NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 1,200,000 IU of benzathine benzylpenicillin.

Once the vial has been 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.

Excipients with known effect

- Lecithin
- Sodium (23 mg 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, almost colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Benzathine benzylpenicillin is indicated in adults, adolescents, children and neonates for the treatment of:

- Pharyngitis and tonsillitis
- Primary and secondary syphilis
- Latent syphilis (except neurosyphilis)
- Erysipelas
- Yaws

And for the prophylaxis of:

- Rheumatic fever
- Post-streptococcal glomerulonephritis
- Erysipelas

4.2 Dose and method of administration

Posology:

1 million IU is 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: 1,200,000 IU once weekly, as a single dose.
- Children < 30 kg: 600,000 IU once weekly, as a single dose.

For streptococcal disease, treatment for at least 10 days is recommended to avoid secondary complications.

Specific indications:

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

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

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

- 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 in single doses up to a maximum of 2,400,000 IU (if clinical symptoms recur or laboratory values remain positive, repeat treatment.)
  - Latent syphilis (latent seropositive syphilis):
    Adults and adolescents: the recommended dose is 2,400,000 IU administered weekly for three weeks.
    Children: the recommended dose is 50,000 IU/kg/day IM in single doses up to a maximum of 2,400,000 IU.
  - Therapy of congenital syphilis: no neurological involvement
    Neonates and infants: the recommended dose is 50,000 IU/kg in single dose.

If the patient reports a lot of pain, it is possible to administer the injection in 2 different sites.

- Rheumatic fever and glomerulonephritis prophylaxis:
  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) no cardiac involvement: at least 5 years or until age 21 years (longer duration should be used),
  (b) transient cardiac involvement: at least 10 years or until the age of 21 years (longer duration should be retained),
  (c) persistent cardiac involvement: at least 10 years or until age 40 (longer duration should be used); Lifetime prophylaxis is sometimes necessary.

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

- Renal insufficiency:
  In patients with renal impairment, the dose should be adjusted according to the degree of severity of renal impairment.

Adult, adolescent and paediatric doses 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	15
Normal daily dosage rate of BENZETACIL	100%	75%	20-50% (1-3 mill of IU/ max day)
Dose interval	In 1 single administration	In 1 single administration	In 2-3 single administrations

- Haemodialysis
  Benzathine benzyl penicillin can be removed by haemodialysis. No data are available on the influence of dialysis on plasma levels of benzyl penicillin. Therefore, the

decision to treat dialysis patients with BENZETACIL must be made on a case-by-case basis.

- Hepatic insufficiency
  In very severe cases of hepatic and renal insufficiency, there may be a delay in the degradation and excretion of penicillins.

Method of administration: **Deep intramuscular injection only.**

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

BENZETACIL should be administered deep intramuscularly in the upper outer quadrant of the gluteus maximus or in the ventro-gluteal region of Hochstetter, aiming towards the iliac crest or according to Hochstetter's method. The puncture should be as perpendicular as possible to the skin surface. The injection should be made as far away as possible from the largest vessels. In any case, before the injection, aspiration should be performed and the injection should be stopped if blood comes out or there is pain.
In children, the mid-lateral thigh muscles (quadriceps femoris) are recommended as the injection site. The deltoid muscle is only suitable if it is well formed. In this case attention should 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 as an injection area only in exceptional cases (e.g. generalised burns), 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 whole vial can be administered at one site. In case of excessive pain, the volume may be divided into two injection sites.
The injection should be administered as slowly as possible and only with gentle pressure. Avoid rubbing after injection.

Serious local reactions may occur during intramuscular administration, especially in young children. Whenever possible, taking into account therapeutic indications and scheduling regimens and weighing the benefit-risk balance of 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 prior to administration, see section 6.6.
In order to see the instructions on reconstitution of the medicinal product prior to administration, see section 6.6..

4.3 Contraindications

- Hypersensitivity to penicillins, cephalosporins, soya, or any excipients
- Known allergy to peanut or soya (due to presence of lecithin)

4.4 Special warnings and precautions for use

Precautions:

BENZETACIL should not be used in tissues with reduced perfusion.
Before initiating therapy with BENZETACIL, careful investigation of previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents should be performed (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 beta-lactam antibiotics (including penicillins) treatment.

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 the medicinal product should be discontinued and appropriate measures taken.

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

Caution should be exercised in patients with the following conditions:
• Allergic diathesis or bronchial asthma (there is an increased risk of a hypersensitivity reaction).
• In renal impairment (for dose adjustment, see section 4.2);
• In hepatic impairment (see section 4.2).

Based on a general principle, in particular in some exposed patients, a medical observation should be ensured if possible 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. Headache, fever, sweating, chills, myalgia, arthralgia, nausea, tachycardia, hypertension followed by hypotension may occur 2 to 12 hours after administration. 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 case of long-term treatment (more than 5 days), monitoring of blood counts and renal function tests is recommended.

Surveillance for overgrowth of resistant germs is required. At the onset of secondary infections, appropriate measures should be taken.

In case of severe and persistent diarrhoea, antibiotic-associated pseudomembranous colitis (bloody/mucous, watery diarrhoea, dull, diffuse to colicky abdominal pain, fever, occasionally tenesmus), which can be life-threatening, should be considered. Therefore in these cases, BENZETACIL should be discontinued immediately and therapy should be initiated on the basis of pathogen detection results. Antiperistaltic agents are contraindicated.
If neurological involvement cannot be excluded in patients with congenital syphilis, forms of penicillin that reach a higher level in the cerebrospinal fluid.

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

<u>Instructions for administration of BENZETACIL</u>

In case of accidental subcutaneous administration, painful induration may occur. In these cases ice packs are useful.

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

In case of unintentional intra-arterial injection, especially in children, serious complications such as vascular occlusion, thrombosis and gangrene may occur. Initial signs are pale marks in the skin area of the gluteal region. After strong pressure during injection, retrograde administration of the injected fluid into the common iliac artery, aorta or spinal arteries may occur.

Repeated injections, associated with long-term treatment with penicillins (e.g. treatment of syphilis), into a limited area of muscle tissue may induce tissue injury and increased local vascularisation.

Subsequent injections promote penetration of the substance into the blood, either by direct injection into a blood vessel, caused by the pressure of the injection itself, or by "deposit friction". Therefore, during long-term treatments, it is recommended to administer each injection as far as possible from the previous injection.

Interference with analytical tests

- A positive direct Coombs' test (≥1% to <10%) is often performed in patients receiving 10 MIU (equivalent to 6g) or more of benzylpenicillin per day. After stopping penicillin, the antiglobulin test may remain positive for 6 to 8 weeks (see section 4.8).
- Urine protein determination using a precipitation method (sulphosalicylic acid, trichloroacetic acid). The Folin-Ciocalteu-Lowry method or the methode du biuret may give false positives. Therefore urinary protein should be determined by other methods.
- The determination of amino acids in urine with the ninhydrin method may also lead to false positive results.
- Penicillins bind to albumin. In electrophoretic methods to determine albumin, pseudo-bis-albuminaemia may be simulated.

- During therapy with BENZETACIL, detection of non-enzymatic urine glucose and urobilinogen may be false positive.
- When determining 17-ketosteroids in urine (using the Zimmerman reaction), values may increase during treatment with BENZETACIL.
- Asthmatic patients with signs of hypersensitivity to other medicinal products should be monitored by a doctor.
- Renal impairment: In patients with severe renal impairment, the dose should be adjusted (see section 4.2).
- Hepatic impairment: In patients with severe hepatic impairment, there may be a delay in the degradation and excretion of penicillins (see section 4.2).
- Epilepsy, cerebral oedema or meningitis (increased risk of seizures, especially with high doses of benzylpenicillin).
- Existence of mononucleosis, as it increases the risk of skin rash.
- In treatment of co-infections in patients with acute lymphocytic leukaemia, as it increases the risk of skin reactions.
- Dermatomycosis.
- Patients with previous allergic reactions to antibiotics or other drugs.

Special warnings:

- Do not administer by IV under any circumstances, due to the risk of irreversible vascular necrosis. In case of the appearance of small exanthematous eruptions, it is advisable to discontinue treatment.
- Do not administer directly or near a peripheral artery or nerve, as the injection may cause neurological or vascular damage.
- Repeated injections of benzathine benzylpenicillin may cause indurations which are treated by heat at the injection site. It is therefore recommended to administer the injections at a different site each time.

Excipients:

BENZETACIL contains soya lecithin. Do not use if you are allergic to peanuts and/or soya.

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

4.5 Interaction with other medicines 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 drugs:

- Allopurinol: studies with other penicillins (amoxicillin, ampicillin) have reported possible potentiation of penicillin toxicity at the level of skin changes. The mechanism is not known.
- Aminoglycoside antibiotics (neomycin): there are some studies with other penicillins (phenoxymethylpenicillin) in which a decrease in plasma concentrations (50%) of penicillin has been recorded, with possible inhibition of its effect, due to the malabsorption syndrome caused by the aminoglycoside. Along the same lines, they would be incompatible with 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 drugs: especially indomethacin, phenylbutazone and salicylates in high doses, it should be noted that excretion is competitively inhibited, resulting in an increase in serum concentration.
- Chloramphenicol: there are studies with ampicillin in which possible antagonism of their actions has been recorded, due to their different mechanisms of action, although it is only of clinical interest in situations where a rapid bactericidal effect is necessary. 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 their actions, due to their different mechanisms of action, although this is only of clinical interest in situations where a rapid bactericidal effect is required.
- Methotrexate: methotrexate excretion is reduced when administered with benzylpenicillin, which may increase the toxicity 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 methotrexate dose and monitoring serum methotrexate levels. The patient should be monitored for additional adverse reactions to methotrexate, such as leukopenia, thrombocytopenia and skin

suppuration. Avoid combination with bacteriostatic antibiotics (e.g. tetracyclines, chloramphenicol)

4.6 Fertility, pregnancy and lactation

Pregnancy

Penicillins cross the placenta.

There are limited or no data (data on less than 300 pregnancies) on the use of benzathine benzylpenicillin in pregnant women.

Animal studies suggest no direct or indirect harmful effects in terms of reproductive toxicity (see section 5.3). The use of BENZETACIL during pregnancy is indicated provided that the risk-benefit balance is assessed.

Lactation

Benzathine benzylpenicillin is excreted in breast milk and effects have been observed in newborns/infants born to women treated with this medicinal product.

There are insufficient data on the effects of benzylpenicillin benzathine on newborns/infants, the possibility of sensitisation or interference with the intestinal flora should be considered.

Breastfeeding should be discontinued if diarrhoea, candidiasis or rash develops in children.

Breastfeeding may be resumed 24 hours after discontinuation of treatment.

Fertility

Fertility studies in humans have not been performed.

Reproduction studies in mice, rats and rabbits showed no adverse effects on fertility.

4.7 Effects on ability to drive and use machines

No or negligible influence on the ability to drive and use machinery

4.8 Undesirable effects

Adverse effects of this medicinal product are generally transient and mild. In most cases the adverse effects are allergic in origin and manifest themselves dermatologically. The toxicological profile of this drug is similar to that of the other penicillins, although allergic manifestations are somewhat more frequent, especially in the parenteral route.

Tabulated list of adverse reactions

Adverse reactions from clinical trials and post-marketing experience are listed in table 1, according to the classification of organ systems and their frequency, which are classified 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)
Frequency not known (cannot be estimated from the available data)

Table 1. Adverse reactions associated with benzathine benzylpenicillin

Organ classification system	**Frequency**	**Adverse reactions**
Infections and infestations	*Common:*	Candidiasis
Blood and lymphatic system disorders	*Very rare:*	Eosinophilia, neutropenia, leukopenia, granulocytopenia, agranulocytosis, pancytopenia and coagulation disorders. Prolongation of bleeding time and prothrombin time. Haemolytic anaemia, thrombocytopenia.
	Frequency not known:	
Immune system disorders	*Rare:*	Allergic reactions: skin rash similar to that caused by a stinging nettle (urticaria), angioedema (swelling), skin reactions (erythema multiforme, exfoliative dermatitis), fever, painful joints, anaphylactic shock with collapse and anaphylactoid reactions (asthma, haemorrhagic skin

		lesion called purpura, gastrointestinal upset).
	Frequency not known:	Serum sickness. When syphilis is treated, a so-called 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 skin mycosis (skin fungus). Angioedema
Nervous system disorders.	*Rare:*	Neuropathy.
	Frequency not known:	Encephalopathy with insomnia, confusion, hallucinations, seizures 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 inflammation of the tongue (glossitis), vomiting.
	Rare:	Pseudomembranous colitis, Diarrhoea caused by Clostridium difficile.

Hepatobiliary disorders	*Frequency not known:*	Inflammation of the liver (hepatitis), bile flow disorder (cholestasis).
Skin and connective tissue disorders:	*Common:* *Frequency not known:*	Rashes, rashes, itching. Acute Generalised Exanthematous Pustulosis (AGEP), pruritus, maculo-papular rash, rash morbilliform, erythema
Renal and urinary disorders	*Rare:*	Renal disease (nephropathy), renal inflammation (interstitial nephritis), albuminuria, cylindruria and haematuria. Oliguria, anuria would occur at high doses which would generally disappear within 48 hours of termination 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 the micro-organisms (bacteria/fungi) normally found 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 (Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematus pustulosis (AGEP)) 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare

professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/}

4.9 Overdose

No cases of overdosage have been reported. Penicillins have minimal toxicity in humans. Excessive blood levels of penicillins can be corrected by haemodialysis.

{For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).}

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial agents for systemic use. Beta-lactamase-sensitive penicillins, ATC code: J01 CE08.

Mechanism of action

Benzathine benzylpenicillin is a beta-lactam antibiotic with bactericidal action. 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 spirochetes. It is a chemical precursor of benzylpenicillin.

Benzylpenicillin inhibits the final cross-linking step in peptidoglycan production by binding to and inactivating transpeptidases, proteins that bind penicillin on the inner side of the bacterial cell membrane. However, it is not yet known whether other early stages of cell wall synthesis may also be inhibited. Other mechanisms involved include bacterial lysis by inactivation of endogenous inhibitors of bacterial autolysins.

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

Pathogen	**Susceptible**	**Resistant**
Staphyloccoccus spp.	≤ 0,1251 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
Streptococcus del grupo Viridans	≤ 0,25 mg/l	>2 mg/l

Neisseria gonorrhoeae4	≤ 0,06 mg/l	>1 mg/l
Neisseria meningitidis	≤ 0,06 mg/l	>0,25 mg/l
Anaerobios Gramnegativos[5]	≤ 0,25 mg/l	>0,5 mg/l
Anaerobios Grampositivos excepto C. difficile5	≤ 0,25 mg/l	>0,25 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 sangunicola and urinae	≤ 0,125 mg/l	>0,125 mg/l
Kingella kingae	≤ 0,03 mg/l	>0,03 mg/l
Non species specific breakpoints	≤ 0,25 mg/l	>2 mg/l

[1] Most staphylococci are penicillinase-producing and some are methicillin resistant.
Any of these mechanisms render them resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Staphylococci that are sensitive to benzylpenicillin and cefoxitin can be reported sensitive to all penicillins. Staphylococci that are resistant to benzylpenicillin but sensitive to cefoxitin are susceptible to combinations of ß-lactamase inhibitors, the isoxazolylpenicillins (oxacillin, cloxacillin, dicloxacillin and flucoxacillin) and nafcillin. For orally administered agents, care must be taken to achieve sufficient exposure at the site of infection. Staphylococci that are resistant to cefoxitin are resistant to all penicillins.

[2] Non-susceptible isolates are rare or have not yet been reported. The identification and antimicrobial susceptibility testing result of any such isolates should be confirmed and sent to the reference laboratory.

[3] Cut-off points and doses in pneumonia, see table:

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

			susceptible. For a dose of 2.4g (4 MU) x 6 iv, isolates with MIC ≤2 mg/L are susceptible.

[4] Always test for beta-lactamase (tests based on a chromogenic cephalosporin can be used). If beta-lactamase positive, report ampicillin and amoxicillin resistant. If beta-lactamase negative, determine MIC of benzylpenicillin. Infer ampicillin and amoxicillin sensitivity from MIC of benzylpenicillin (do not report benzylpenicillin sensitivity).

[5] Sensitivity to ampicillin, amoxicillin, piperacillin and ticarcillin can be inferred from benzylpenicillin sensitivity.

Sensitivity

The prevalence of acquired resistance for a species may vary according to geography and time. Therefore, it is useful to have information on the prevalence of local resistance, especially for the treatment of serious infections. If necessary, expert advice may be appropriate when interest in the drug is questioned at the level of prevalence of local resistance, certain types of infections especially severe ones, or ineffective during treatment, situations for which a microbiological diagnosis should be made and the bacteria and sensitivity to benzylpenicillin should be identified.

Classification of relevant species according to benzylpenicillin susceptibility.

Susceptible and intermediate susceptible micro-organisms		
Type of microorganisms	**Microorganisms**	**Range of acquired resistance**
Gram-positive aerobes	*Bacillus anthracis*	0%**
	Corynebacterium diphtheriae	0%*
	Haemolytic streptococci (included *Streptococcus pyogenes*)	0%* - 3%**
	Listeria monocytogenes	0%**
	Streptococcus pneumoniae	4%* - 40%**

	Streptococcus viridans	3 – 32%*
Gram-negative aerobes	*Neisseria gonorrhoeae*	9 – 10%*
	Neisseria meningitidis	18%*
	Pasteurella multocida	0%***
Anaerobes	*Actinomyces israellii*	8%**
	Fusobacterium nucleatum and Fusobacterium necrophorum	Normally sensitive
	*Gram-positive spore-forming bacilli (*including *Clostridium tetani and Clostridium perfringens (welchii))*	14%**
	*Gram-positive Cocos (*including*peptostreptococcus)*	7%*
Other microorganisms	*Borrelia bugdorferi*	Normally sensitive
	Capnocytophaga canimorosus	Normally sensitive
	Leptospirae	Normally sensitive
	Streptobacillus moniliformis and spirrillum minus	Normally sensitive
	Treponema pallidum	0%***

*UK Data **European Data ***Global Data

Species where acquired resistance may be a problem		
Type of microorganisms	**Microorganisms**	**Range of acquired resistance**
Gram-positive aerobes	Staphylococcus Coagulase negative	71-81%*
	Enterococcus Spp	Resistant
	Staphylococcus aureus	79 – 87%*
Gram-negative aerobes	Acinetobacter	Resistant
	Bordetella pertussis	Generally Resistant
	Brucella spp.	Resistant
	Enterobacteriaceae (including Escherichia coli, Slamonella,	Generally Resistant

	Shigella, Enterobacter, Klebsiella, Proteus, Citrobacter).	
	Haemophilus influenzae	Resistant
	Pseudomonas	Resistant
	Gram-positive Cocos (includingpeptostreptococcus)	100%***
Anaerobes	Bacteroides fragilis	100%***

*UK Data **European Data ***Global Data

Intrinsically resistant species

Most strains of *Staphylococcus aureus* are currently resistant to benzylpenicillin. Increasing cases of *Streptococcus pneumoniae* with reduced sensitivity or complete resistance to benzylpenicillin have been observed. *Neisseria meningitidis* strains with reduced susceptibility to benzylpenicillin have been identified. Penicillinase-producing *Neisseria gonorrhoeae* is widespread; reduced sensitivity of gonococcus to benzylpenicillin may also be the result of alterations in its penicillin-binding proteins. Most strains of *Haemophilus influenzae* and *Moraxella catarrhalis (Branhamella catarrhalis*) are now resistant.

Known mechanisms of resistance and cross-resistance

Resistance to penicillin and other beta-lactams can occur by four mechanisms:

1) Destruction of the antibiotic by β-lactamase. This is the most common mechanism of resistance.
2) Failure of the antibiotic to penetrate the outer membrane of gram-negative bacteria to reach PBPs (penicillin-binding proteins).
3) Outflow of the drug through the outer membrane of gram-negative bacteria. Binding of low affinity antibiotic to PBPs.

5.2 Pharmacokinetic properties

Absorption

Benzathine benzylpenicillin has a low solubility and therefore the drug is 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. The maximum plasma concentration is reached within 12-48 hours.

Approximately 60% is bound to plasma proteins. plasma proteins. It is widely distributed in all tissues of the body, especially if they are 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 the urine. Elimination is 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 (about 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 longer.

5.3 Preclinical safety data

Data from non-clinical studies in mouse, rat and rabbit show no special risks to humans based on

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Do not mix with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Vial: 5 years

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

6.4 Special precautions for storage

Powder for suspension for injection (vial) should be stored in a dry place

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

6.5 Nature and contents of container

Glass vial with bromobutyl stopper and flip-off cap

Glass ampoule of water for injection

Pack sizes: Unit (1 vial + 1 ampoule)

6.6 Special precautions for disposal and other handling

Disposal of unused medicinal product and all materials that have been in contact with the medicinal product shall be carried out in accordance with local regulations.

Reconstitution and administration of the medicinal product

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

BENZETACIL is administered exclusively by deep intramuscular administration in the upper outer quadrant of the gluteous or in the ventroglacial area of Hochstetter with the needle pointing towards the iliac crest. In children, administer preferably in the mid-lateral thigh area. 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, to prevent injury to the sciatic nerve. Before injection, intravascular administration should be excluded by aspiration. In case of repeated doses, change the injection site.

Preparation instructions:

A long 0.9 mm needle should be used for the injection of BENZETACIL. Prepare the suspension aseptically by injecting the water for injections from the ampoule provided in the package into the vial. 4 ml ampoule for BENZETACIL 600.000 and 1.200.000 doses and 6 ml ampoules for BENZETACIL 2.400.000 doses.

Shake until a homogeneous suspension is obtained. Aspirate the contents of the vial with the syringe. To inject, insert the needle deeply into the gluteous, attach the syringe and aspirate by pulling the plunger of the syringe and checking that no blood comes out to ensure that the needle is not in the lumen of a blood vessel. Apply as soon as possible to avoid crystallising inside the injection needle and causing the patient further pain.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

ORSPEC Pharma Management Limited

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9. DATE OF FIRST APPROVAL

29 May 2026

10. DATE OF REVISION OF THE TEXT

SUMMARY TABLE OF CHANGES