Gram-positive micro-organisms

Enterococcus faecium

Nocardia asteroides

Aerobic Gram-negative micro-organisms

All *Enterobacterales* species

Legionella pneumophila

Moraxella catarrhalis

Pseudomonas aeruginosa

Anaerobic micro-organisms

Bacteroides spp.

Other micro-organisms

Chlamydia spp.

Chlamydophila spp.

Mycoplasma 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 0.00009-0.00012 g/ml 0.09-0.12 mg/ml are reached15 - 30 min. after IM injection of

10 mega IU 6 g 6000 mg [Benzylpenicillin for injection].After a short infusion (30 min.), peak levels of up to 500 IU/mL 0.0003 g/ml 0.3 mg/ml maybe 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 hydrochloride
- Dopamine hydrochloride
- Heparin
- Hydroxyzine hydrochloride
- lactate
- lincomycin hydrochloride
- metaraminol
- Sodium hydrogen carbonate
- oxytetracycline- pentobarbital
- Tetracycline hydrochloride
- Thiopental sodium
- Vancomycin

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

6.3 Shelf life

Unopened 36 months.

From a microbiological point of view, the product should be used immediately

6.4 Special precautions for storage

Do not store above 30°C

6.5 Nature and contents of container

7ml mould vial with rubber stopper and flip-off cap

Pack size: 50 vials/box or 10vials/box

6.6 Special precautions for disposal and other handling

After contact with skin, wash immediately with water. In case of contact with eyes, rinse immediately with plenty of water and seek medical advice if discomfort persists.

7. Marketing authorization holder

Marketing authorization holder:

Name: Topstone Pharma Limited

Address: 60653-00200 Nairobi. 2nd Floor, Suite 12-13. Aqua Plaza, Muranga Road. Nairobi, Kenya.

Tel: 0768217670

E-mail: admin@topstonepharma.co.ke

Manufacturing site addresses:

Name: Reyoung Pharmaceutical Co., Ltd.

Address: No. 1, Ruiyang Road, Yiyuan County, Shandong Province, China

Tel: 86 533 3223935

Fax:86 533 3224277

E-mail: wang.shijun@reyoungh.com

8. Marketing authorisation number

CTD 13813

9. Date of first authorization or renewal

23 Jan 2026

10. Date of revision of the text

June 5, 2025