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†.

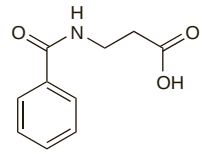
Multi-ingredient: ***Austria:*** Fortepen; Ophcillin N; Retarpen compositum; ***Braz.:*** Benapen; Benzapen G; Despacilina; Drenovac†; Expectovac†; Ginurovac†; Linfocilin†; Odontovac†; Ortocilin†; Pencil 400; Penkaron; Wycillin; ***Chile:*** Karbasalin†; Prevepen Forte; ***Fr.:*** Biclinocilline; ***Ger.:*** 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

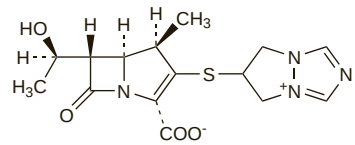
Proprietary Preparations (details are given in Part 3)
Multi-ingredient: ***Jpn:*** Carbenin.

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.

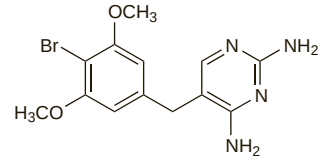
1. Perry CM, Ibbotson T. Biapenem. *Drugs* 2002; **62:** 2221–34.

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

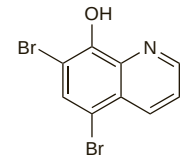
Proprietary Preparations (details are given in Part 3)
Mex.: Novatrim†.

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

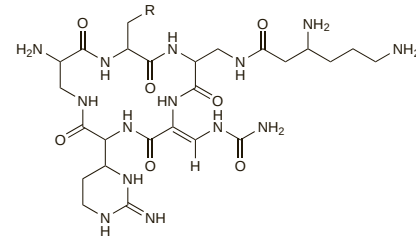
Proprietary Preparations (details are given in Part 3)
Fin.: Starogyn.
Multi-ingredient: ***Fin.:*** Senikolp†.

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)

Description. Capreomycin I consists of capreomycin IA ($C_{25}H_{44}N_{14}O_8$ = 668.7) and capreomycin IB ($C_{25}H_{44}N_{14}O_7$ = 652.7), which predominates. Capreomycin II, which makes up about 10% of the mixture, consists of capreomycin IIA and capreomycin IIB.

Pharmacopoeias. In *Chin.* and *US.*

USP 31 (Capreomycin Sulfate). The disulfate of capreomycin, a polypeptide mixture produced by the growth of *Streptomyces capreolus*. It contains not less than 90% of capreomycin I. A white to practically white amorphous powder. Freely soluble in water; practically insoluble in most organic solvents. pH of a 3% solution in water is between 4.5 and 7.5. Store in airtight containers.

Adverse Effects and Treatment

The effects of capreomycin on the kidney and eighth cranial nerve are similar to those of aminoglycosides such as gentamicin (p.282). Nitrogen retention, renal tubular dysfunction, and progressive renal damage may occur. Hypokalaemia and other electrolyte abnormalities have been reported. Vertigo, tinnitus, and hearing loss may also occur and are sometimes irreversible. Abnormalities in liver function have been reported when capreomycin has been used with other antituberculous drugs. Hypersensitivity reactions including urticaria, maculopapular rashes, and sometimes fever have been reported. Leucocytosis and leucopenia have also been observed. Thrombocytopenia has been reported rarely. Eosinophilia commonly occurs with capreomycin. Capreomycin also has a neuromuscular blocking action. There may be pain, induration, and excessive bleeding at the site of intramuscular injection; sterile abscesses may also form.

Teratogenicity has been seen after high doses in *rodents*.

Treatment of overdose is generally supportive. Patients with normal renal function should be hydrated to maintain adequate urine output. Capreomycin may be removed by haemodialysis in patients with significant renal impairment.

Impurities. The manufacturer of a highly-purified capreomycin product (*Capacin; Cheiljedang, Kor.*) has claimed that such purification reduces the toxicity and alters the pharmacokinetics in *animal* studies, suggesting that some of the toxicity of capreomycin is due to such impurities.[1]

1. Lee SH, *et al.* The impurities of capreomycin make a difference in the safety and pharmacokinetic profiles. *Int J Antimicrob Agents* 2003; **22:** 81–3.

Precautions

Capreomycin should be given with care and in reduced dosage to patients with renal impairment. Care is also essential in patients with signs of eighth cranial nerve damage. It is advisable to monitor renal and auditory function and serum-potassium concentrations in patients before and during therapy. Periodic assessment of hepatic function is also recommended.

Interactions

Care should be taken when capreomycin is used with other drugs that have neuromuscular blocking activity. It should not be given with other drugs that are ototoxic or nephrotoxic.

Antimicrobial Action

Capreomycin has activity against various mycobacteria. Resistance develops readily if capreomycin is used alone. It shows cross-resistance with kanamycin and neomycin.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.
2. Maus CE, *et al.* Molecular analysis of cross-resistance to capreomycin, kanamycin, amikacin, and viomycin in Mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2005; **49:** 3192–7.

Pharmacokinetics

Capreomycin is poorly absorbed from the gastrointestinal tract. An intramuscular dose of 1 g has been reported to give a peak serum concentration of about 30 micrograms/mL after 1 or 2 hours. About 50% of a dose is excreted unchanged in the urine by glomerular filtration within 12 hours. Capreomycin is removed by haemodialysis.

Uses and Administration

Capreomycin is a second-line antimycobacterial that may be used in the treatment of tuberculosis (p.196) as part of a multidrug regimen when resistance to primary drugs has developed.

Capreomycin is given as the sulfate by deep intramuscular injection or by intravenous infusion. The usual dose is the equivalent of 1 g of capreomycin base (maximum 20 mg/kg) given daily for 2 to 4 months, then 2 or 3 times weekly for the remainder of therapy.

For details of doses in infants, children, and adolescents, see below.

Administration in children. For the treatment of drug-resistant tuberculosis in infants, children, and adolescents the American Academy of Pediatrics (AAP) suggests an intramuscular dose of capreomycin 15 to 30 mg/kg daily, to a maximum dose of 1 g daily.

Administration in renal impairment. As with aminoglycosides, the dose of capreomycin in patients with renal impairment must be reduced based on creatinine clearance; the desired steady-state serum capreomycin level is 10 micrograms/mL.

Preparations

USP 31: Capreomycin for Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Capastat; ***Austria:*** Capastat; ***Cz.:*** Capastat†; ***Gr.:*** Capastat; ***Rus.:*** Capastat (Капастат); Lykocin (Лайкоцин); ***Spain:*** Capastat; ***UK:*** Capastat; ***USA:*** Capastat.

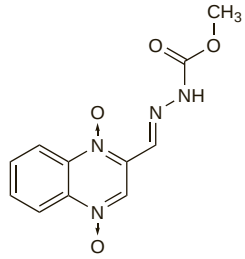
Carbadox *(BAN, USAN, pINN)*

Carbadoxum; GS-6244. Methyl 3-quinoxalin-2-ylmethylenecarbazate 1,4-dioxide.

Карбадокс

$C_{11}H_{10}N_4O_4$ = 262.2.

CAS — 6804-07-5.



Profile

Carbadox is an antibacterial that has been used in veterinary practice for treating swine dysentery and enteritis and for promoting growth. However, its use has been prohibited in the EU and some other countries after reports of carcinogenicity.

Carbenicillin Sodium *(BANM, rINNM)*

BRL-2064; Carbenicilina sódica; Carbenicillin Disodium *(USAN)*; Carbénicilline sodique; Carbenicillinum natricum; α-Carboxybenzylpenicillin Sodium; CP-15-639-2; GS-3159 (carbenicillin potassium); Karbenicillin-nátrium; Karbenicylina sodowa; Natrii Carbenicillinum; NSC-111071. The disodium salt of (6*R*)-6-(2-carboxy-2-phenylacetamido)penicillanic acid .

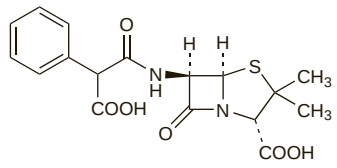
Натрий Карбенициллин

$C_{17}H_{16}N_2Na_2O_6S$ = 422.4.

CAS — 4697-36-3 (carbenicillin); 4800-94-6 (carbenicillin disodium); 17230-86-3 (carbenicillin potassium).

ATC — J01CA03.

ATC Vet — QJ01CA03.



(carbenicillin)

Pharmacopoeias. In *Pol.* and *US.*

USP 31 (Carbenicillin Disodium). A white to off-white crystalline powder. Freely soluble in water; soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of carbenicillin 1% is between 6.5 and 8.0. Store in airtight containers.

Incompatibility. Carbenicillin sodium has been reported to be incompatible with aminoglycosides, tetracyclines, and a number of other drugs including other antimicrobials and these drugs should therefore be given separately.

Adverse Effects

As for Benzylpenicillin, p.213.

Hypersensitivity reactions have been reported to be less frequent and less severe with carbenicillin than with benzylpenicillin. Pain at the injection site and phlebitis may occur. Electrolyte disturbances, particularly hypokalaemia or hypernatraemia, may follow large doses of carbenicillin sodium.

A dose-dependent coagulation defect has been reported, especially in patients with renal impairment. Carbenicillin appears to interfere with platelet function thereby prolonging bleeding time; purpura and haemorrhage from mucous membranes and elsewhere may result.

Precautions

As for Benzylpenicillin, p.214.

Sodium content. Each g of carbenicillin sodium contains about 4.7 mmol of sodium. Carbenicillin sodium should therefore be given with caution to patients on a restricted sodium diet.

Interactions

As for Benzylpenicillin, p.214.

Antimicrobial Action

Carbenicillin has a bactericidal mode of action similar to that of benzylpenicillin, but with an extended spectrum of activity against Gram-negative bacteria. The most important feature of carbenicillin is its activity against *Pseudomonas aeruginosa*, although high concentrations are generally necessary. Activity against *Ps. aeruginosa* and some other organisms can be enhanced by gentamicin and other aminoglycosides. Carbenicillin is also active against *Proteus*, including indole-positive spp. such as *Pr. vulgaris*. It is comparable with ampicillin against other Gram-negative bacteria. Sensitive organisms include some Enterobacteriaceae, for example *Escherichia coli* and *Enterobacter* spp.; *Haemophilus influenzae*; and *Neisseria* spp. *Klebsiella* spp. are usually not susceptible. Its activity against Gram-positive bacteria is less than that of benzylpenicillin. Anaerobic organisms are generally susceptible to carbenicillin, but high concentrations are required for *Bacteroides fragilis*.

Resistance. Carbenicillin is inactivated by penicillinases and some other beta-lactamases, although it is more stable to the chromosomally mediated beta-lactamases produced by some Gram-negative organisms, including *Ps. aeruginosa* and some *Proteus* spp. Resistance to carbenicillin may develop in *Ps. aeruginosa* during treatment with carbenicillin or other beta lactams. This resistance may be intrinsic where there are changes in cell wall permeability or penicillin-binding proteins, or it may be due to plasmid-mediated beta-lactamase production that may be transferred to and from certain strains of Enterobacteriaceae.

There may be cross-resistance between carbenicillin and other antipseudomonal penicillins.

Outbreaks of pseudomonal resistance to carbenicillin have been associated with extensive use in, for example, hospital burns units.

Pharmacokinetics

Carbenicillin is not absorbed from the gastrointestinal tract and has therefore been given either intramuscularly or intravenously.

The half-life of carbenicillin is reported to be about 1 to 1.5 hours; it is increased in patients with renal impairment, especially if there is also hepatic impairment, and also in neonates. Half-lives of 10 to 18 hours have been reported in renal impairment. Clearance is enhanced in patients with cystic fibrosis. Carbenicillin is about 50% bound to plasma proteins. Distribution of carbenicillin in the body is similar to that of other penicillins. Small amounts have been detected in breast milk. There is little diffusion into the CSF except when the meninges are inflamed.

Relatively high concentrations have been reported in bile, but carbenicillin is excreted principally by renal tubular secretion and glomerular filtration.

Probenecid increases and prolongs plasma concentrations of carbenicillin.

Carbenicillin is removed by haemodialysis and, to some extent, by peritoneal dialysis.

Uses and Administration

Carbenicillin is a carboxypenicillin that has been given by injection as the disodium salt, often with gentamicin, in the treatment of infections due to *Pseudomonas aeruginosa*; however, other antipseudomonal penicillins such as ticarcillin (p.352) or piperacillin (p.315) are now preferred. It has also been given to treat serious infections due to non-penicillinase-producing strains of *Proteus* spp.

Esters of carbenicillin, such as carfecillin (p.217) and carindacillin (p.217), have been given orally in the treatment of urinary-tract infections.

Preparations

USP 31: Carbenicillin for Injection.

Proprietary Preparations (details are given in Part 3)

Mex.: Carbecin†.