25-06-2026

Direct Healthcare Professional Communication
Penicillin G Infectopharm (Benzylpenicillin Sodium) Important Safety Information Regarding Distribution of certain Batches without English Package Leaflet

Dear Healthcare Professional,

Dhai Taiba Pharmaceutical Company, in agreement with the Saudi Food and Drug Authority (SFDA), would like to notify you of an important safety concern regarding Penicillin G Infectopharm 1 Mega IU Powder for Solution for Injection.

Summary of the Safety Concern

- Certain batches were distributed without an English package leaflet.
- Missing leaflet may limit access to essential prescribing and safety information
- Healthcare professionals should consult the attached English product information
- Patients should be provided with appropriate counselling
- Future batches will contain the English package leaflet

Recommendations for Healthcare Professionals

- Ensure patients receive the necessary medical guidance and counseling in the absence of the English leaflet.
- Refer to the approved English product information provided by the company for full details on indications, dosing, contraindications, warnings, and safety profile.
- Report any suspected adverse reactions related to Penicillin G Infectopharm promptly to the National Pharmacovigilance Center.

Background on the Safety Concern

- Penicillin G Infectopharm (Benzylpenicillin Sodium) is indicated for the treatment of susceptible bacterial infections as described in the approved Saudi SPC.
- The package leaflet is a key reference for healthcare professionals and patients.
- Its absence may increase the risk of inappropriate use, lack of awareness of contraindications, and under-reporting of adverse events.
- Corrective actions are currently being implemented to ensure all future batches distributed in Saudi Arabia will contain the English package leaflet.

Call for Reporting

Healthcare professionals are strongly encouraged to report any suspected adverse reactions associated with Penicillin G Infectopharm

To the National Pharmacovigilance Center NPC – Saudi Food and Drug Authority

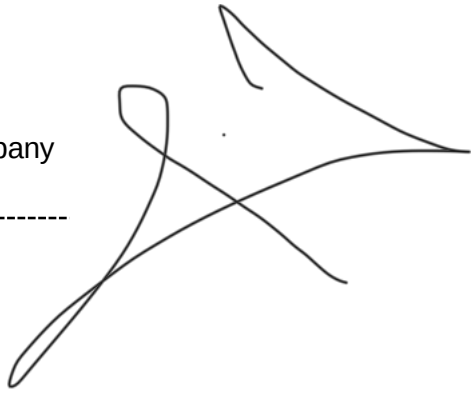
- SFDA Call Center : 19999
- Email: npc.drug@sfda.gov.sa
- Website: https://ade.sfda.gov.sa

Contact Information

For any inquiries regarding this communication, please contact:
Email: pharmacovigilance@dhaitaiba.com
Phone: 0504815709

Sincerely,

Dr. Norah Fahd El Saqr
Pharmacovigilance Director
On behalf of Dhai Taiba Pharmaceutical Company



1. NAME OF THE MEDICINAL PRODUCT

Penicillin G INFECTOPHARM®1 Mega
1 million IU, powder for solution for injection or infusion

Penicillin G INFECTOPHARM®5 Mega
5 million IU, powder for solution for injection or infusion

Penicillin G INFECTOPHARM®10 Mega
10 million IU, powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Benzylpenicillin sodium

Penicillin G INFECTOPHARM 1 Mega 1 vial of powder for solution for injection or infusion contains:

Benzylpenicillin sodium 0.599 g corresponding to 1 million international (IU) benzylpenicillin corresponding units

Penicillin G INFECTOPHARM 5 Mega 1 vial of powder for solution for injection or infusion contains:

Benzylpenicillin sodium 2.994 g equivalent to 5 million International Units (IU) of benzylpenicillin

Penicillin G INFECTOPHARM 10 Mega 1 vial of powder for solution for injection or infusion contains:

Benzylpenicillin sodium 5.988 g equivalent to 10 million International Units (IU) of benzylpenicillin

Penicillin G INFECTOPHARM does not contain any other ingredients (see section 6.1). However, please note the information on sodium content in section 4.4.

3. PHARMACEUTICAL FORM

Powder (in vial) for solution for injection or infusion

4. CLINICAL INFORMATION

4.1 Areas of application

Systemic and/or local infections caused by benzylpenicillin-sensitive pathogens, particularly streptococci, pneumococci, gonococci, meningococci and spirochetes (see section 5.1),

– Acute bacterial sinusitis
– Acute bacterial otitis media
– Tonsillitis
– Community-acquired pneumonia
– Acute exacerbation of chronic bronchitis

– Infections of the gynecological area

– Actinomycosis
– Diphtheria
– Endocarditis and endoplastitis
– Erysipelas
– Gas gangrene
– Meningitis and brain abscess
– Osteomyelitis
– Peritonitis
– Septicemia
– Tetanus
– Wound infections.

Glomerular filtration tion rate (ml/min)	Serum creatinine (mg/100ml)	Single dose Mill. IU of benzylpenicillin (mg benzylpenicillin-Sodium)	Dosing interval (h)
120	0.8	5 (3,000)	6
45	2.0	5 (3,000)	8th
18	3.5	4 (2,400)	8th
8th	6.0	5 (3,000)	12
2	15.5	3 (1,800)	12
under 2	–	2 (1,200)	12

If necessary, combination with another suitable antibiotic is indicated.

In infections caused predominantly by staphylococci, such as osteomyelitis and wound infections, it must now be assumed that benzylpenicillin-resistant staphylococci are present. Treatment with Penicillin G INFECTOPHARM is only indicated after resistance testing.

Penicillin G INFECTOPHARM should not be used as monotherapy in severe infections caused by unknown pathogens.

Official guidelines for the appropriate use of antibacterial agents should be taken into account when using Penicillin G INFECTOPHARM.

4.2 Dosage and method of administration

The International Biological Reference Standard for benzylpenicillin was abolished in 1968 after the substance could be fully characterized by analytical test methods. However, the (biological) International Units are still preferred for the quantitative indication of the dosage.

The following relationships apply to international units (IU) and mass measurements:

1 mg benzylpenicillin sodium corresponds to 1,670 IU benzylpenicillin.

1 million IU of benzylpenicillin corresponds to 598.9 mg of benzylpenicillin sodium.

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

dosage
Benzylpenicillin has a wide dosage range, with the method of administration, the dose level and the dosing interval depending on the type and sensitivity of the pathogen, the severity of the infection and the condition of the patient.

At*Adults and adolescents over 12 years*

For normally sensitive germs, a daily dose of 1 to 5 million IU of benzylpenicillin (corresponding to 600 to 3,000 mg of benzylpenicillin sodium), divided into 4 to 6 individual doses, is recommended. In severe infections, such as bacterial endocarditis or meningitis, the daily dose should be increased to 20 to 60 million IU of benzylpenicillin (corresponding to 12,000 to 36,000 mg of benzylpenicillin sodium).

Children (1 to 12 years)
0.05 to 0.5 million IU benzylpenicillin (equivalent to 30 to 300 mg benzylpenicillin) cillin sodium)/kg body weight (BW) per day in 4 to 6 divided doses.

Infants (1st to 12th month of life)
0.05 to 1.0 million IU benzylpenicillin (equivalent to 30 to 600 mg benzylpenicillin sodium)/kg body weight and day in 3 to 4 individual doses.

Caution: If the infusion is too rapid, cerebral convulsions may occur.

Newborns (up to 4 weeks of age)
0.05 to 0.1 (up to 0.5) million IU benzylpenicillin (corresponding to 30 to 60 [up to 300] mg benzylpenicillin sodium)/kg body weight and day in 2 divided doses.

At*Premature and newborn babies*Due to liver immaturity and reduced excretion of benzylpenicillin, a dosing interval of at least 12 hours should be observed.

Dosage in case of impaired renal function
In patients with impaired renal function, the initial dose is the same as in patients with healthy kidneys.

However, the maintenance dose should be reduced or the dosing interval extended. In patients with impaired renal function, the following dosages are recommended (based on a standard dose with normal renal function of 20 million IU/day and a body weight of 70 kg):

See table above

type of application
Penicillin G INFECTOPHARM is injected or infused intravenously or administered intramuscularly.
In exceptional cases, Penicillin G INFECTOPHARM can also be administered intrathecally.

To prepare the injection or infusion solution, the benzylpenicillin powder should be dissolved in water for injection. 5% glucose solution can also be used as a solvent.

The vials are not suitable for multiple use.

Penicillin G INFECTOPHARM injection or infusion solutions must always be freshly prepared and checked for clarity before administration. Solutions that are cloudy or have precipitates should not be used.

Intravenous injection and infusion
For intravenous injection or infusion, isotonic solutions should be aimed for.

Isotonic solutions contain approximately 100,000 IU benzylpenicillin (equivalent to 60 mg benzylpenicillin sodium)/ml water

for injection purposes, corresponding to a volume of:
– 10 ml for Penicillin G INFECTOPHARM 1 Mega,
– 50 ml for Penicillin G INFECTOPHARM 5 Mega and
– 100 ml for Penicillin G INFECTOPHARM 10 Mega.

Doses exceeding 2 million IU of benzylpenicillin (equivalent to 1,200 mg of benzylpenicillin sodium) should be administered slowly (maximum 0.5 million IU or 300 mg/min) to avoid central nervous system disturbances.

Intramuscular injection
Solutions containing up to 100,000 IU benzylpenicillin (equivalent to 60 mg benzylpenicillin sodium)/ml water for injections are best tolerated.

The intramuscular administration of more highly concentrated solutions, e.g. 0.5 to 1.0 million IU benzylpenicillin (equivalent to 300 to 600 mg benzylpenicillin sodium)/ml water for injections, is possible, but is not completely painless due to the hypertonicity of the solution. The latter applies to a greater extent to solutions of benzylpenicillin in isotonic sodium chloride solution.

It is not recommended to administer single doses of more than 10 million IU of benzylpenicillin (equivalent to 6,000 mg of benzylpenicillin sodium) dissolved in 10 to 20 ml of water for injections intramuscularly.

Intrathecal application
Penicillin G INFECTOPHARM should only be used intrathecally in exceptional cases, whereby a daily dose of 5,000 IU benzylpenicillin (equivalent to 3 mg benzylpenicillin sodium) should not be exceeded.

The freshly prepared solution, warmed to 37 °C, must be injected very slowly after the amount of the injection volume has been drawn from cerebrospinal fluid.

Duration of application
The duration of treatment depends on the response of the pathogens and the clinical presentation; it should be continued for at least 3 days after the fever has subsided.

If no therapeutic effect is apparent after 3 to 4 days, treatment with Penicillin G INFECTOPHARM should be reconsidered.

A notice:
In case of high doses and long-term use, close monitoring of the patient's electrolyte balance is recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Due to the risk of anaphylactic shock, Penicillin G INFECTOPHARM must not be used in patients with proven penicillin hypersensitivity.

In case of hypersensitivity to other beta-lactam antibiotics (e.g. cephalosporins, imipenem), except monobactame (aztreonam), a cross allergy may exist.

4.4 Special warnings and precautions for use

Penicillin G INFECTOPHARM is not the drug of choice for the treatment of otitis media and acute exacerbation of chronic bronchitis, as these are often caused by pathogens that are common (*Staphylococcus aureus*) or always (*Moraxella catarrhalis*, chlamydia, mycoplasma, legionella) are resistant to benzylpenicillin or against which benzylpenicillin is only partially effective (*Haemophilus influenzae*). Therefore, in the cases of the diseases mentioned, the pathogen causing the infection should be identified and its sensitivity should be demonstrated if necessary before starting treatment with Penicillin G INFECTOPHARM. In patients with community-acquired pneumonia with additional risk factors (e.g. structural lung changes, previous antibiotic therapy), empirical therapy with benzylpenicillin is not recommended due to the expected spectrum of pathogens.

Acute hypersensitivity reactions
If anaphylactic shock occurs, appropriate emergency measures must be initiated immediately. Careful monitoring of the patient is necessary as symptoms may recur.

An immediate urticarial reaction must always be considered a threatening sign and strictly requires discontinuation of therapy.

Severe cutaneous skin reactions
Severe cutaneous reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with treatment with beta-lactam antibiotics (including penicillins).

Benzylpenicillin is contraindicated in patients with penicillin hypersensitivity. Patients with a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibiotics 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 other beta-lactam antibiotics (e.g. cephalosporins or carbapenems) and should not be used at all in patients with a history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with benzylpenicillin, treatment with the drug should be discontinued and appropriate measures taken.

Jarisch-Herxheimer reaction
When treating spirochete infections (syphilis, borreliosis), a Jarisch-Herxheimer reaction may occur (usually 2 to 12 hours after the first dose), which is characterized by fever, frostbite, general and focal symptoms (see section 4.8).

Effects on the blood and lymphatic system
After long-term, high-dose benzylpenicillin therapy, dose-dependent neutropenia may occur. With total doses of over 200 million IU (equivalent to 120 g) of benzylpenicillin, this side effect is observed frequently (≥ 1% to < 10%) to very frequently (≥ 10%); below this dose, it is very rare. After discontinuation of therapy, rapid recovery occurs in 90% of cases within 2 to 8 days. If therapy is continued, complete agranulocytosis may occur.

Blood coagulation disorders due to inhibition of platelet aggregation during treatment with benzylpenicillin are also dose-dependent. A significant prolongation of bleeding time occurs in patients with healthy kidneys above a daily dose of 20 million IU (equivalent to 12 g) of benzylpenicillin. The disorder occurs within 24 hours of starting therapy and persists for up to 4 days after discontinuation of benzylpenicillin. At higher concentrations, disorders of plasmatic coagulation can also occur due to disruption of fibrin polymerization, increased antithrombin III activity and inhibition of factor Xa activation.
A small percentage of patients receiving long-term, high-dose therapy develop immune-mediated haemolytic anaemia. The mean total dose was calculated to be 411 million IU (equivalent to 246.6 g) of benzylpenicillin, administered over a mean treatment period of 20 days. Other allergic manifestations are usually not present. Haemolysis may persist for 6 to 8 weeks after discontinuation of penicillin (see sections 4.5 and 4.8).

Effects on the nervous system
Neurotoxic reactions are possible during high-dose benzylpenicillin therapy, particularly in patients with impaired renal function or a tendency to seizures (epilepsy) (see section 4.8). The latter can progress to focal, later generalized seizures and comatose states. In a few of these cases, a fatal outcome has been reported. In the case of cerebral seizures, appropriate treatment is indicated.

Neurotoxic reactions have been observed with daily doses of benzylpenicillin of 40 to 60 million IU (equivalent to 24 to 36 g) in subjects with normal kidney function, 20 million IU (equivalent to 12 g) in patients with mild to moderate renal impairment and 10 million IU (equivalent to 6 g) in patients with severe renal insufficiency.

Special predispositions also exist in infants and the elderly, in patients with a tendency to convulsions, septicemia caused by gram-negative pathogens, endocarditis or cardiac surgery with heart-lung machines.

In case of neurotoxic reactions, which usually occur 12 to 72 hours after starting therapy, Penicillin G INFECTO-PHARM should be discontinued immediately or, if necessary, the dose reduced.

Effects on the gastrointestinal tract
If severe, watery diarrhoea occurs during or after treatment, which may be accompanied by fever or abdominal pain, antibiotic-induced pseudomembranous enterocolitis (see section 4.8) should be considered, which can be life-threatening. In these rare cases (≥ 0.01% to < 0.1%), Penicillin G INFECTOPHARM should be discontinued immediately and appropriate therapy initiated. Agents that inhibit peristalsis are contraindicated.

Effects on the kidney
Interstitial nephritis has been reported occasionally (≥ 0.1% to < 1%) after high-dose, long-term therapy with benzylpenicillin. The daily benzylpenicillin dose varied between 12 and 60 million IU or 7.2 and 36 g (on average 28 million IU or 16.8 g), and the duration of therapy was 7 to 42 days (on average 17 days). In addition to proteinuria and hematuria, fever, eosinophilia and rashes are usually present. However, severe renal insufficiency with anuria can also occur. Angiitic and glomerulonephritic lesions and acute renal failure with complete anuria after a single benzylpenicillin injection have also been described.

Effects on electrolyte balance

Sodium intoxication (hypokalemia, metabolic alkalosis) was observed after administration of 100 million IU (equivalent to 60 g) benzylpenicillin sodium/day.

Precautionary measures for risk groups
- In patients with heart disease or severe electrolyte disturbances of other origin, attention should be paid to electrolyte intake, especially potassium intake.
- In diabetics, delayed absorption from the intramuscular depot is to be expected.
- In patients with dermatomycoses, paraallergic reactions are possible even with the first administration of Penicillin G INFECTOPHARM, since an antigen community may exist between penicillins and metabolic products of dermatophytes.
- For dosage adjustment in patients with impaired renal function, see section 4.2.
- For dosage in premature infants and newborns, see section 4.2.

Note on necessary monitoring measures
During long-term therapy, especially at high doses, blood count, renal function and serum electrolytes should be checked at regular intervals.

Note on topical use
Benzylpenicillin, like all other penicillins, should not be used topically, e.g. in the form of ointments, Powders or drops, since the allergenic potency is particularly high when applied topically.

Instructions for long-term and repeated use
Long-term and repeated use of Penicillin G INFECTOPHARM can lead to superinfections with resistant bacteria and fungi.

Influence on laboratory diagnostic tests
A positive direct Coombs test develops frequently (≥ 1% to < 10%) in patients receiving 10 million IU (equivalent to 6 g) of benzylpenicillin or more per day. After discontinuation of penicillin, the direct antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).

The determination of protein in urine using precipitation methods (sulfosalicylic acid, trichloroacetic acid), the Folin-Ciocalteu-Lowry method or the biuret method can lead to false positive results. The determination of protein in urine should therefore be carried out using other methods.

The determination of amino acids in urine using the ninhydrin method can also lead to false positive results.

Penicillins bind to albumin. In electrophoretic methods for albumin determination, this can simulate pseudobisalbuminemia.

During treatment with benzylpenicillin, the non-enzymatic urine glucose test and the urobilinogen test may be false positive.

When determining 17-ketosteroids (using the Zimmermann reaction) in urine, increased values may occur during therapy with benzylpenicillin.

Notes on certain excipients

Penicillin G INFECTOPHARM 1 Mega contains 38 mg sodium per vial, corresponding to 2% of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

Penicillin G INFECTOPHARM 5 Mega contains 193 mg sodium per vial, corresponding to 9% of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

Penicillin G INFECTOPHARM 10 Mega contains 386 mg sodium per vial, corresponding to 19% of the WHO recommended maximum daily dietary intake of 2 g of sodium for an adult.

4.5 Interactions with other medicinal products and other Interactions

Combination therapy with suitable antibiotics can lead to a synergistic effect. However, Penicillin G INFECTOPHARM should not be combined with bacteriostatic chemotherapeutic agents such as tetracyclines, chloramphenicol, macrolides and sulfonamides.

The simultaneous administration of probenecid leads to increased serum concentrations and a prolongation of the elimination half-life by inhibiting the tubular secretion of benzylpenicillin. Furthermore, probenecid also inhibits the transport of penicillin from the cerebrospinal fluid, so that the already poor penetration of benzylpenicillin into the brain tissue is further reduced when probenecid is administered simultaneously.

The elimination half-life of benzylpenicillin is also prolonged to varying degrees by salicylates, phenylbutazone, indomethacin and sulfinpyrazone.

If diarrhea occurs, the absorption of other orally administered medicines may be disrupted and thus their effectiveness may be impaired.

4.6 Fertility, pregnancy and lactation

pregnancy
Animal experiments and previous experience with the use of benzylpenicillin in pregnant women have not shown any evidence of teratogenic effects. Penicillin G INFECTOPHARM can be used throughout pregnancy if there is an appropriate indication.

Breastfeeding
Benzylpenicillin is only slightly permeable to milk. The concentration in breast milk can reach 2 to 15% of the maternal serum levels. Although no adverse reactions have been reported to date in breast-fed infants, the possibility of sensitisation or impairment of the intestinal flora must be taken into account (see also section 5.3. “Preclinical safety data”).

Attention should be paid to diarrhea and fungal colonization of the mucous membranes in infants.

4.7 Effects on ability to drive and use machines

According to experience to date, Penicillin G INFECTOPHARM generally has no influence on the ability to concentrate or react. However, the occurrence of side effects may alter the ability to react and thus impair active participation in road traffic and the operation of machines (see also section 4.8. “Side effects”).

4.8 Side effects

The following side effects have been observed:

See table on page 4

Frequently ≥1/100 to < 1/10	Clutch nitively ≥1/1,000 by s < 1/100	Rarely ≥1/10,000 to < 1/1,000	Squite rare < 1/10,000	frequency not known
Infections and parasitic diseases				
				Superinfection with resistant germs or fungi (see section 4.4)
Diseases of the blood and lymphatic system ms				
			Leukop enever, granulocyto-penny, Neutropenia, agra-nulocyte Ose, thrombocytosis penny, Pancytopenia, Eosinop hilie, hemolytic Anemia, Blood clotting disturbance en (see section 4.4)	
Diseases of the immune system				
Occasional to frequent allergic reaction (section en (see section 4.4), e.g. allergic vasculitis, angioedema, bronchospasm, laryngeal edema, pulmonary infiltrates, serum sickness syndrome (morbilli- orom, poly-scarlatiniformes) Ex and without eosinophilia, urticaria, edematous symptoms, erythema nodosum, allergic	nEuropean inophile anthem with e Hauter-He Purpura	Anaphylactic shock (very rarely life-threatening; see section 4.4)		Jarisch-Herxheimer-Reaction (see section 4.4)
Metabolic and nutritional disorders				
				Under high doses Therapy: Hypokalaemia and metabolic acidosis due to sodium intoxication (see section 4.4)
Psychiatric disorders				
				Under high doses Therapy: Hallucinations
Diseases of the nervous system				
Under high-dose therapy: neurotoxic effects such as dizziness, hyperreflexia and myoclonus (see section 4.4)				Metabolic encephalopathy; under high-dose therapy: coma, seizures (see section 4.4)
Vascular diseases				
				Arterial vascular occlusions
Diseases of the gastrointestinal tract				
	Glossitis, Stomach atitis, Lingua villosa nigra, Ü nausea, Vomiting, you rchfall	Pseudomembranous Enterocolitis (see section 4.4), diarrhoea (caused by *Clostridium difficile*)		
Liver and gallbladder diseases				
			Acute H epatitis, cholestasis	
Diseases of the skin and subcutaneous tissue ebest				
			Exfoliates ve Dermatitis	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous Pustulosis (AGEP), pruritus, maculopapular lesion stroke, morbilliform rash, erythema
Diseases of the kidneys and urinary tract				
	Interstitial Ne phthisis (see section 4. 4)			Acute renal failure with anuria (see section 4.4)
General ma diseases and complaints at the administration cation location				
Drug fever, pain at the injection site after IM administration, irritation of the vein wall after IV administration, thrombophlebitis				
Investigations				
Positive direct Coombs test (see section 4.4)				

Description of selected side effects

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

Reporting suspected side effects

Reporting suspected side effects after authorisation is very important. It allows continuous monitoring of the benefit-risk ratio of the medicinal product. Healthcare professionals are requested to report any suspected side effects to the Federal Institute for Drugs and Medical Devices, Pharmacovigilance Department, Kurt-Georg-Kiesinger-Allee 3, D-53175 Bonn, website: www.bfarm.de.

4.9 Overdose

No special measures are required in case of overdose with Penicillin G INFECTOPHARM, other than discontinuing the medication.

Benzylpenicillin can be hemodialyzed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Benzylpenicillin (penicillin G) is a semisynthetic, non-beta-lactamase-resistant beta-lactam antibiotic.

ATC code
J01CE01

How it works
The mechanism of action of benzylpenicillin is based on the inhibition of bacterial cell wall synthesis (in the growth phase) by blocking penicillin-binding proteins (PBPs) such as transpeptidases. This results in a bactericidal effect.

Relationship between pharmacokinetics and pharmacodynamics
The effectiveness depends essentially on the length of time during which the drug level is above the MIC of the pathogen.

Resistance mechanisms
Resistance to benzylpenicillin may be due to the following mechanisms:
- Inactivation by beta-lactamases: Benzylpenicillin is not beta-lactamase-resistant and therefore is not effective against beta-lactamase-producing bacteria (e.g. staphylococci or gonococci).
- Reduced affinity of PBPs to benzylpenicillin: The acquired resistance of pneumococci and some other streptococci to benzylpenicillin is based on modifications of existing PBPs as a result of a mutation. The resistance of methicillin (oxacillin)-resistant staphylococci, on the other hand, is due to the formation of an additional PBP with different reduced affinity to benzylpenicillin.
- Insufficient penetration of benzylpenicillin through the outer cell wall of Gram-negative bacteria may result in insufficient inhibition of PBPs.
- Benzylpenicillin can be actively transported out of the cell by efflux pumps.

Partial or complete cross-resistance of benzylpenicillin exists with other penicillins and cephalosporins.

Limit values
Definitions –**S**: sensitive at standard exposure;**I**: sensitive to increased exposure; **R**: resistant
Benzylpenicillin is tested using the usual dilution series. The results are evaluated on the basis of the limit values for benzylpenicillin. The following minimum inhibitory concentrations for sensitive and resistant germs have been established:

EUCAST (European Committee on Antimicrobial Susceptibility Testing) limits (v. 13.0)

Pathogens	S	R
Staphylococcus aureus, Staphylococcus lugdunensis	≤ 0.125 mg/l	> 0.125 mg/l
Streptococcus spp. (Groups A, B, C, G; Infections ßer Meningitis)	≤ 0.25 mg/l	> 0.25 mg/l
Streptococcus spp. (Group B; Meningitis)	≤ 0.125 mg/l	> 0.125 mg/l
Streptococcus pneumoniae (Infections except Meningitis)	≤ 0.06 mg/l	> 2 mg/l
Streptococcus pneumoniae (Meningitis)	≤ 0.06 mg/l	> 0.06 mg/l
Streptococci the "Viridans" group	≤ 0.25 mg/l	> 2 mg/l
Streptococci the "Viridans" Group (only to check fung)	≤ 0.25 mg/l[1)]	0.25mg/l[1)]
Neisseria meningitis	≤ 0.25 mg/l	> 0.25 mg/l
Neisseria gonorrhoeae (only as a surrogate gatmarker)	≤ 0.06 mg/l	> 1 mg/l
*Prevotella*spp.	≤ 0.5 mg/l	> 0.5 mg/l
Fusobacterium necrophorum	≤ 0.06 mg/l	> 0.06 mg/l
Clostridium perfringens	≤ 0.5 mg/l	> 0.5 mg/l
Cutibacterium acne	≤ 0.06 mg/l	> 0.06 mg/l
Listeria monocytogenetic (Infections except meningitis)	1 mg/l	1 mg/l
Non-species-specific Limit values*	≤ 0.25 mg/l	> 2 mg/l

The I category is not displayed. The minimum inhibitory concentrations of the I category are between the limits of the S and R categories.

[1)]Isolates with minimum inhibitory concentrations up to and including 0.25 mg penicillin per liter can be reported as sensitive to those beta-lactam antibiotics for which there is either a clinical breakpoint or a corresponding indication from the test result with penicillin G. For isolates with minimum inhibitory concentrations above 0.25 mg penicillin per liter, sensitivity to other beta-lactam antibiotics should be tested individually.

* Based mainly on serum pharmacokinetics (see www.nak-deutschland.org)

Prevalence of acquired resistance in Germany
The prevalence of acquired resistance in individual species can vary locally and over time. Therefore, local information on the resistance situation is required, particularly for the adequate treatment of severe infections. If the effectiveness of benzylpenicillin is called into question due to the local resistance situation, treatment advice from experts should be sought. In the case of severe infections or treatment failure, a microbiological diagnosis with detection of the pathogen and its sensitivity to benzylpenicillin should be sought.

Prevalence of acquired resistance in Germany based on data from the last 5 years from national resistance surveillance projects and studies (as of April 2023):

Typically sensitive species
Aerobic Gram-positive microorganisms
Actinomyces israelii °
Corynebacterium diphtheriae °
Erysipelothrix rhusiopathiae °
Gardnerella vaginalis °
Listeria monocytogenes
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
*Streptococcus dysgalactiae*subsp. *equisimilis* ° (Streptococci of groups C & G)
Streptococci of the "Viridans" group °^

Aerobic Gram-negative microorganisms
Borrelia burgdorferi °
Eikenella spp. °$
Haemophilus influenzae$
Neisseria meningitidis °
Anaerobic microorganisms
Clostridium perfringens °
Clostridium tetani °
Fusobacterium spp. °
Peptoniphilus spp. °
Peptostreptococcus spp. °
Veillonella parvula °
Other microorganisms
Treponema pallidum °
Species where acquired resistance may pose a problem for use
Aerobic Gram-positive microorganisms
Enterococcus faecalis$
Staphylococcus aureus+
Staphylococcus epidermidis+
Staphylococcus haemolyticus+
Staphylococcus hominis+
Aerobic Gram-negative microorganisms
Neisseria gonorrhoeae$
Naturally resistant species
Aerobic Gram-positive microorganisms
Enterococcus faecium
Nocardia asteroides
Aerobic Gram-negative microorganisms
All *Enterobacterales*-species
Legionella pneumophila
Moraxella catarrhalis
Pseudomonas aeruginosa
Anaerobic microorganisms
Bacteroides spp.
Other microorganisms
Chlamydia spp.
Mycoplasma spp.

° At the time of publication of the table No current data are available. The primary literature, standard works and treatment recommendations assume sensitivity.

$ The natural sensitivity of most ten isolates is in category I (susceptible with increased exposure).

\+ In at least one region the resistance rate is over 50%.
Collective term for a heterogeneous group of streptococcal species. Resistance rate can vary depending on the streptococcal species present.

5.2 Pharmacokinetic properties

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

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

After intramuscular injection of 0.2, 0.5, 1 or 5 million IU (corresponding to 120, 300, 600 or 3,000 mg) of benzylpenicillin sodium, plasma concentrations of 1.7, 4.8, 12 or 42 mg/l are measured after one hour.

After intravenous injection of 1 or 5 million IU (corresponding to 600 or 3,000 mg) of benzylpenicillin sodium, the maximum plasma concentrations are 45 or 234 mg/l, respectively.

After a 1-hour short infusion of 1, 5 or 10 million IU (corresponding to 600, 3,000 or 6,000 mg) of benzylpenicillin sodium, maximum plasma concentrations of approximately 15, 78 or 240 mg/l are reached.

Distribution:
Benzylpenicillin penetrates tissues well, reaching therapeutically effective concentrations in most organs and body fluids. Diffusion in muscles, bones, nerve tissue and the brain is poor. Permeability to the cerebrospinal fluid is low, but is significantly increased in inflamed meninges, so that up to 50% of serum levels can be reached in the cerebrospinal fluid. Benzylpenicillin crosses the placenta. 10 to 30% of the maternal plasma concentrations are found in the fetal circulation. High concentrations are also reached in the amniotic fluid.
In contrast, the transfer into milk is low (2 to 15% of maternal plasma levels).

The volume of distribution is approximately 0.3 to 0.4 l/kg, in children approximately 0.75 l/kg.

Benzylpenicillin binds approximately 45 to 65% to plasma proteins.

Elimination:
Benzylpenicillin is excreted almost exclusively renally, 90% by tubular secretion and 10% by glomerular filtration. A small portion is excreted via the bile.

When administered intravenously, 50 to 70% of the dose is eliminated renally in antibacterially active form, and a further 20% in the form of inactive degradation products, of which penicilloic acid forms the main part.

The plasma half-life is on average 30 to 40 minutes in people with healthy kidneys. It increases to 1.5 hours in old age, to 2 hours in children and to 3 hours in infants.

In case of impaired renal function, the half-life is also prolonged; in anuria it can be 10 hours.

5.3 Preclinical safety data

acute toxicity
The toxicity of benzylpenicillin is very low. Animal experiments have shown only minor acute toxic effects after parenteral administration.

Chronic toxicity
There are no animal studies on the toxicity after repeated administration of benzylpenicillin.

Mutagenic and tumorigenic potential

Benzylpenicillin has not been adequately tested for mutagenic effects. Several bacterial tests showed no evidence of induction of gene mutations. In vitro and in vivo tests to detect chromosomal aberrations are methodologically inadequate, but do not reveal any relevant suspicions.

There are no long-term animal studies of benzylpenicillin to determine its tumorigenic potential.

Reproductive toxicity
Benzylpenicillin crosses the placenta. 1 to 2 hours after application, fetal serum concentrations corresponding to maternal serum levels are reached. Previous experience with pregnant women and studies on rats, rabbits and monkeys have shown no evidence of teratogenic potential.

The concentration in breast milk can be 2 to 15% of the maternal serum levels.

6. PHARMACEUTICAL INFORMATION

6.1 List of excipients

Penicillin G INFECTOPHARM does not contain any other ingredients. However, please note the information on sodium content in section 4.4.

6.2 Incompatibilities

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

Benzylpenicillin is incompatible in solution with, among others, vancomycin, chlorpromazine hydrochloride, heparin sodium, hydroxyzine hydrochloride, lincomycin hydrochloride, oxytetracycline hydrochloride, prochlorperazine mesylate, tetracycline hydrochloride, thiopental sodium.

Benzylpenicillin is incompatible with vitamin B complex and ascorbic acid in joint solution.

Benzylpenicillin must also not be mixed with metaraminol tartrate, pentobarbital, hydrogen carbonates or lactates.

6.3 Shelf life

5 years

The Penicillin G INFECTOPHARM injection or infusion solution must be prepared fresh immediately before use.

Chemical and physical stability of the prepared solution was demonstrated for 8 hours at room temperature (15 to 25 °C).

From a microbiological point of view, the prepared solution should be used immediately. If the prepared solution is not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not store above 25 °C!

Keep the vial in the carton in order to protect from light.

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

6.5 Nature and contents of the container

Vial with powder for solution for injection or infusion in folding box

Pack of
1 × 10 vials with powder

6.6 Special precautions for disposal and other handling

Reconstitution and dilution of injection or infusion solutions:
The contents of a vial of Penicillin G INFECTOPHARM are first dissolved in water for injections (2 – 4 ml for 1 Mega; 20 ml for 5 or 10 Mega). The solution must be further diluted immediately after reconstitution to the target volume of an isotonic solution (see section 4.2):

– 10 ml for Penicillin G INFECTOPHARM 1 Mega,
– 50 ml for Penicillin G INFECTOPHARM 5 Mega and
– 100 ml for Penicillin G INFECTOPHARM 10 Mega.

Instead of water for injections, an appropriate amount of 5% glucose solution can be used. The manufacturer's instructions for use must be observed. Observe the shelf life of the ready-to-use solution (see section 6.3)!

7. AUTHORISATION HOLDER

INFECTOPHARM Pharmaceuticals
and Consilium GmbH
Von-Humboldt-Str. 1
64646 Heppenheim
Phone: 06252/95-7000
Fax: 06252/95-8844
Email: kontakt@infectopharm.com
Internet: www.infectopharm.com

8. APPROVAL NUMBERS

Penicillin G INFECTOPHARM 1 Mega:
3000333.03.00

Penicillin G INFECTOPHARM 5 Mega:
42702.01.00

Penicillin G INFECTOPHARM 10 Mega:
3000333.02.00

9. DATE OF GRANT OF AUTHORISATION/EXTENSION OF APPROVAL

Date of grant of authorisation

Penicillin G INFECTOPHARM 1 Mega:
03/25/1999

Penicillin G INFECTOPHARM 5 Mega:
05/03/1999

Penicillin G INFECTOPHARM 10 Mega:
08/03/1998

Date of last renewal of authorisation

Penicillin G INFECTOPHARM 1 Mega:
04/09/2013

Penicillin G INFECTOPHARM 5 Mega:
02/25/2004

Penicillin G INFECTOPHARM 10 Mega:
04/09/2013

10. STATUS OF INFORMATION

October 2023

11. SALES DEFINITION

Prescription only