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.

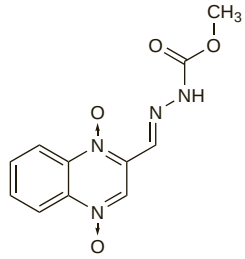
Carbadox *(BAN, USAN, pINN)*

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 .

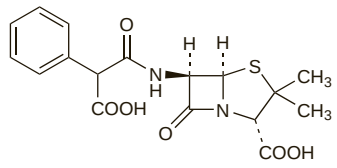
Натрий Карбенициллин

$C_{17}H_{16}N_2Na_2O_6S$ = 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†.

Carfecillin Sodium *(BANM, pINNM)*

BRL-3475; Carbenicillin Phenyl Sodium *(USAN)*; Carfecilina sódica; Carfécilline Sodique; Natrii Carfecillinum. Sodium (6*R*)-6-(2-phenoxycarbonyl-2-phenylacetamido)penicillanate.

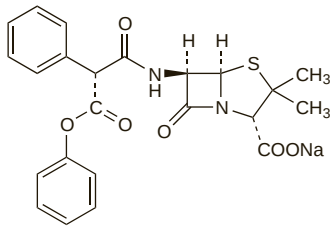
Натрий Карфециллин

$C_{23}H_{21}N_2NaO_6S$ = 476.5.

CAS — 27025-49-6 (carfecillin); 21649-57-0 (carfecillin sodium).

ATC — G01AA08.

ATC Vet — QG01AA08.



Profile

Carfecillin is the phenyl ester of carbenicillin (p.216) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use has been restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin Sodium *(BANM, pINNM)*

Carbenicillin Indanyl Sodium *(USAN)*; Carindacilina sódica; Carindacilline Sodique; CP-15464-2; Natrii Carindacillinum. Sodium (6*R*)-6-[2-(indan-5-yloxycarbonyl)-2-phenylacetamido]penicillanate.

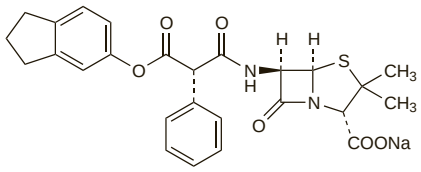
Натрий Кариндациллин

$C_{26}H_{25}N_2NaO_6S$ = 516.5.

CAS — 35531-88-5 (carindacillin); 26605-69-6 (carindacillin sodium).

ATC — J01CA05.

ATC Vet — QJ01CA05.



Pharmacopoeias. In *US*.

USP 31 (Carbenicillin Indanyl Sodium). A white to off-white powder. Soluble in water and in alcohol. pH of a 10% solution in water is between 5.0 and 8.0. Store in airtight containers.

Profile

Carindacillin is the indanyl ester of carbenicillin (p.216) to which it is hydrolysed after absorption from the gastrointestinal tract. Its use is restricted to the treatment of urinary-tract infections due to *Pseudomonas* spp. and other sensitive bacteria including *Proteus* spp.

Carindacillin is given orally as the sodium salt; 535 mg of carindacillin sodium is equivalent to about 382 mg of carbenicillin. Usual doses, expressed in terms of carbenicillin, are 382 to 764 mg four times daily.

Sodium content. Each g of carindacillin sodium contains about 1.9 mmol of sodium.

Preparations

USP 31: Carbenicillin Indanyl Sodium Tablets.

Proprietary Preparations (details are given in Part 3)
USA: Geocillin†.

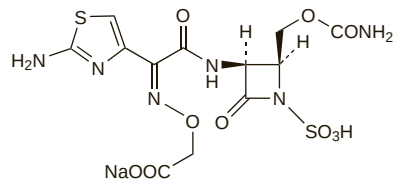
Carumonam Sodium *(BANM, USAN, rINNM)*

AMA-1080 (carumonam); Carumonam sódico; Carumonam Sodique; Natrii Carumonamum; Ro-17-2301 (carumonam); Ro-17-2301/006 (carumonam sodium). (*Z*)-(2-Aminothiazol-4-yl){[(2*S*,3*S*)-2-carbamoyloxymethyl-4-oxo-1-sulphoazetidin-3-yl]carbamoyl}methyleneamino-oxyacetic acid, disodium salt.

Натрий Карумонам

$C_{12}H_{12}N_6Na_2O_{10}S_2$ = 510.4.

CAS — 87638-04-8 (carumonam); 86832-68-0 (carumonam sodium).



(carumonam)

Pharmacopoeias. In *Jpn*.

Profile

Carumonam is a monobactam antibacterial with a spectrum of antimicrobial action *in vitro* similar to that of aztreonam (p.209). It is given by intramuscular or intravenous injection as the sodium salt and doses are expressed in terms of carumonam; 1.09 g of carumonam sodium is equivalent to about 1 g of carumonam. The usual dose is 1 to 2 g daily in two divided doses.

Sodium content. Each g of carumonam sodium contains about 3.92 mmol of sodium.

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Amasulin.

Cefaclor *(BAN, USAN, pINN)*

Céfaclor; Cefaclorum; Cefaclorum Monohydricum; Cefaklór; Cefaklor; Cefaklor monohydrát; Cefakloras; Compound 99638; Kefakloori; Sefaklor. (7*R*)-3-Chloro-7-(α-D-phenylglycylamino)-3-cephem-4-carboxylic acid monohydrate.

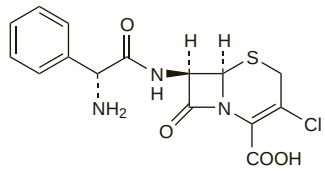
Цефаклор

$C_{15}H_{14}ClN_3O_4S,H_2O$ = 385.8.

CAS — 53994-73-3 (anhydrous cefaclor); 70356-03-5 (cefaclor monohydrate).

ATC — J01DC04.

ATC Vet — QJ01DC04.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), and *US*. *Jpn* includes the anhydrous substance.

Ph. Eur. 6.2 (Cefaclor). A white or slightly yellow powder. Slightly soluble in water; practically insoluble in dichloromethane and in methyl alcohol. A 2.5% suspension in water has a pH of 3.0 to 4.5.

USP 31 (Cefaclor). A white to off-white crystalline powder. Slightly soluble in water; practically insoluble in chloroform, in methyl alcohol, and in benzene. pH of a 2.5% suspension in water is between 3.0 and 4.5. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalexin, p.218.

Hypersensitivity. Serum-sickness-like reactions may be more common with cefaclor than several other oral antibacterials[1] especially in young children who have received a number of courses of cefaclor;[2] typical features include skin reactions and arthralgia. A relatively high incidence of anaphylactic reactions has been reported from Japan.[3]

There has been a report of myocarditis that developed as a hypersensitivity reaction to cefaclor in a 12-year-old child.[4]

1. McCue JD. Delayed detection of serum sickness caused by oral antimicrobials. *Adv Therapy* 1990; **7**: 22–7.
2. Vial T, *et al.* Cefaclor-associated serum sickness-like disease: eight cases and review of the literature. *Ann Pharmacother* 1992; **26:** 910–14.
3. Hama R, Mori K. High incidence of anaphylactic reactions to cefaclor. *Lancet* 1988; **i**: 1331.
4. Beghetti M, *et al.* Hypersensitivity myocarditis caused by an allergic reaction to cefaclor. *J Pediatr* 1998; **132:** 172–3.

Interactions

As for Cefalexin, p.218.

Anticoagulants. UK licensed product information recommends that monitoring of prothrombin time should be considered in patients receiving cefaclor and *warfarin* after rare reports of increased prothrombin times. It is not known whether this interaction is related to the vitamin K-related hypoprothrombinaemia observed with some cephalosporins (see Adverse Effects of Cefamandole, p.221), but cefaclor does not contain the side-chain usually implicated in this reaction.

Antimicrobial Action

Cefaclor is bactericidal and has antimicrobial activity similar to that of cefalexin (p.218) but is reported to be more active against Gram-negative bacteria including *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, and *Proteus mirabilis*, and especially against *Haemophilus influenzae*. It is active against some beta-lactamase-producing strains of *H. influenzae*. It may be less resistant to staphylococcal penicillinase than cefalexin or cefradine and a marked inoculum effect has been reported *in vitro*.

Pharmacokinetics

Cefaclor is well absorbed from the gastrointestinal tract. Oral doses of 250 mg, 500 mg, and 1 g produce peak plasma concentrations of about 7, 13, and 23 micrograms/mL respectively after 0.5 to 1 hour. The presence of food may delay the absorption of cefaclor, but the total amount absorbed is unchanged. A plasma half-life of 0.5 to 1 hour has been reported; it may be slightly prolonged in patients with renal impairment. About 25% is bound to plasma proteins.

Cefaclor appears to be widely distributed in the body; it crosses the placenta and low concentrations have been detected in breast milk. It is rapidly excreted by the kidneys; up to 85% of a dose appears unchanged in the urine within 8 hours, the greater part within 2 hours. High concentrations of cefaclor are achieved in the urine within 8 hours of a dose; peak concentrations of 600, 900, and 1900 micrograms/mL have been reported after doses of 0.25, 0.5, and 1 g respectively. Probenecid delays excretion. Some cefaclor is removed by haemodialysis.

◊ References.

1. Wise R. The pharmacokinetics of the oral cephalosporins—a review. *J Antimicrob Chemother* 1990; **26** (suppl E): 13–20.
2. Sourgens H, *et al.* Pharmacokinetic profile of cefaclor. *Int J Clin Pharmacol Ther* 1997; **35:** 374–80.

Uses and Administration

Cefaclor is a cephalosporin antibacterial given orally similarly to cefalexin in the treatment of susceptible infections including upper and lower respiratory-tract infections, skin infections, and urinary-tract infections. Some classify cefaclor as a second-generation cephalosporin and its greater activity against *Haemophilus influenzae* makes it more suitable than cefalexin for the treatment of infections such as otitis media. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefaclor is given as the monohydrate. Doses are expressed in terms of the equivalent amount of anhydrous cefaclor; 1.05 g of cefaclor monohydrate is equivalent to about 1 g of anhydrous cefaclor. The usual adult dose is 250 to 500 mg every 8 hours; up to 4 g daily has been given. A suggested dose for children over 1 month of age is 20 mg/kg daily in three divided doses, increased if necessary to 40 mg/kg daily, but not exceeding a total daily dose of 1 g. A common dosage regimen is: children over 5 years, 250 mg three times daily; 1 to 5 years, 125 mg three times daily; under 1 year, 62.5 mg three times daily.

Modified-release formulations of cefaclor are available in some countries.

Preparations

BP 2008: Cefaclor Capsules; Cefaclor Oral Suspension; Prolonged-release Cefaclor Tablets;
USP 31: Cefaclor Capsules; Cefaclor Chewable Tablets; Cefaclor Extended-Release Tablets; Cefaclor for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Arg.: Cec†; Cefaklon†; Cefral†; Kwicap†; ***Austral.:*** Aclor; Ceclor; Cefkor; Karlor; Keflor; Ozcef; ***Austria:*** Cec; Ceclor; Cefastad; Cefax; Lanacef†; ***Belg.:*** Ceclor; Doccefaclo; ***Braz.:*** Ceclor†; Cefaclorem; Clorcin-Ped; Faclor†; Plecor†; Reflax†; ***Canad.:*** Ceclor; ***Chile:*** Keflor†; ***Cz.:*** Cec†; Ceclor; Serviclor; Vercef; ***Fin.:*** Kefolor; ***Fr.:*** Alfatil; Alphexine†; Haxifal; ***Ger.:*** Cec; Ceclorbeta; Cef-Diolan; Cefa-Wolff†; Cephalodoc†; Hefaclor†; InfectoCef; Panoral; Sigacefal†; ***Gr.:*** Afecton; Camirox; Ceclor; Cefacloril; Fredyren; Hetaclox; Makovan; Panclor; Phacotrex; Ufoxillin†; ***Hong Kong:*** Castal; Ceclor; Cefalor; Medoclor; Qualiceclor; Qualiphor; Soficlor; Vercef; ***Hung.:*** Ceclor; Cecloretta; Vercef; ***India:*** Halocef; Keflor; ***Indon.:*** Capabi-