Preparations

USP 31: Penicillin V Benzathine Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Abbocillin-V; Cilicaine V; ***Austria:*** Ospen; ***Canad.:*** Pen-Vee†; ***Cz.:*** Ospen; ***Fr.:*** Oracilline; ***Ger.:*** InfectoBicillin; ***Gr.:*** Ospen; ***Hung.:*** Ospen; Oxybion†; ***Pol.:*** Ospen; ***Rus.:*** Ospen (Оспен); ***Spain:*** Benoral; ***Switz.:*** Ospen; Phenocillin; ***Turk.:*** Pen-Os; ***Venez.:*** Ospen.

Benzylpenicillin *(BAN, rINN)*

Bencilpenicilina; Bensylpenicillin; Bentsyylipenisilliini; Benzil Penisiliin; Benzylpénicilline; Benzylpenicillinum; Crystalline Penicillin G; Penicillin; Penicillin G; Penisilin G. (2*S*,5*R*,6*R*)-3,3-Dimethyl-7-oxo-6-(2-phenylacetamido)-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid; (6*R*)-6-(2-Phenylacetamido)penicillanic acid.

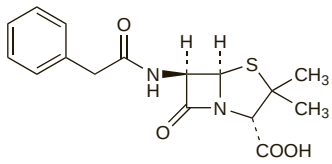
Бензилпенициллин

$C_{16}H_{18}N_2O_4S$ = 334.4.

CAS — 61-33-6.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QJ51CE01; QS01AA14.



Description. The name benzylpenicillin is commonly used to describe either benzylpenicillin potassium or benzylpenicillin sodium as these are the forms in which benzylpenicillin is used. In *Martindale*, benzylpenicillin means either the potassium or sodium salt.

Benzylpenicillin Potassium *(BANM, rINNM)*

Bencilpenicilina potásica; Bensylpenicillinkalium; Bentsyylipenisilliinikalium; Benzilpenicilino kalio druska; Benzilpenicillin-kálium; Benzylopenicylina potasowa; Benzylpenicilin draselná sůl; Benzylpénicilline potassique; Benzylpenicillinum kalicum; Kalii Benzylpenicillinum; Penicillin G Potassium; Penisilin G Potasyum.

Калия Бензилпенициллин

$C_{16}H_{17}KN_2O_4S$ = 372.5.

CAS — 113-98-4.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Potassium). The potassium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Potassium). Colourless or white crystals, or white crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Very soluble in water, in sodium chloride 0.9%, and in glucose solutions; sparingly soluble in alcohol. Its solutions retain substantially full potency for several days at temperatures below 15°, but are rapidly inactivated by acids, by alkali hydroxides, by glycerol, and by oxidising agents. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility and stability. As for Benzylpenicillin Sodium, below.

Benzylpenicillin Sodium *(BANM, rINNM)*

Bencilpenicilina sódica; Bensylpenicillinnatrium; Bentsyylipenisilliininatrium; Benzilpenicilino natrio druska; Benzilpenicillin-nátrium; Benzylopenicylina sodowa; Benzylpenicilin sodná sůl; Benzylpénicilline sodique; Benzylpenicillinum natricum; Natrii Benzylpenicillinum; Penicillin G Sodium; Sodyum Penisilin G.

Натрий Бензилпенициллин

$C_{16}H_{17}N_2NaO_4S$ = 356.4.

CAS — 69-57-8.

ATC — J01CE01; S01AA14.

ATC Vet — QJ01CE01; QS01AA14.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *US*, and *Viet.*

Ph. Eur. 6.2 (Benzylpenicillin Sodium). The sodium salt of a substance produced by growing certain strains of *Penicillium notatum* or related organisms or obtained by any other means. A white or almost white crystalline powder. Very soluble in water; practically insoluble in fatty oils and in liquid paraffin. A 10% solution in water has a pH of 5.5 to 7.5. Store in airtight containers.

USP 31 (Penicillin G Sodium). Colourless or white crystals, or white to slightly yellow crystalline powder. It is odourless or practically so, and is moderately hygroscopic. Its solutions lose potency fairly rapidly at room temperature, but retain substantially full potency for several days at temperatures below 15°. Its solutions are rapidly inactivated by acids, by alkali hydroxides, by oxidising agents, and by penicillinase. pH of a 6% solution in water is between 5.0 and 7.5. Store in airtight containers.

Incompatibility. Benzylpenicillin has been reported to be incompatible with metal ions and some rubber products. Its stability may be affected by ionic and nonionic surfactants, oxidising and reducing agents, alcohols, glycerol, glycols, macrogols and other hydroxy compounds, some paraffins and bases, some preservatives such as chlorocresol or thiomersal, carbohydrate solutions in an alkaline pH, fat emulsions, blood and blood products, and viscosity modifiers. Benzylpenicillin is incompatible with a wide range of acidic and basic drugs (see Stability, below) and with a number of other antimicrobials, including amphotericin B, some cephalosporins, and vancomycin. Benzylpenicillin and aminoglycosides are mutually incompatible and injections should be given at separate sites.

Stability. Benzylpenicillin is hydrolysed in aqueous solutions by degradation of the beta-lactam ring and hydrolysis is accelerated by increased temperature or alkaline conditions; inactivation also occurs under acid conditions. Degradation products include penillic, penicillenic, and penicilloic acids which lower the pH and cause a progressive increase in the rate of deterioration; *N*-formylpenicillamine and very small amounts of penicillamine have also been detected. Degradation is minimal at about pH 6.8 and deterioration of benzylpenicillin in solution may be retarded by using a citrate buffer. Dilute solutions are more stable than concentrated ones.

References.

1. Lynn B. The stability and administration of intravenous penicillins. *Br J Intraven Ther* 1981; **2** (Mar): 22–39.
2. Bird AE, *et al.* N-Formylpenicillamine and penicillamine as degradation products of penicillins in solution. *J Pharm Pharmacol* 1986; **38:** 913–17.

Units

The second International Standard Preparation (1952) of benzylpenicillin sodium contained 1670 units of penicillin per mg but was withdrawn in 1968 since penicillin can now be characterised completely by chemical tests. Despite this, doses of benzylpenicillin are still expressed in units in some countries.

Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

Adverse Effects

The most common adverse effects of benzylpenicillin are hypersensitivity reactions, especially skin rashes; anaphylaxis occasionally occurs and has sometimes been fatal.

Gastrointestinal effects such as diarrhoea and nausea are the most common adverse effects after oral use of benzylpenicillin; a sore mouth or tongue or a black hairy tongue have occasionally been reported. Pseudomembranous colitis has been associated with the use of most antibiotics; ampicillin or amoxicillin are the most frequently implicated penicillins (see Antibiotic-associated Colitis, p.171).

Other adverse effects have generally been associated with large intravenous doses of benzylpenicillin; patients with renal impairment are also at increased risk. These adverse effects include haemolytic anaemia and neutropenia, both of which might have some immunological basis; prolongation of bleeding time and defective platelet function; convulsions and other signs of CNS toxicity (encephalopathy has followed intrathecal dosage and can be fatal); and electrolyte disturbances because of the large amounts of potassium or sodium given when benzylpenicillin potassium or sodium, respectively, are used.

Hepatitis and cholestatic jaundice have been reported rarely with some penicillins, notably penicillinase-resistant penicillins such as flucloxacillin and oxacillin, and also combinations of amoxicillin or ticarcillin with clavulanic acid.

Nephropathy and interstitial nephritis, which may have some immunological basis, have been especially associated with meticillin, but may be produced by other penicillins.

Some patients with syphilis and other spirochaete infections may experience a Jarisch-Herxheimer reaction shortly after starting treatment with penicillin, which is probably due to the release of endotoxins from the killed treponemes and should not be mistaken for a hypersensitivity reaction. Symptoms include fever, chills, headache, and reactions at the site of the lesions. The reaction can be dangerous in cardiovascular syphilis, or where there is a serious risk of increased local damage, such as with optic atrophy.

Hypersensitivity. The overall incidence of allergic reactions to penicillin has been reported to vary from about 1 to 10% although some patients may have been incorrectly labelled 'allergic to penicillin'. Anaphylactic reactions occur in about 0.05% of patients, usually after parenteral use, but they have also been reported after taking oral penicillin.

Hypersensitivity to penicillin gives rise to immediate reactions including anaphylaxis, angioedema, urticaria, and some maculopapular rashes. Late reactions may include serum sickness-like reactions and haemolytic anaemia. Reactions are considered to be due mainly to breakdown products produced *in vitro* before use or to metabolites of penicillin, and possibly penicillin itself. These act as haptens which, when combined with proteins and other macromolecules, produce potential antigens. As the hypersensitivity is related to the basic penicillin structure, patients who are genuinely allergic to benzylpenicillin must be assumed to be allergic to all penicillins; sensitised patients may also react to the cephalosporins and other beta-lactam antibiotics.

Tests for hypersensitivity may be used to determine those patients most likely to develop serious allergic reactions to penicillins. Skin tests are used to evaluate the current risk of immediate or accelerated IgE-mediated reactions, the most serious being anaphylaxis. Both the major and minor determinants of penicillin hypersensitivity should be used; the major determinant is available as penicilloyl-polylysine (p.2364) and a minor-determinant mixture consisting of benzylpenicillin and its derivatives, including penicilloic acid and benzylpenicilloylamine, can be used, although if this is not available a solution of benzylpenicillin may be substituted. Adrenaline should be available in case an anaphylactic reaction develops. The results of skin tests are unreliable if a significant time has elapsed before beginning therapy. A number of *in-vitro* tests including the radioallergosorbent test (RAST) have been developed.

Desensitisation may be attempted in patients allergic to penicillin when treatment with penicillin is considered essential. It involves very small doses of penicillin given at relatively short intervals of 15 minutes or more, and gradually increased to therapeutic concentrations. However, desensitisation may be hazardous and should only be carried out if the patient can be monitored continuously and adrenaline and resuscitation equipment are immediately available. Desensitisation should be regarded as temporary, and allergic reactions may recur during the next exposure to penicillin.

Neutropenia. Neutropenia has been widely reported in patients given high doses of beta lactams and an incidence of from 5 to more than 15% has been reported in patients treated for 10 days or more. Warning signs include fever, rash, and eosinophilia. Monitoring of the leucocyte count is recommended during long-term treatment with high doses. Some have proposed a direct toxic effect whereas others have postulated an immune mechanism.

Effects on the blood. References to neutropenia associated with penicillins.

1. Anonymous. Antibiotic-induced neutropenia. *Lancet* 1985; **ii:** 814.
2. Neftel KA, *et al.* Inhibition of granulopoiesis in vivo and in vitro by β-lactam antibiotics. *J Infect Dis* 1985; **152:** 90–8.
3. Olaison L, Alestig K. A prospective study of neutropenia induced by high doses of β-lactam antibiotics. *J Antimicrob Chemother* 1990; **25:** 449–53.
4. Scheetz MH, *et al.* Systematic review of piperacillin-induced neutropenia. *Drug Safety* 2007; **30:** 295–306.

Effects on the nervous system. References to CNS effects associated with penicillins.

1. Schliamser SE, *et al.* Neurotoxicity of β-lactam antibiotics: predisposing factors and pathogenesis. *J Antimicrob Chemother* 1991; **27:** 405–25.

Hypersensitivity. References to hypersensitivity reactions associated with penicillins.

1. Sullivan TJ, *et al.* Skin testing to detect penicillin allergy. *J Allergy Clin Immunol* 1981; **68:** 171–80.
2. Beeley L. Allergy to penicillin. *BMJ* 1984; **288:** 511–12.
3. Holgate ST. Penicillin allergy: how to diagnose and when to treat. *BMJ* 1988; **296:** 1213–14.
4. Anonymous. Penicillin allergy in childhood. *Lancet* 1989; **i:** 420.
5. Surtees SJ, *et al.* Allergy to penicillin: fable or fact? *BMJ* 1991; **302:** 1051–2. Correspondence. *ibid.*: 1462–3.
6. Anonymous. Penicillin allergy. *Drug Ther Bull* 1996; **34:** 87–8.
7. Salkind AR, *et al.* Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. *JAMA* 2001; **285:** 2498–2505.

Precautions

Patients known to be hypersensitive to penicillins should be given an antibacterial of another class. However, sensitised patients may also react to the cephalosporins and other beta lactams. Desensitisation may be attempted if treatment with a penicillin is considered essential (see Adverse Effects, above). Penicillins should be given with caution to patients with a history of allergy, especially to drugs.

Care is necessary if very high doses of penicillins are given, especially if renal function is poor, because of the risk of neurotoxicity. The intrathecal route should be avoided. Renal, hepatic, and haematological status should be monitored during prolonged and high-dose therapy. Because of the Jarisch-Herxheimer reaction, care is also necessary when treating patients with spirochaete infections, particularly syphilis.

Skin contact with penicillins should be avoided since sensitisation may occur.

Penicillin therapy changes the normal bacterial flora and can lead to superinfection with penicillin-resistant organisms including *Clostridium difficile* or *Candida*, particularly with prolonged use.

Penicillins may interfere with some diagnostic tests such as those for urinary glucose using copper sulfate, direct antiglobulin (Coombs') tests, and some tests for urinary or serum proteins. Penicillins may interfere with tests that use bacteria, for example the Guthrie test for phenylketonuria using *Bacillus subtilis* organisms.

Potassium and sodium content. Each g of benzylpenicillin potassium contains about 2.7 mmol of potassium and each g of benzylpenicillin sodium contains about 2.8 mmol of sodium. Care is necessary if large doses of the potassium or sodium salts are given to patients with renal impairment or heart failure. High doses of benzylpenicillin potassium should also be used with caution in patients receiving potassium-containing drugs or potassium-sparing diuretics.

Interactions

Probenecid prolongs the half-life of benzylpenicillin by competing with it for renal tubular secretion and may be used therapeutically for this purpose. Benzylpenicillin may also interact with bacteriostatic antibacterials such as chloramphenicol and tetracyclines (see Antimicrobial Action, below), and may be incompatible *in vitro* with other drugs, including some other antibacterials (see above).

The possibility of a prolonged bleeding time after oral treatment with a broad-spectrum drug like ampicillin should be borne in mind in patients receiving anticoagulants.

Hormonal contraceptives. For the effect of penicillins on oral contraceptives, see p.2068.

Methotrexate. For the effect of penicillins on methotrexate, see p.748.

Antimicrobial Action

Benzylpenicillin is a beta-lactam antibiotic and has a bactericidal action against Gram-positive bacteria, Gram-negative cocci, some other Gram-negative bacteria, spirochaetes, and actinomycetes.

Mechanism of action. It exerts its killing action on growing and dividing bacteria by inhibiting bacterial cell-wall synthesis, although the mechanisms involved are still not precisely understood. Bacterial cell walls are held rigid and protected against osmotic rupture by peptidoglycan. Benzylpenicillin inhibits the final cross-linking stage of peptidoglycan production by binding to and inactivating transpeptidases, penicillin-binding proteins on the inner surface of the bacterial cell membrane. However, it is now realised that other earlier stages in cell-wall synthesis can also be inhibited. Other mechanisms involved include bacterial lysis by the inactivation of endogenous inhibitors of bacterial autolysins.

Its action is inhibited by penicillinase and other beta-lactamases that are produced during the growth of certain micro-organisms.

Many Gram-negative organisms are intrinsically resistant by virtue of the inability of benzylpenicillin to penetrate their outer membranes. Intrinsic resistance can also be due to structural differences in the target penicillin-binding proteins. See under Resistance, below, for reference to acquired resistance.

Spectrum of activity. The following pathogenic organisms are usually sensitive to benzylpenicillin:

- Gram-positive aerobes and anaerobes including *Bacillus anthracis*, *Clostridium perfringens*, *Cl. tetani*, *Corynebacterium diphtheriae*, *Erysipelothrix rhusiopathiae*, *Listeria monocytogenes*, *Peptostreptococcus* spp., non-beta-lactamase-producing staphylococci, and streptococci including *Streptococcus agalactiae* (group B), *Str. pneumoniae* (pneumococci), *Str. pyogenes* (group A), and some viridans streptococci; enterococci are relatively insensitive.
- Gram-negative cocci including *Neisseria meningitidis* (meningococci) and *Neisseria gonorrhoeae* (gonococci), although beta-lactamase-producing strains are common.
- Gram-negative bacilli including *Pasteurella multocida*, *Streptobacillus moniliformis*, and *Spirillum minus* (or *minor*); most Gram-negative bacilli, including *Pseudomonas* spp. and Enterobacteriaceae, are insensitive although some strains of *Proteus mirabilis* and *Escherichia coli* may be inhibited by high concentrations of benzylpenicillin.
- Gram-negative anaerobes including *Prevotella* (non-fragilis *Bacteroides*) and *Fusobacterium* spp.
- Other organisms including *Actinomyces* and the spirochaetes, *Borrelia*, *Leptospira*, and *Treponema* spp.
- Mycobacteria, fungi, mycoplasmas, and rickettsias are not sensitive.

Activity with other antimicrobials. Benzylpenicillin may exhibit synergy with other antimicrobials, particularly the aminoglycosides, and such combinations have been used against enterococci and other relatively insensitive bacteria. Its activity may be enhanced by clavulanic acid and other beta-lactamase inhibitors, and both enhancement and antagonism have been demonstrated for beta-lactam combinations. Antagonism has been reported to occur with some bacteriostatic drugs, such as chloramphenicol or tetracyclines, that interfere with active bacterial growth necessary for benzylpenicillin to achieve its effect.

Resistance. Susceptible Gram-positive bacteria acquire resistance to beta lactams mainly through the induction of beta-lactamases, including penicillinases. These enzymes are liberated extracellularly and hydrolyse the beta-lactam ring. This resistance is usually plasmid-mediated and can be transferred from one bacterium to another. Gram-negative bacteria produce beta-lactamases within their cell membranes which may be chromosomally or plasmid-mediated; all Gram-negative species probably contain small amounts of beta-lactamases. Resistance in Gram-negative species may also be due to changes in their outer membrane resulting in the failure of beta lactams to reach their target penicillin-binding proteins. Changes in the binding characteristics of penicillin-binding proteins may also result in resistance in Gram-positive and Gram-negative bacteria.

Most strains of *Staphylococcus aureus* are now resistant to benzylpenicillin. *Streptococcus pneumoniae* with reduced susceptibility or complete resistance to benzylpenicillin have increasingly been reported. Strains of *Neisseria meningitidis* with reduced sensitivity to benzylpenicillin have been identified. Penicillinase-producing *Neisseria gonorrhoeae* are widespread; reduced sensitivity 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.

Some organisms, usually Gram-positive cocci such as staphylococci or streptococci, may develop tolerance and are inhibited but not killed by benzylpenicillin; in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration.

Pharmacokinetics

Benzylpenicillin rapidly appears in the blood after intramuscular injection of water-soluble salts, and maximum concentrations are usually reached in 15 to 30 minutes; peak plasma concentrations of about 12 micrograms/mL have been reported after single doses of 600 mg.

When given orally, benzylpenicillin is inactivated fairly rapidly by gastric acid and only up to about 30% is absorbed, mainly from the duodenum; maximum plasma-penicillin concentrations usually occur in about 1 hour. In order to attain plasma-penicillin concentrations after oral use similar to those after intramuscular injection, up to 5 times as much benzylpenicillin may be necessary. Absorption varies greatly in different individuals and is better in patients with reduced gastric acid production, including neonates and the elderly. Food decreases the absorption of benzylpenicillin and oral doses are best given at least half an hour before or 2 to 3 hours after a meal.

Benzylpenicillin is widely distributed at varying concentrations in body tissues and fluids. It appears in pleural, pericardial, peritoneal, and synovial fluids, but in the absence of inflammation diffuses only to a small extent into abscess cavities, avascular areas, the eye, the middle ear, and the CSF. Inflamed tissue is, however, more readily penetrated and, for example, in meningitis higher concentrations of benzylpenicillin are achieved in the CSF. Active transport out of the CSF is reduced by probenecid. In patients with uraemia, other organic acids may accumulate in the CSF and compete with benzylpenicillin for active transport; toxic concentrations of benzylpenicillin sufficient to cause convulsions can result.

Benzylpenicillin diffuses across the placenta into the fetal circulation, and small amounts appear in breast milk.

The plasma half-life is about 30 minutes, although it may be longer in neonates and the elderly because of reduced renal function. In renal impairment the half-life may be increased to about 10 hours. Approximately 60% is reported to be bound to plasma protein.

Benzylpenicillin is metabolised to a limited extent and the penicilloic acid derivative has been recovered in the urine. Benzylpenicillin is rapidly excreted in the urine, principally by tubular secretion and about 20% of a dose given by mouth appears unchanged in the urine; about 60 to 90% of a dose of aqueous benzylpenicillin given intramuscularly appears in the urine, mainly within the first hour. Significant concentrations are achieved in bile, but in patients with normal renal function only small amounts are excreted via the bile. Benzylpenicillin is removed by haemodialysis.

Renal tubular secretion is inhibited by probenecid (p.558), which is sometimes given to increase plasma-penicillin concentrations.

Uses and Administration

Benzylpenicillin is used in the treatment of infections due to susceptible organisms (see Antimicrobial Action, above). They include abscess, actinomycosis, anthrax, bites and stings, diphtheria, endocarditis, gas gangrene, leptospirosis, Lyme disease, meningitis, meningococcal infections, necrotising enterocolitis, necrotising fasciitis, neonatal conjunctivitis (if gonococci are sensitive), perinatal streptococcal infections (intrapartum prophylaxis against group B streptococci), pharyngitis (or tonsillitis), pneumonia, skin infections, syphilis (neurosyphilis and congenital syphilis), tetanus, toxic shock syndrome, and Whipple's disease. It is also used for surgical infection prophylaxis in first trimester abortion in women at high risk of pelvic infection. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Benzylpenicillin is usually given intramuscularly or intravenously. For some indications benzathine benzylpenicillin (p.212) or procaine benzylpenicillin (p.319), which provide a prolonged effect, are preferred; they are given intramuscularly. Benzylpenicillin is sometimes given orally for infections of moderate severity, but one of the acid-resistant penicillins such as phenoxymethylpenicillin (p.314) is preferable.

Benzylpenicillin is available as the potassium or sodium salt. The dose of benzylpenicillin should be sufficient to achieve an optimum bactericidal concentration in the blood as rapidly as possible; concentrations may be increased by giving it with probenecid (p.559). In some countries, doses are still expressed in units. Benzylpenicillin potassium 600 mg or benzylpenicillin sodium 600 mg have generally been considered to be equivalent to about 1 million units (1 mega unit).

For some infections, adult doses of 0.6 to 4.8 g of benzylpenicillin daily in 2 to 4 divided doses by intramuscular or slow intravenous injection or intravenous infusion may be adequate, but higher doses given intravenously, often by infusion, are more usual for severe infections. For example, in endocarditis, benzylpenicillin 7.2 g daily (1.2 g every 4 hours) intravenously, usually with an aminoglycoside, is recommended; doses of up to 18 g daily are not unusual for less sensitive streptococci and enterococci. In meningococcal and pneumococcal meningitis, benzylpenicillin 14.4 g daily (2.4 g every 4 hours) intravenously is recommended; up to 18 g daily has been recommended for meningococcal meningitis. High doses should be given slowly to avoid irritation of the CNS and electrolyte imbalance, and a rate of not more than 300 mg/minute is recommended for intravenous doses above 1.2 g. High doses may need to be reduced in patients with renal impairment.

Infants and children from 1 month to 12 years may be given 100 mg/kg daily in 4 divided doses; infants aged 1 to 4 weeks, 75 mg/kg daily in 3 divided doses; and neonates 50 mg/kg daily in 2 divided doses.

As in adults, higher paediatric doses may be necessary in severe infections. A dose of 180 to 300 mg/kg daily given intravenously in 4 to 6 divided doses is recommended for meningococcal meningitis in infants and children from 1 month to 12 years of age; infants aged 1 to 4 weeks may be given 150 mg/kg daily in 3 divided doses; neonates up to 7 days old may be given 100 mg/kg daily in 2 divided doses.

In patients with suspected meningococcal infection, an intravenous or intramuscular injection of benzylpenicillin should be given before transfer to hospital. Doses are: adults and children aged 10 years or more, 1.2 g; children aged 1 to 9 years, 600 mg; children under 1 year, 300 mg.

A dose for intrapartum prophylaxis against group B streptococcal infection is benzylpenicillin 3 g intravenously initially, then 1.5 g every 4 hours until delivery.

Other routes. Benzylpenicillin eye drops and eye ointment are used in the treatment of susceptible eye infections. For subconjunctival injection, 300 or 600 mg of benzylpenicillin has been dissolved in 0.5 to 1.0 mL of water, or another suitable solvent such as lidocaine 2% with or without adrenaline 1 in 200 000 or similar.

Benzylpenicillin has also been given orally on an empty stomach in adult doses of 125 to 312 mg every 4 to 6 hours.

Intrathecal injections are no longer recommended.

Preparations

BP 2008: Benzylpenicillin Injection;
USP 31: Penicillin G Potassium Capsules; Penicillin G Potassium for Injection; Penicillin G Potassium for Oral Solution; Penicillin G Potassium Injection; Penicillin G Potassium Tablets; Penicillin G Sodium for Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Penilfedrin P; ***Austral.:*** Benpen; ***Braz.:*** Aricilina; Benzecilin; Cristalpen; Megapen†; Pencil P; ***Canad.:*** Crystapen; ***Fin.:*** Geepenil; ***India:*** Pencip; Pentids; ***Irl.:*** Crystapen; ***Mex.:*** Farmabep; Pendiben L-A; Pengesod; Penisol; Procasol; Prosodina; Sodipen; Unicil 3/1; Unicil 6:3:3; Unicil Mega; Xozacil†; ***NZ:*** Benpen; ***Philipp.:*** Pencarv; ***S.Afr.:*** Benzatec; Bio-Pen; Novopen†; ***Spain:*** Coliriocilina†; Penibiot; Penilevel; Peniroger†; Sodiopen; Unicilina; ***Turk.:*** Benzapen 6.3.3; Deposilin 6.3.3; Devapen; Iecilline; Kristapen; Kristasil; Penadur 6.3.3; Pencrist; Penkain-K; Pensilina; Procillin; ***UK:*** Crystapen; ***USA:*** Pfizerpen; ***Venez.:*** Pebencil†; Pronapen; Silcopen†.

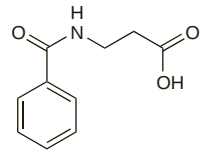
Multi-ingredient: ***Austria:*** Fortepen; Ophcillin N; Retarpen compositum; ***Braz.:*** Benapen; Benzapen G; Despacilina; Drenovac†; Expectovac†; Ginurovac†; Linfocilin†; Odontovac†; Ortocilin†; Pencil 400; Penkaron; Wycillin; ***Chile:*** Karbasalin†; Prevepen Forte; ***Fr.:*** Biclinocilline; ***Ger.:*** Bipensaar; Jenacillin A†; Retacillin compositum; ***Hong Kong:*** Penicillin G Procaine Fortified; ***Hung.:*** Promptcillin Forte; ***India:*** Bistrepen; ***Ital.:*** Tri-Wycillina†; ***Mex.:*** Aguipental; Anapenil; Bencelin Combinado; Benzanil Compuesto; Benzetacil Combinado; Hidrocilina; Lugaxil; Megapenil Forte; Pecivax; Pendiben Compuesto; Penicil; Penipot; Penisodina; Penprocilina; Procilin; Robencaxil; Suipen; ***Neth.:*** Penidural D/F†; ***Port.:*** Atralcilina; Atralmicina; Lentocilin; Penadur 6.3.3†; Prevecilina; ***Rus.:*** Bicillin-3 (Бициллин-3); ***S.Afr.:*** Penilente Forte†; Ultracillin; ***Spain:*** Aquicilina D A; Benzetacil Compuesta; Cepacilina 633; Neopenyl; Penilevel Retard; ***Venez.:*** Benzetacil 3-3; Benzetacil 6-3-3.

Betamipron *(rINN)*

N-Benzoyl-β-alanine; Bétamipron; Betamipronum; CS-443. 3-Benzamidopropionic acid.

Бетамипрон

$C_{10}H_{11}NO_3$ = 193.2.
CAS — 3440-28-6.



Profile

Betamipron is a renal protectant used with the carbapenem antibacterial panipenem to reduce its adverse renal effects.

Preparations

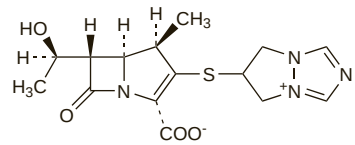
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Jpn:*** Carbenin.

Biapenem *(USAN, rINN)*

Biapénem; Biapenemum; CL-186815; L-627; LJC-10627. 6-{[(4*R*,5*S*,6*S*)-2-Carboxy-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-en-3-yl]thio}-6,7-dihydro-5*H*-pyrazolo[1,2-*a*]-s-triazol-4-ium hydroxide, inner salt.

Биапенем

$C_{15}H_{18}N_4O_4S$ = 350.4.
CAS — 120410-24-4.



Profile

Biapenem is a carbapenem beta-lactam antibacterial similar to imipenem (p.286), although it is reported to be more stable to renal dehydropeptidase I than imipenem.

◊ Reviews.

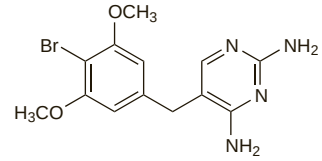
1. Perry CM, Ibbotson T. Biapenem. *Drugs* 2002; **62:** 2221–34.

Brodimoprim *(rINN)*

Brodimoprima; Brodimoprime; Brodimoprimum. 2,4-Diamino-5-(4-bromo-3,5-dimethoxybenzyl)pyrimidine.

Бродимоприм

$C_{13}H_{15}BrN_4O_2$ = 339.2.
CAS — 56518-41-3.
ATC — J01EA02.
ATC Vet — QJ01EA02.



Profile

Brodimoprim is closely related structurally to trimethoprim (p.355) and has been used in the treatment of infections of the respiratory tract and ear.

◊ References.

1. Braunsteiner AR, Finsinger F. Brodimoprim: therapeutic efficacy and safety in the treatment of bacterial infections. *J Chemother* 1993; **5:** 507–11.

Preparations

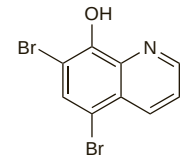
Proprietary Preparations (details are given in Part 3)
Mex.: Novatrim†.

Broxyquinoline *(rINN)*

Broksikinoliini; Broxichinolinum; Broxikinolin; Broxiquinolina; Broxyquinolinum. 5,7-Dibromoquinolin-8-ol.

Броксихинолин

$C_9H_5Br_2NO$ = 303.0.
CAS — 521-74-4.
ATC — A07AX01; G01AC06; P01AA01.
ATC Vet — QA07AX01; QG01AC06.



Profile

Broxyquinoline is a halogenated hydroxyquinoline used topically in vaginal infections. It was formerly given by mouth, with broxaldine, in the treatment of intestinal protozoal infections, including amoebiasis, but less toxic drugs are preferred.

Preparations

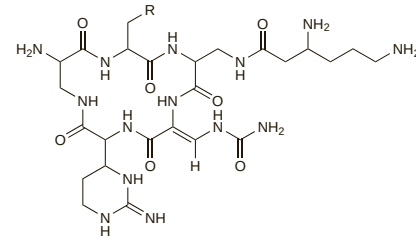
Proprietary Preparations (details are given in Part 3)
Fin.: Starogyn.
Multi-ingredient: ***Fin.:*** Senikolp†.

Capreomycin Sulfate *(USAN, rINNM)*

34977; Capreomycin Sulphate *(BANM)*; Capréomycine, Sulfate de; Capreomycini Sulfas; Capromycin Sulphate; Sulfato de capreomicina.

Капреомицина Сульфат

CAS — 11003-38-6 (capreomycin); 1405-37-4 (capreomycin sulfate).
ATC — J04AB30.
ATC Vet — QJ04AB30.



Capreomycin IA R = OH
Capreomycin IB R = H

(capreomycin)