Licensläkemedel – Benzetacil

LÄKEMEDELSINFORMATION

Läkemedelsnamn	Benzetacil
Aktiv substans	bensylpenicillin
Beredningsform	Pulver och vätska till injektionsvätska, suspension
Styrka	1200000 IE
Förpackningsstorlek	1st
Förvaring	Rumstemperatur

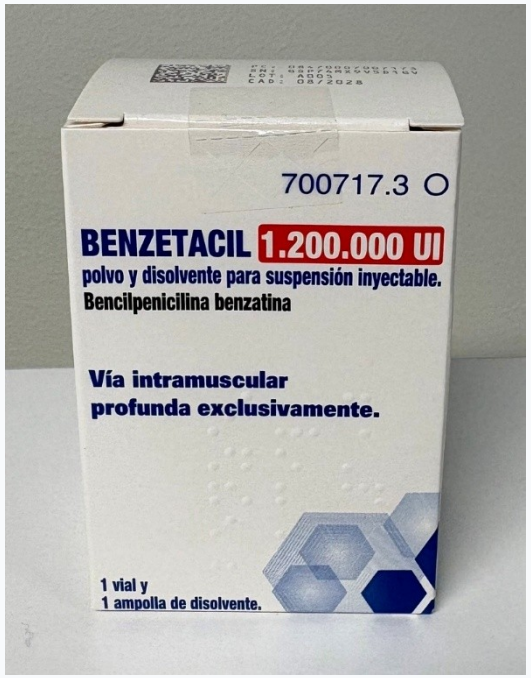
ARTIKEL- & VARUNUMMER

VGR-interna artikelnummer	**10V141**
Varunummer	**693805**

INNEHÅLLSINFORMATION

Skapats av	**annfa33**
Bild tagen	**2026-09-18**
SPC hämtat	**2026-09-18**

FÖRPACKNINGSBILD



The English language text below is provided by Specific Pharma a/s as guidance for healthcare personnel for a better understanding of the original foreign language product information. Specific Pharma a/s cannot be held responsible for any inaccuracies in or misuse of the translation. The translation is for healthcare personnel use only.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

BENZETACIL 2,400,000 IU powder and solvent for suspension for injection
BENZETACIL 1,200,000 IU powder and solvent for suspension for injection
BENZETACIL 600,000 IU powder and solvent for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BENZETACIL 2,400,000 IU powder and solvent for suspension for injection:

Each vial contains 2,400,000 IU of benzathine benzylpenicillin.

- Once the vial is reconstituted with 6 ml of water, the final volume is 7.9 ml, containing 2,400,000 IU of benzathine benzylpenicillin.
- There are 400,000 IU of benzathine benzylpenicillin in 1.31 ml of suspension.

BENZETACIL 1,200,000 IU powder and solvent for suspension for injection:

Each vial contains 1,200,000 IU of benzathine benzylpenicillin.
- Once the vial is reconstituted with 4 ml of water, the final volume is 4.8 ml, containing 1,200,000 IU of benzathine benzylpenicillin.
- There are 300,000 IU of benzathine benzylpenicillin in 1.2 ml of suspension.

BENZETACIL 600,000 IU powder and solvent for suspension for injection:

Each vial contains 600,000 IU of benzathine benzylpenicillin.
- Once the vial is reconstituted with 4 ml of water, the final volume is 4.2 ml, containing 600,000 IU of benzathine benzylpenicillin.
- There are 150,000 IU of benzathine benzylpenicillin in 1.05 ml of suspension.

Excipients with known effect:

BENZETACIL 2,400,000 IU contains 43.78 mg of sodium per vial.

BENZETACIL 1,200,000 IU contains less than 23 mg of sodium per vial.

BENZETACIL 600,000 IU contains less than 23 mg of sodium per vial.

BENZETACIL 2,400,000 IU contains 20.15 mg of soya lecithin per vial.

BENZETACIL 1,200,000 IU contains 10.25 mg of soya lecithin per vial.

BENZETACIL 600,000 IU contains 5.128 mg of soya lecithin per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.
The powder is white or almost white and the solvent is a clear and practically colourless liquid.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Benzathine benzylpenicillin is indicated in the treatment of infections in adults, adolescents, children and neonates (see section 5.1).

For the treatment of:
- Pharyngitis and tonsillitis
- Syphilis: primary and secondary
- Latent syphilis (except neurosyphilis)
- Erysipelas
- Yaws or pinta

For prophylaxis of:

- Rheumatic fever
- Post-streptococcal glomerulonephritis
- Erysipelas

Official guidance on the appropriate use of antibacterial agents should be taken into account.

4.2. Posology and method of administration

Posology

1 million IU are equivalent to 750 mg of pure benzathine benzylpenicillin.

General treatment:
Adults and adolescents: 1,200,000 IU once weekly, as a single dose.
Children >30 kg body weight: 1,200,000 IU once weekly, as a single dose.
Children <30 kg body weight: 600,000 IU once weekly, as a single dose.
For streptococcal diseases, treatment for at least 10 days is recommended to prevent secondary complications.
A single injection of BENZETACIL 600,000 IU, BENZETACIL 1,200,000 IU or BENZETACIL 2,400,000 IU (IM) is generally sufficient.

Pharyngitis, tonsillitis: 1,200,000 IU as a single dose.

Treatment of syphilis:

- *Primary and secondary*:

Adults and adolescents: the recommended dose is 2,400,000 IU administered as a single dose.

Children: the recommended dose is 50,000 IU/kg/day IM as a single dose up to a maximum of 2,400,000 IU (if clinical symptoms recur or laboratory values remain positive, repeat treatment)

- *Late latent syphilis (latent seropositive syphilis):*

Adults and adolescents: the recommended dose is 2,400,000 IU administered weekly for three weeks.
Children: 50,000 IU/kg/day IM as a single dose up to a maximum of 2,400,000 IU.

- *Treatment of congenital syphilis without neurological involvement.*

Neonates and infants: the recommended dose is 50,000 IU/kg as a single dose.

If the patient experiences marked pain, the injection may be administered at two different sites.

Erysipelas: 1,200,000 IU as a single dose.

Yaws or pinta: Adults and adolescents: 1,200,000 IU as a single dose.
Children >30 kg: 1,200,000 IU as a single dose.
Children <30 kg: 600,000 IU as a single dose.

Prophylaxis of rheumatic fever, post-streptococcal glomerulonephritis and erysipelas
Adults and adolescents: 1,200,000 IU every 3 to 4 weeks.

- Children >30 kg: 1,200,000 IU every 3 to 4 weeks.
- Children <30 kg: 600,000 IU every 3 to 4 weeks.
- Duration of treatment:
- a) without cardiac involvement: at least 5 years or until 21 years of age (the longer duration should be used);
- b) transient cardiac involvement: at least 10 years or until 21 years of age (the longer duration should be used);
- c) persistent cardiac involvement: at least 10 years or until 40 years of age (the longer duration should be used); lifelong prophylaxis may sometimes be necessary.

Elderly patients:

Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal impairment:

In patients with renal impairment, the dose should be adjusted according to the degree of renal impairment.

Dosage for adults, adolescents and children according to creatinine clearance			
Creatinine clearance (ml/min)	100-60	50-10	<10
Serum creatinine (mg %)	0.8-1.5	1.5-8	15

Proportion of the normal daily dose of Benzetacil	100%	75%	20–50% (maximum 1–3 million IU/day)
Dose interval	Single administration	Single administration	2–3 separate administrations

Haemodialysis
Benzathine benzylpenicillin can be removed by haemodialysis. There are no data on the influence of dialysis on plasma levels of benzylpenicillin. Therefore, the decision to treat dialysis patients with Benzetacil should be made on a case-by-case basis.

Hepatic impairment
In very severe hepatic and renal impairment, degradation and excretion of penicillins may be delayed.

Method of administration:
Deep intramuscular route only (see section 4.4).

The injection must not be administered into tissues with reduced blood flow (see section 4.4).

BENZETACIL must be administered by deep intramuscular injection into the upper outer quadrant of the gluteus maximus or the ventrogluteal region of Hochstetter, with the needle directed towards the iliac crest. The puncture should be as perpendicular as possible to the skin surface. The injection should be performed as far as possible from major blood vessels. Aspiration must always be performed before injection and the injection must be stopped if blood appears or pain occurs.
In children, the recommended injection site is the lateral mid-thigh muscles (quadriceps femoris). The deltoid muscle is suitable only if well developed; in this case, attention must be paid to the radial nerve.
In infants and young children, the peripheral area of the upper outer quadrant of the gluteal region should be used only in exceptional cases to avoid injury to the sciatic nerve.
For depot preparations, although it is recommended not to administer more than 5 ml per injection site as a tolerance limit, the entire vial may be administered at one site. In case of excessive pain, the volume may be divided between two injection sites.
The injection must be administered as slowly as possible and only with gentle pressure. Avoid rubbing after injection.

Severe local reactions may occur during intramuscular administration, particularly in young children. Whenever possible, taking into account the therapeutic indications and dosing regimens and weighing the benefit–risk balance of the treatments, alternative treatments such as intravenous therapy with an appropriate penicillin should be considered (see section 4.4). For instructions on reconstitution of the medicinal product before administration, see section 6.6.

For instructions on reconstitution, see section 6.6.

4.3. Contraindications

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

– Allergy to penicillins.

– Allergy to cephalosporins: although allergy to cephalosporins does not necessarily imply the existence of allergy to this penicillin, it should be determined whether the patient has previously experienced immediate, moderate or severe allergic reactions following administration of a cephalosporin, in which case use of this penicillin should be avoided.

– This medicinal product contains peanut oil and/or soya oil. It must not be used in cases of peanut or soya allergy.

4.4. Special warnings and precautions for use

Precautions:

BENZETACIL must not be used in tissues with reduced perfusion.
Before initiating therapy with BENZETACIL, a careful investigation of previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents must be carried out (see sections 4.3 and 4.8).

Severe cutaneous adverse reactions (SCARs), 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 treatment with beta-lactam antibiotics (including penicillins).

BENZETACIL is contraindicated in patients hypersensitive to penicillins. Patients with a history of hypersensitivity to cephalosporins, penicillins or other beta-lactam antibacterials may also be hypersensitive to benzylpenicillin (see section 4.3). BENZETACIL should be used with caution in patients with a history of non-severe hypersensitivity reactions to any other beta-lactam antibiotic (e.g. cephalosporins or carbapenems) and must not be used in patients with a history of severe hypersensitivity reactions. If a severe allergic reaction or SCAR occurs during treatment with benzylpenicillin, treatment must be discontinued and appropriate measures instituted.

Before treatment, a hypersensitivity test should be performed if possible. The patient must be made aware of the possible occurrence of allergic symptoms and the need to report them.

Caution is required in patients with the following conditions:
- Allergic diathesis or bronchial asthma (increased risk of hypersensitivity reactions).
- Renal impairment (for dose adjustment, see section 4.2).
- Hepatic impairment (see section 4.2).

Based on a general principle, particularly in some exposed patients, medical observation should be ensured if possible for at least half an hour after administration of this antibiotic, as severe immediate allergic reactions may occur even after the first administration.

When treating syphilis, a Jarisch–Herxheimer reaction may occur due to the action of penicillin on the pathogens. From 2 to 12 hours after administration, headache,

fever, sweating, chills, myalgia, arthralgia, nausea, tachycardia, hypertension followed by hypotension may occur. These symptoms resolve after 10 to 12 hours. Patients should be informed that this is a common transient sequela of antibiotic therapy. Appropriate therapy should be instituted to suppress or attenuate a Jarisch–Herxheimer reaction (see section 4.8)

In the case of long-term treatment (more than 5 days), monitoring of blood count and renal function tests is recommended.

Surveillance for overgrowth of resistant organisms is required. At the onset of secondary infections, appropriate measures should be taken.
In the event of severe and persistent diarrhoea, antibiotic-associated pseudomembranous colitis (bloody/mucous diarrhoea, watery diarrhoea, dull diffuse to colicky abdominal pain, fever, occasionally tenesmus), which may be life-threatening, must be considered. In such cases, BENZETACIL must be discontinued immediately and therapy initiated based on pathogen detection results. Antiperistaltic agents are contraindicated.
If neurological involvement cannot be excluded in patients with congenital syphilis, penicillin forms that achieve higher levels in the cerebrospinal fluid should be used.

In diseases such as severe pneumonia, empyema, sepsis, meningitis or peritonitis, which require higher serum penicillin levels, alternative treatment such as the water-soluble alkaline salt of benzylpenicillin should be considered.

Instructions for administration of BENZETACIL

In the event of accidental subcutaneous administration, painful induration may occur. In such cases, ice packs are useful.

Hoigné syndrome may occur with inadvertent intravascular injection (shock-like symptoms with a sensation of impending death, confusion, hallucinations, possibly cyanosis, tachycardia and motor disturbances, but without circulatory collapse), caused by micro-emboli of the suspension. Symptoms disappear within one hour. If worsening is significant, parenteral administration of sedatives is recommended.

In the event of inadvertent intra-arterial injection, particularly in children, serious complications may occur, such as vascular occlusion, thrombosis, ischaemia, and gangrene of the affected limb. Early signs of these complications may include pallor, coldness, pain, or paraesthesia in the affected limb. If any of these signs occur, immediate medical intervention is required to prevent permanent damage.

Repeated injections associated with long-term treatment with penicillins (e.g. treatment of syphilis) in a limited area of muscle tissue may induce tissue damage and increased local vascularisation. Subsequent injections promote penetration of the substance into the blood, either by direct injection into a blood vessel, caused by injection pressure itself, or by “friction of the depot”. Therefore, during long-term treatments it is recommended to administer each injection as far as possible from the previous injection site.

Interference with analytical tests

- A positive direct Coombs test (≥1% to <10%) is often observed in patients receiving 10 MIU (equivalent to 6 g) or more of benzylpenicillin per day. After discontinuation of penicillin, the antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).
- Determination of protein in urine using precipitation methods (sulphosalicylic acid, trichloroacetic acid). The Folin–Ciocalteu–Lowry method or the biuret method may give false-positive results. Urinary protein should therefore be determined by other methods.
- Determination of amino acids in urine using the ninhydrin method may also lead to false-positive results.
- Penicillins bind to albumin. In electrophoretic methods for albumin determination, pseudo-bis-albuminaemia may be simulated.
- During therapy with BENZETACIL, non-enzymatic detection of glucose in urine and urobilinogen may be falsely positive.
- When determining 17-ketosteroids in urine (using the Zimmerman reaction), values may be increased during treatment with BENZETACIL.

- Asthmatic patients with signs of hypersensitivity to other medicinal products must be medically monitored.

- Renal impairment: in patients with severe renal impairment, dose adjustment is required (see section 4.2).

- Hepatic impairment: in patients with severe hepatic impairment, degradation and excretion of penicillins may be delayed (see section 4.2).

- Epilepsy, cerebral oedema or meningitis (increased risk of seizures, particularly with high doses of benzylpenicillin).

- Presence of mononucleosis, as the risk of skin rash is increased.

- Treatment of co-infections in patients with acute lymphatic leukaemia, as the risk of skin reactions is increased.

- Dermatomycoses.

- Patients with previous allergic reactions to antibiotics or other medicinal products.

Special warnings:

- Under no circumstances administer intravenously, due to the risk of irreversible vascular necrosis.

- In the event of mild exanthematous eruptions, discontinuation of treatment is recommended.

- Do not administer directly into or near an artery or peripheral nerve, as injection may cause neurological or vascular damage.

- Repeated injection of benzathine benzylpenicillin may cause indurations, which are treated with heat applied to the injection site. Therefore, injections should be administered at a different site each time.

- Excipients:

BENZETACIL contains soya lecithin. This medicinal product must not be used in cases of peanut and/or soya allergy.

BENZETACIL 2,400,000 IU contains 43.78 mg of sodium per vial, equivalent to 2.19% of the WHO-recommended maximum daily intake of 2 g sodium for an adult.

BENZETACIL 1,200,000 IU contains less than 1 mmol (23 mg) sodium per vial, i.e. essentially "sodium-free".

BENZETACIL 600,000 IU contains less than 1 mmol (23 mg) sodium per vial, i.e. essentially "sodium-free".

4.5. Interaction with other medicinal products and other forms of interaction

Based on the general principle of not combining bactericidal antibiotics with bacteriostatic antibiotics, benzylpenicillin should not be combined with bacteriostatic antibiotics.

Caution is required when co-administering the following medicinal products:

- Allopurinol: studies with other penicillins (amoxicillin, ampicillin) have reported a possible potentiation of penicillin toxicity at the level of cutaneous reactions. The mechanism is unknown.
- Aminoglycoside antibiotics (neomycin): studies with other penicillins (phenoxymethylpenicillin) have reported a reduction (50%) in plasma concentrations of penicillin, with possible inhibition of its effect, due to malabsorption syndrome caused by the aminoglycoside. In the same context, incompatibility would also apply to vancomycin, amphotericin B, erythromycin, heparin and sodium bicarbonate.
- Anticoagulants: concomitant use with oral anticoagulants may increase the effect of vitamin K antagonists and the risk of bleeding.
- Anti-inflammatory, antirheumatic and antipyretic medicinal products: especially indometacin, phenylbutazone and salicylates at high doses; it should be noted that excretion is competitively inhibited, resulting in an increase in serum concentration.
- Chloramphenicol: studies with ampicillin have reported possible antagonism of action due to their different mechanisms of action, although this is of clinical relevance only in situations where a rapid bactericidal effect is required. Other studies contradict the existence of this interaction.
- Digoxin: should be used with caution as there is a risk of bradycardia.
- Probenecid: studies with benzylpenicillin have reported increased plasma concentrations of benzylpenicillin due to decreased tubular secretion.
- Tetracyclines (chlortetracycline, doxycycline, oxytetracycline): studies have reported possible antagonism of action due to their different mechanisms of action, although this is of clinical relevance only in situations where a rapid bactericidal effect is required.
- Methotrexate: excretion of methotrexate is reduced when administered with benzylpenicillin, which may increase the toxic effects of methotrexate. Concomitant use of methotrexate and penicillin should be avoided if possible. If concomitant use is unavoidable, consideration should be given to reducing the dose of methotrexate and monitoring its serum levels. The patient should be monitored for possible

additional adverse reactions to methotrexate, such as leucopenia, thrombocytopenia and skin ulceration.

4.6. Fertility, pregnancy and lactation

Pregnancy
Penicillins cross the placenta.
There are no or limited data (data on fewer than 300 pregnancies) on the use of benzathine benzylpenicillin in pregnant women.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Use of BENZETACIL during pregnancy is indicated provided that the benefit–risk balance has been assessed.

Breast-feeding
Benzathine benzylpenicillin is excreted in breast milk and effects have been observed in newborns/breast-fed infants of women treated with this medicinal product.
There are insufficient data on the effects of benzathine benzylpenicillin in newborns/children; the possibility of sensitisation or interference with intestinal flora must be taken into account.
Breast-feeding must be discontinued if diarrhoea, candidiasis or skin rash develops in the infant.
Breast-feeding may be resumed 24 hours after discontinuation of treatment.

Fertility
No fertility studies have been conducted in humans.
Reproduction studies conducted in mice, rats and rabbits showed no harmful effects on fertility.

4.7. Effects on ability to drive and use machines

The influence of Benzetacil on the ability to drive and use machines is none or negligible.

4.8. Undesirable effects

Summary of the safety profile
The adverse effects of this medicinal product are generally transient and mild. In most cases, adverse effects are of allergic origin and manifest dermatologically. The toxicological profile of this medicinal product is similar to that of other penicillins, although allergic manifestations are somewhat more frequent, particularly with parenteral administration.

Tabulated list of adverse reactions
Adverse reactions from clinical trials and post-marketing experience are listed in Table 1, according to system organ class and frequency, which are defined as follows:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Table 1. Adverse reactions associated with benzathine benzylpenicillin

System organ class	Frequency	Adverse reactions
Infections and infestations	*Common*	Candidiasis
Blood and lymphatic system disorders	*Very rare*	Eosinophilia, neutropenia, leucopenia, granulocytopenia, agranulocytosis, pancytopenia and coagulation disorders. Prolongation of bleeding time and prothrombin time.
	Not known	Haemolytic anaemia, thrombocytopenia
Immune system disorders	*Rare*	Allergic reactions: urticaria-like rash, angioedema, skin reactions (erythema multiforme, exfoliative dermatitis), fever, painful joints, anaphylactic shock with collapse and anaphylactoid reactions (asthma, haemorrhagic skin lesions called purpura, gastrointestinal disturbances).
	Not known	Serum sickness. When treating syphilis, a Jarisch–Herxheimer reaction may occur due to bacterial destruction, characterised by fever, chills, general and focal symptoms. Para-allergic reactions may occur in patients with cutaneous mycoses. Angioedema
Nervous system disorders	*Rare*	Neuropathy.
	Not known	Encephalopathy with insomnia, confusion, hallucinations, convulsions and status epilepticus, myoclonus, and more rarely aseptic meningitis and benign intracranial hypertension. Metabolic encephalopathy
Gastrointestinal disorders	*Common*	Nausea and diarrhoea.
	Uncommon	Inflammation of the oral mucosa (stomatitis) and tongue (glossitis), vomiting.
	Rare	Pseudomembranous colitis, diarrhoea caused by *Clostridium difficile*
Hepatobiliary disorders	*Not known*	Inflammation of the liver (hepatitis), cholestasis
Skin and subcutaneous tissue disorders	*Common*	Rashes, exanthema, pruritus.
	Not known	Acute generalised exanthematous pustulosis (AGEP), pruritus, maculopapular rash, morbilliform rash, erythema
Renal and urinary disorders	*Rare*	Renal disease (nephropathy), renal inflammation (interstitial nephritis), albuminuria, cylindruria and haematuria. Oliguria and anuria may occur at high doses and generally disappear within 48 hours after the end of treatment
General disorders and administration site conditions	*Common*	Pain and/or infiltrates at the injection site

Any antibacterial treatment that destroys certain germs may result in an imbalance of microorganisms (bacteria/fungi) normally present in humans. As a consequence, the number of other bacteria or fungi may increase, which in rare cases requires treatment.

Description of selected adverse reactions:
Severe cutaneous adverse reactions (SCARs), 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 treatment with beta-lactams, 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 Spanish System of Pharmacovigilance for Medicinal Products for Human Use: https://www.notificaram.es.

4.9. Overdose

Penicillins at extremely high doses may induce neuromuscular excitability or epileptiform convulsions. In the event of suspected overdose, clinical monitoring and symptomatic measures are indicated. Excessive blood levels of penicillins can be corrected by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial agents for systemic use. Beta-lactam-sensitive penicillins, ATC code: J01CE08.

Mechanism of action:

Benzathine benzylpenicillin is a beta-lactam antibiotic with bactericidal activity. It acts by inhibiting bacterial cell wall synthesis during the growth phase. It is active against most aerobic Gram-positive and Gram-negative bacteria, as well as some Gram-positive aerobic and anaerobic bacilli. It is also active against most spirochaetes. It is a chemical precursor of benzylpenicillin.
Benzylpenicillin inhibits the final stage of cross-linking in peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins located on the inner surface of the bacterial cell membrane. However, it is not yet known whether earlier stages of cell wall synthesis may also be inhibited. Other mechanisms involved include bacterial lysis by inactivation of endogenous inhibitors of bacterial autolysins.

Breakpoints

According to EUCAST recommendations (version 10.0, 1 January 2020)

Microorganisms	Susceptible	Resistant
Staphylococcus spp.	≤ 0.125[1] mg/L	> 0.125[1] mg/L
Streptococcus spp. (A, B, C, G)[2]	≤ 0.25 mg/L	> 0.25 mg/L
S. pneumoniae[3]	≤ 0.06 mg/L	> 2 mg/L
Viridans group streptococci	≤ 0.25 mg/L	> 2 mg/L
Neisseria gonorrhoeae[4]	≤ 0.06 mg/L	> 1 mg/L
Neisseria meningitidis	≤ 0.06 mg/L	> 0.25 mg/L
Gram-negative anaerobes[5]	≤ 0.25 mg/L	> 0.5 mg/L
Gram-positive anaerobes except *C. difficile*[5]	≤ 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 *A. urinae*	≤ 0.125 mg/L	> 0.125 mg/L
Kingella kingae	≤ 0.03 mg/L	> 0.03 mg/L
Non-species-related breakpoints	≤ 0.25 mg/L	> 2 mg/L

[1] Most staphylococci produce penicillinase and some are methicillin-resistant. Either mechanism renders them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci susceptible to benzylpenicillin and cefoxitin testing may be reported susceptible to all penicillins. Staphylococci resistant to benzylpenicillin but susceptible to cefoxitin are susceptible to beta-lactamase inhibitor combinations, isoxazolyl penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin) and nafcillin. For orally administered agents, care should be taken to ensure sufficient exposure at the site of infection. Staphylococci resistant to cefoxitin are resistant to all penicillins.
[2] Non-susceptible isolates are rare or not yet reported. Identification and antimicrobial susceptibility test results for such isolates must be confirmed and referred to a reference laboratory.
[3] Breakpoints and doses in pneumonia, see table below:

Penicillin	Standard dose	High dose	Special situations
Benzylpenicillin	0.6 g (1 MU) × 4 IV	1.2 g (2 MU) × 4–6 IV	Meningitis: For a dose of 2.4 g (4 MU) × 6 IV, isolates with MIC ≤ 0.06 mg/L are susceptible. Pneumonia caused by *S. pneumoniae*: dose-related breakpoints: For a dose of 1.2 g (2 MU) × 4 IV, isolates with MIC ≤ 0.5 mg/L are susceptible; For a dose of 2.4 g (4 MU) × 4 IV or 1.2 g (2 MU) × 6 IV, isolates with MIC ≤ 1 mg/L are susceptible. For a dose of 2.4 g (4 MU) × 6 IV, isolates with MIC ≤ 2 mg/L are susceptible.

[4] Always test for beta-lactamase (chromogenic cephalosporin-based tests may be used). If beta-lactamase is positive, report resistance to ampicillin and amoxicillin. If beta-lactamase is negative, determine the MIC of benzylpenicillin. Infer susceptibility to ampicillin and amoxicillin from the benzylpenicillin MIC (do not report susceptibility to benzylpenicillin).
[5] Susceptibility to ampicillin, amoxicillin, piperacillin and ticarcillin may be inferred from susceptibility to benzylpenicillin.

Susceptibility

The prevalence of acquired resistance for a species may vary geographically and over time. Therefore, local information on resistance prevalence is useful, particularly for the treatment of severe infections. If necessary, specialist advice should be sought when the usefulness of the medicinal product is questionable due to local resistance prevalence, certain infection types (especially severe infections), or treatment failure, situations in which microbiological diagnosis and identification of the organism and susceptibility to benzylpenicillin should be performed.

Classification of relevant species according to susceptibility to benzylpenicillin.

Microorganisms usually susceptible or with intermediate susceptibility		
Type of microorganism	Microorganisms	Range of acquired resistance
Aerobic Gram-positive	*Bacillus anthracis*	0%**
	Corynebacterium diphtheriae	0%*
	Haemolytic streptococci (including *Streptococcus pyogenes*)	0%*–3%**
	Listeria monocytogenes	0%**
	Streptococcus pneumoniae	4%*–40%**
	Streptococcus viridans	3–32%*
Aerobic Gram-negative	*Neisseria gonorrhoeae*	9–10%*
	Neisseria meningitidis	18%*
	Pasteurella multocida	0%***
Anaerobes	*Actinomyces israelii*	8%**
	Fusobacterium nucleatum and *Fusobacterium necrophorum*	Usually susceptible
	Gram-positive spore-forming bacilli (including *Clostridium tetani* and *Clostridium perfringens* (welchii))	14%**

	Gram-positive cocci (including *Peptostreptococcus*)	7%*
Other microorganisms	*Borrelia burgdorferi*	Usually susceptible
	Capnocytophaga canimorsus	Usually susceptible
	Leptospirae	Usually susceptible
	Streptobacillus moniliformis and *Spirillum minus*	Usually susceptible
	Treponema pallidum	0%***

* UK data ** European data *** Global data

Species in which acquired resistance may be a problem		
Type of microorganism	Microorganisms	Range of acquired resistance
Aerobic Gram-positive	Coagulase-negative *Staphylococcus*	71–81%*
	Enterococcus spp.	Resistant
	Staphylococcus aureus	79–87%*
Aerobic Gram-negative	*Acinetobacter*	Resistant
	Bordetella pertussis	Generally resistant
	Brucella spp.	Resistant
	Enterobacteriaceae (including *Escherichia coli*, *Salmonella*, *Shigella*, *Enterobacter*, *Klebsiella*, *Proteus*, *Citrobacter*)	Generally resistant
	Haemophilus influenzae	Resistant
	Pseudomonas	Resistant
Anaerobes	*Bacteroides fragilis*	100%***

* UK data ** European data *** Global data

Intrinsically resistant species

Most strains of Staphylococcus aureus are currently resistant to benzylpenicillin. An increasing number of cases of Streptococcus pneumoniae with reduced susceptibility or complete resistance to benzylpenicillin have been observed. Strains of Neisseria meningitidis with reduced susceptibility to benzylpenicillin have been identified. Penicillinase-producing Neisseria gonorrhoeae is widespread; reduced susceptibility of gonococci to benzylpenicillin may also result from alterations in penicillin-binding proteins. Most strains of Haemophilus influenzae and Moraxella catarrhalis (Branhamella catarrhalis) are now resistant.

Known resistance mechanisms and cross-resistance

Resistance to penicillin and other beta lactams may occur via four mechanisms:

1) Destruction of the antibiotic by beta lactamase (the most common resistance mechanism).
2) Failure of the antibiotic to penetrate the outer membrane of Gram negative bacteria to reach penicillin binding proteins (PBPs).
3) Efflux of the drug through the outer membrane of Gram negative bacteria.

Low affinity binding of the antibiotic to PBPs.

5.2. Pharmacokinetic properties

Absorption

Benzathine benzylpenicillin has low solubility and is therefore released slowly at intramuscular injection sites. It is hydrolysed to penicillin G. This combination of hydrolysis and slow absorption results in much lower but more prolonged serum blood levels than other parenteral penicillins.

Distribution

Benzathine benzylpenicillin forms a tissue depot. It enters the bloodstream very slowly and is hydrolysed to benzylpenicillin, providing low and very prolonged serum levels. Maximum plasma concentration is reached between 12 and 48 hours. Approximately 60% is bound to plasma proteins. It is widely distributed to all tissues of the body, especially if inflamed. It crosses the blood–brain barrier to a small extent and the placental barrier to a much greater extent.

Elimination

Benzylpenicillin is metabolised in the liver to a limited extent and its penicilloic acid derivative has been recovered in urine. Elimination occurs largely (50–80%) unchanged via the kidneys (85–95%) as a result of glomerular filtration and active tubular secretion; to a lesser extent, biliary excretion occurs (approximately 5%).

In adults with normal renal function, the half-life is 0.4–0.9 hours. In patients with renal impairment, plasma concentrations may be higher and half-lives prolonged.

5.3. Preclinical safety data

Data from non-clinical studies conducted in mice, rats and rabbits reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and reproductive and developmental toxicity.

6 . PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Vial: Polysorbate 80 (Tween 80), lecithin, sodium citrate (E-331).
Solvent ampoule: Water for injections.

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3. Shelf life

Vial: 5 years

Reconstituted vial: The reconstituted product must be used immediately for intramuscular administration.

6.4. Special precautions for storage

The powder for suspension for injection (vial) must be stored in a dry place.
For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5. Nature and contents of container

Glass vial with bromobutyl stopper sealed with flip-off cap.
Glass ampoule.

Pack sizes:
– Unit packs: 1 vial and 1 ampoule.
– Hospital packs: 100 vials and 100 ampoules.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Disposal of unused medicinal product and all materials that have been in contact with it must be carried out in accordance with local requirements.

Reconstitution and administration of the medicinal product

Once the vial is reconstituted with the contents of the solvent ampoule, a milky white or almost white suspension is obtained.

BENZETACIL must be administered exclusively by deep intramuscular injection into the upper outer quadrant of the gluteal region or into the ventro-gluteal region of Hochstetter, with the needle directed towards the iliac crest. In children, administration into the mid-lateral thigh region is preferred. In infants and young children, the peripheral area of the upper outer quadrant of the gluteal region should only be used as an injection site in exceptional cases, in order to prevent injury to the sciatic nerve.
Before injection, intravascular administration must be excluded by aspiration. In the case of repeated doses, the injection site must be changed.

Instructions for preparation:
For injection of BENZETACIL, a long needle with a gauge of 0.9 mm must be used. Prepare the injectable suspension aseptically by injecting into the vial the water for injections from the ampoule provided in the pack. Use a 4 ml ampoule for BENZETACIL 600,000 IU and 1,200,000 IU doses, and a 6 ml ampoule for the BENZETACIL 2,400,000 IU dose.
Shake until a homogeneous suspension is obtained. Aspirate the contents of the vial with the syringe.
For injection, insert the needle deeply into the gluteal muscle, attach the syringe and aspirate by pulling back the plunger to check that no blood appears, ensuring that the needle is not within the lumen of a blood vessel. Administer as soon as possible to avoid crystallisation within the injection needle, which could cause increased pain to the patient.

7. MARKETING AUTHORISATION HOLDER

LABORATORIO REIG JOFRÉ, S.A.
Gran Capitán, 10
08970 Sant Joan Despí (Barcelona)
Spain

8. MARKETING AUTHORISATION NUMBER(S)

BENZETACIL 2,400,000 IU powder and solvent for suspension for injection – Registration No. 22.295
BENZETACIL 1,200,000 IU powder and solvent for suspension for injection – Registration No. 55.835
BENZETACIL 600,000 IU powder and solvent for suspension for injection – Registration No. 53.848

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: Benzetacil 2,400,000 IU powder and solvent for suspension for injection	30/11/1954
Benzetacil 1,200,000 IU powder and solvent for suspension for injection	12/11/1981
Benzetacil 600,000 IU powder and solvent for suspension for injection	10/09/1976
Date of latest renewal: Benzetacil 2,400,000 IU powder and solvent for suspension for injection	Oct 2007
Benzetacil 1,200,000 IU powder and solvent for suspension for injection	Nov 2011
Benzetacil 600,000 IU powder and solvent for suspension for injection	September 2011
10. DATE OF REVISION OF THE TEXT	
June 2023	

Detailed information on this medicinal product is available on the website of the Spanish Agency for Medicines and Medical Devices (AEMPS): http://www.aemps.gob.es/