Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Benzylpenicillin sodium 600 mg Powder for Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 600 mg benzylpenicillin sodium equivalent to 1,000,000 IU benzylpenicillin.
Each vial contains 38.6 mg of sodium.

3 PHARMACEUTICAL FORM

Powder for solution for injection / infusion.

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

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):
- 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), 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 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): 18 mg/kg/day, equivalent to approximately 600-3000 mg per day, divided into 4-6 doses.
High dosage (intravenous): 180 mg/kg/day, equivalent to about 6000-2400 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): 18-60 mg/kg/day, divided into 4-6 doses.
High dosage (intravenous): 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 300 mg/minute is recommended for intravenous doses above 1200 mg.

Newborn infants (2-4 weeks of age):
Normal dosage (intramuscular or intravenous): 18-60 mg/kg/day, in 3-4 single doses.
High dosage (intravenous): 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): 18-60 mg/kg/day, in 2 single doses.
High dosage (intravenous): 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 sodium be adjusted to the clearance values in each individual case:

Benzylpenicillin sodium dosage for adults and adolescents based on creatinine clearance **CAVE:** related to **a normalized dosage of 6000-24000 mg 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 sodium (daily dose)	Below 60 years of age: 24000 (-36000 mg) Above 60 years of age: 6000-24000 mg	6000-12000 mg	3000-6000 mg	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 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)	18-60 mg/kg	12-36 mg/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 m^2), 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 m^2), 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 6000-48000 mg/day intravenously in combination with aminoglycosides.
Meningitis: Due to increased seizure susceptibility and Jarisch-Herxheimer reactions, no more than 12000-18000 mg/day should be administered in adults and no more than 7200 mg/day in children.
Lyme borreliosis: In adults, 12000-18000 mg/day intravenously in 2-3 doses over 14 days and in children, 300 mg/kg/day intravenously in 2-3 doses over 14 days.

Method of administration
Benzylpenicillin sodium can be given **intravenously** (injection or short infusion at 6000 mg/100 mL or also **intramuscularly**.
Notes for IM injection:
Up to a maximum of 6000 mg 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 infusions are too rapid. A rate of not more than 300 mg/minute is recommended for intravenous doses above 1200 mg.
For further information on preparation, see section 6.6.

Duration of use
The duration of treatment with Benzylpenicillin sodium 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 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.

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 or carbapenems) 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 (> 12000 mg) 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 6000 mg/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 6000 mg and, due to the possibility of seizure reactions, when administering more than 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 receiving 6000 mg benzylpenicillin sodium 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.

Benzylpenicillin sodium contains sodium

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.

4.5 Interaction with other medicinal products and other forms of interaction

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

Generally, Benzylpenicillin sodium 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 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 (≥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			Serum sickness, Jarisch-Herxheimer reaction in association with spirochete infections (syphilis and Lyme borreliosis), angioedema

		and metabolic products of 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 pseudomembranous colitis should be considered (see section 4.4).	Diarrhoea caused by Clostridium difficile		
Hepatobiliary disorders					Hepatitis, cholestasis
Skin and subcutaneous tissue disorders					Pemphigoid, acute generalised exanthematous pustulosis (AGEP), pruritus, maculo-papular rash, rash morbilliform, erythema.
Renal and urinary disorders			Nephropathy (after intravenous administration of		

			more than 6000 mg 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			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: 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 (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**(indications other than meningitis)**	£ 0.06 mg/L	> 2 mg/L
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 0.09-0.12 mg/ml are reached 15 - 30 min. after IM injection of 6000 mg Benzylpenicillin sodium. After a short infusion (30 min.), peak levels of up to 0.3 mg/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 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 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**
300-546 mg/ml (this range includes the recommended concentration for IM injection)	48 hours	8 hours
60 mg/ml (the recommended concentration for IV injection/infusion)	24 hours	4 hours

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, and 100 vials (with nominal volume of 5 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.

This medicinal product is for single use only.

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 60 mg/ml

An isotonic solution is obtained when using WFI as solvent (osmolarity of 60 mg/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 **600 mg** 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 60 mg/ml.

Reconstitution and dilution instructions for IV injection / infusion				
	Reconstitution step		***Dilution step***	
1 vial	*Recommended volume of solvent to be added for reconstitution*	*Resulting (concentrate for) solution for IV injection/infusion*	*Dilution until 6000 mg/100 ml (or 60 mg/ml)*	*Resulting solution for IV injection/infusion*

Benzylpenicillin sodium 600 mg powder for solution for injection / infusion *(contains ± 0.6 gram powder)*	4.6 ml	**concentrate to be diluted before use** 5 ml = 600 mg (120 mg/ml)	1 volume concentrate + 1 volume diluent e.g. add 5 ml concentrate to 5 ml diluent	**ready for use** 10 ml = 600 mg (60 mg/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 60 mg/ml is hypertonic).

The maximum volume for intramuscular administration is 5 ml per injection site and the maximum intramuscular dose is 6000 mg. 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		
1 vial	*Recommended volume of solvent to be added for reconstitution*	*Resulting solution for IM injection* **(maximum 5 ml per injection site)**
Benzylpenicillin sodium **600 mg** powder for solution for injection / infusion *(contains ± 0.6 gram powder)*	0.6 - 1 ml	
	e.g. 0.6 ml	1.1 ml = 600 mg (545 mg/ml)
	e.g. 1 ml	1.5 ml = 600 mg (400 mg/ml)

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/310/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th January 2021
Date of last renewal: 28th September 2021

10 DATE OF REVISION OF THE TEXT