

Cefamandole Sodium (BANM, rINN)

Cefamandol sodico; Cefamandole Sodique; Cephamandole Sodium; Natrii Cefamandolum.

Натрий Цефамандол

$C_{18}H_{17}N_6NaO_5S_2 = 484.5$.

CAS — 30034-03-8.

ATC — J01DC03.

ATC Vet — QJ01DC03.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

As mentioned under Cefalotin, cephalosporins with an *N*-methylthiotetrazole side-chain such as cefamandole (and possibly those with methylthiadiazolethiol or *N*-methylthiotriazine side-chains as well) may produce bleeding disorders associated with hypoprothrombinemia and/or platelet disorders.

Sodium content. 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate each contain about 2.2 mmol of sodium.

Interactions

A disulfiram-like interaction with alcohol may occur and has been attributed to the *N*-methylthiotetrazole side-chain of cefamandole; patients should avoid alcohol during, and for at least several days after, cefamandole treatment. Interactions are also possible with preparations containing significant amounts of alcohol.

Cefamandole, and other cephalosporins with an *N*-methylthiotetrazole side-chain, may enhance the hypoprothrombinemic response to anticoagulants as discussed under Warfarin (p.1428).

Probenecid reduces the renal clearance of cefamandole and many other cephalosporins.

♦ References.

- Portier H, et al. Interaction between cephalosporins and alcohol. *Lancet* 1980; **ii**: 263.
- Drummer S, et al. Antabuse-like effect of β -lactam antibiotics. *N Engl J Med* 1980; **303**: 1417–18.

Antimicrobial Action

Cefamandole is bactericidal and acts similarly to cefalotin, but has a broader spectrum of activity. It generally has similar or less activity against Gram-positive staphylococci and streptococci, but is resistant to some beta-lactamases produced by Gram-negative bacteria. It is more active than cefalotin against many of the Enterobacteriaceae including some strains of *Enterobacter*, *Escherichia coli*, *Klebsiella*, *Salmonella*, and some *Proteus* spp. However, resistance to cefamandole and other beta lactams has emerged in some species, notably *Enterobacter*, during treatment with cefamandole. Cefamandole is very active *in vitro* against *Haemophilus influenzae* although an inoculum effect has been reported for beta-lactamase-producing strains. Like cefalotin, most strains of *Bacteroides fragilis* are resistant to cefamandole, as are *Pseudomonas* spp.

♦ References.

- Sabath LD. Reappraisal of the antistaphylococcal activities of first-generation (narrow-spectrum) and second-generation (expanded-spectrum) cephalosporins. *Antimicrob Agents Chemother* 1989; **33**: 407–11.

Pharmacokinetics

Cefamandole is poorly absorbed from the gastrointestinal tract. It is given intramuscularly or intravenously, usually as the nafate which is rapidly hydrolysed to release cefamandole *in vivo*. Peak plasma concentrations for cefamandole of about 13 and 25 micrograms/mL have been achieved 0.5 to 2 hours after intramuscular doses of 0.5 and 1 g respectively; concentrations are very low after 6 hours. About 70% is bound to plasma proteins. The plasma half-life varies from about 0.5 to 1.2 hours depending on the route of injection; it is prolonged in patients with renal impairment.

Cefamandole is widely distributed in body tissues and fluids including bone, joint fluid, and pleural fluid; it diffuses into the CSF when the meninges are inflamed, but concentrations are unpredictable. Cefamandole has also been detected in breast milk. It is rapidly excreted unchanged by glomerular filtration and renal tubular secretion; about 80% of a dose is excreted within 6

hours and high urinary concentrations are achieved. Probenecid competes for renal tubular secretion with cefamandole resulting in higher and prolonged plasma concentrations of cefamandole. Therapeutic concentrations of cefamandole are achieved in bile.

Cefamandole is removed by haemodialysis to some extent.

Uses and Administration

Cefamandole is a second-generation cephalosporin antibacterial used in the treatment of infections due to susceptible bacteria and for surgical infection prophylaxis.

It is given principally as cefamandole nafate (the sodium salt of cefamandole formyl ester). Doses are expressed in terms of the equivalent amount of cefamandole; 1.05 g of cefamandole sodium and 1.11 g of cefamandole nafate are each equivalent to about 1 g of cefamandole. It is given by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous infusion in doses of 0.5 to 2 g every 4 to 8 hours for adults depending on the severity of the infection. Children over 1 month of age may be given 50 to 100 mg/kg daily in equally divided doses; 150 mg/kg daily may be given in severe infections, but this dose should not be exceeded. For details of reduced doses in patients with renal impairment, see below. If cefamandole is used with an aminoglycoside, the drugs should be given separately.

For surgical infection prophylaxis, a dose of 1 or 2 g intravenously or intramuscularly 30 to 60 minutes before surgical incision, followed by 1 or 2 g every 6 hours for 24 to 48 hours, is recommended. For patients undergoing procedures involving implantation of prosthetic devices, cefamandole should be continued for up to 72 hours. Children over 3 months of age may be treated similarly to adults and given 50 to 100 mg/kg daily in equally divided doses.

Administration in renal impairment. Doses of cefamandole should be reduced for patients with renal impairment. After an initial dose of 1 to 2 g the following maintenance doses have been recommended based on creatinine clearance (CC):

- CC 50 to 80 mL/minute: 0.75 to 2 g every 6 hours
- CC 25 to 50 mL/minute: 0.75 to 2 g every 8 hours
- CC 10 to 25 mL/minute: 0.5 to 1.25 g every 8 hours
- CC 2 to 10 mL/minute: 0.5 to 1 g every 12 hours
- CC less than 2 mL/minute: 0.25 to 0.75 g every 12 hours

Preparations

USP 31: Cefamandole Nafate for Injection.

Proprietary Preparations (details are given in Part 3)

Austral: Mandol; **Austria:** Mandokel; **Belg:** Mandol; **Cz:** Mandol†; **Gr:** Acemycin; **Cefadin:** Mandokel; **Hong Kong:** Mandol†; **Hung:** Cefam; **Mandokel†:** Indon; **Dardokel:** Dofacef; **Irl:** Kefadol†; **Ital:** Cefam; **Cemado:** Lampomandol; **Mancef:** Mandokel†; **Mandolsan†:** Septomandol†; **Neth:** Mandol; **NZ:** Mandol; **Pol:** Tarcefanol; **Port:** Mandokel†; **Rus:** Cefat (Лефат); **Mandol (Мацандол):** S.Afr.: Kefdol†; **Mandokel:** **Switz:** Mandokel; **Thai:** Cefadol; **Cefmandol;** Mandol†.

Cefapirin Sodium (BANM, pINN)

BL-P-1322; Cefapirin sodná sůl; Cefapirina sodica; Cefapirine sodique; Cefapirinnatrium; Cefapirin-natrium; Cefapirino natrio druska; Cefapirinum natrium; Cepapirin Sodium (USAN); Cefapirininatrium; Natrii Cefapirinum. Sodium (7R)-7-[2-(4-pyridylthio)acetamido]cephalosporanate; Sodium (7R)-3-acetoxymethyl-7-[2-(4-pyridylthio)acetamido]-3-cephem-4-carboxylate.

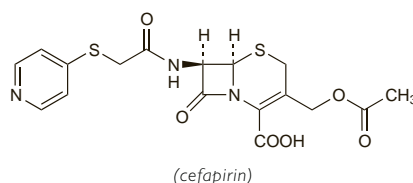
Натрий Цефепирин

$C_{17}H_{16}N_4NaO_6S_2 = 445.4$.

CAS — 21593-23-7 (cefapirin); 24356-60-3 (cefapirin sodium).

ATC — J01DB08.

ATC Vet — QJ01DB08.

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

US also includes Cefapirin Benzathine for veterinary use.

Ph. Eur. 6.2 (Cefapirin Sodium). A white or pale yellow powder. Soluble in water; practically insoluble in dichloromethane. A 1% solution in water has a pH of 6.5 to 8.5. Protect from light.

USP 31 (Cefapirin Sodium). A white to off-white crystalline powder, odourless or having a slight odour. Very soluble in water; insoluble in most organic solvents. pH of a solution in water containing the equivalent of cefapirin 1% is between 6.5 and 8.5. Store in airtight containers.

Profile

Cefapirin is a first-generation cephalosporin antibacterial with actions and uses very similar to those of cefalotin (p.219). It is used as the sodium salt but doses are expressed in terms of cefapirin base; 1.05 g of cefapirin sodium is equivalent to about 1 g of cefapirin. The usual dose is the equivalent of 0.5 to 1 g of cefapirin every 4 to 6 hours by intramuscular injection or intravenously. In severe infections up to 12 g daily may be given, preferably intravenously.

Administration in renal impairment. Reduced doses of cefapirin sodium may be necessary in patients with renal impairment. One regimen, based on creatinine clearance (CC), that has been suggested is:

- CC 5 to 20 mL/minute: 1 g every 12 hours
- CC less than 5 mL/minute: 1 g every 24 hours

Patients undergoing haemodialysis may receive 7.5 to 15 mg/kg after each dialysis.

Sodium content. Each g of cefapirin sodium contains about 2.2 mmol of sodium.

Preparations

USP 31: Cefapirin for Injection.

Proprietary Preparations (details are given in Part 3)

Cz: Cefatrex†; **Fr:** Cefaloject; **Gr:** Cefatrex†; **Spain:** Brisfrina.

Cefatrizine (BAN, USAN, pINN)

BL-S640; Cefatrizina; Cefatrizine; Cefatrizinum; SKF-60771; S-640P. (7R)-7-(α -D-4-Hydroxyphenylglycylamino)-3-(1H-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylic acid.

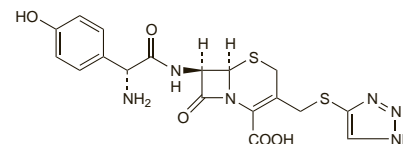
Цефатризин

$C_{18}H_{18}N_6O_5S_2 = 462.5$.

CAS — 51627-14-6.

ATC — J01DB07.

ATC Vet — QJ01DB07.

**Cefatrizine Propylene Glycol** (BANM, pINN)

Cefatrizina propilenglikol; Cefatrizinas propilenglikolis; Cefatrizine propylèneglycol; Cefatrizin-propilènglikol; Cefatrizinpropylenglykol; Cefatrizin-propylenglykol; Cefatrizinum propylen glycolum; Cefatrizinum Propylenglyolum; Kefatritsinipropyleenglykoli. (7R)-7-(α -D-4-Hydroxyphenylglycylamino)-3-(1H-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylate propylene glycol.

Цефатризин Пропиленгликол

$C_{18}H_{18}N_6O_5S_2 \cdot (C_3H_8O_2)_n$.

CAS — 64217-62-5.

ATC — J01DB07.

ATC Vet — QJ01DB07.

Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*

Ph. Eur. 6.2 (Cefatrizine Propylene Glycol). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol and in dichloromethane.

Profile

Cefatrizine is a cephalosporin antibacterial with actions and uses similar to those of cefalexin (p.218), although it might be more active *in vitro*. It is given orally as the base or, more often, as a compound with propylene glycol, in usual doses equivalent to 500 mg twice daily of cefatrizine.

Preparations

Proprietary Preparations (details are given in Part 3)

Belg: Cefapero; **Fr:** Cefapero†; **Gr:** Anflagladin; Axelorax; Banadroxin†; Cefazin; Cefazin; Clomint; Fica-F; Gertemycin; Izerin; Kentacef; Klevasin; Liamycin; Liferost; Lingone; Mekant; Nibocin; Northiron; Phacobioc†; Relyovix; Specifex-N; Traxilan; **Ital:** Biotrixina†; Cefatix†; Cetrazil†; Cetrix†; Faretzin; Ipatrizina†; Ketazin; Miracef†; Novacef†; Tamy†; Tricef†; Trizina; **Port:** Macropren; Supracefa.

Cefazolin (BAN, pINN)

Cefazolina; Céfazoline; Cefazolinum; Cephazolin; Kefatsolini; Se-fazolin. 3-[[[5-Methyl-1,3,4-thiadiazol-2-yl]thiomethyl]-7-(tetra-zol-1-ylacetamido)-3-cephem-4-carboxylic acid.

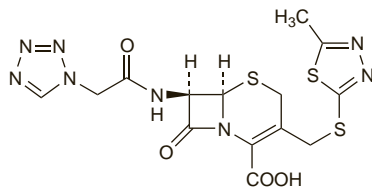
Цефазолин

$C_{14}H_{14}N_8O_4S_3 = 454.5$.

CAS — 25953-19-9.

ATC — J01DB04.

ATC Vet — QJ01DB04; QJ51DA04.



Pharmacopoeias. In US.

USP 31 (Cefazolin). A white to slightly off-white, odourless crystalline powder. Slightly soluble in water, in alcohol, and in methyl alcohol; sparingly soluble in acetone; practically insoluble in chloroform, in dichloromethane, in ether, and in benzene; soluble in dimethylformamide and in pyridine; very slightly soluble in ethyl acetate, in isopropyl alcohol, and in methyl isobutyl ketone. Store in airtight containers.

Cefazolin Sodium (BANM, USAN, pINN)

46083; Cefazolin sodná sůl; Cefazolina sódica; Céfazoline sodique; Cefazolinнатрий; Cefazolin-nátrium; Cefazolino natrio druska; Cefazolinum natrium; Cephazolin Sodium; Kefatsolini-natrium; Natrii Cefazolinum; Sefazolin Sodyum; SKF-41558.

Натрий Цефазолин

$C_{14}H_{13}N_8NaO_4S_3 = 476.5$.

CAS — 27164-46-1.

ATC — J01DB04.

ATC Vet — QJ01DB04.

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

Jpn also includes the pentahydrate.

Ph. Eur. 6.2 (Cefazolin Sodium). A white or almost white, very hygroscopic powder. It exhibits polymorphism. Freely soluble in water; very slightly soluble in alcohol. A 10% solution in water has a pH of 4.0 to 6.0. Store in airtight containers. Protect from light.

USP 31 (Cefazolin Sodium). A white to off-white, practically odourless, crystalline powder, or a white to off-white solid. Freely soluble in water, in sodium chloride 0.9%, and in glucose solutions; very slightly soluble in alcohol; practically insoluble in chloroform and in ether. pH of a solution in water containing the equivalent of cefazolin 10% is between 4.0 and 6.0. Store in airtight containers.

Incompatibility and stability. Cefazolin sodium has been reported to be incompatible with aminoglycosides and many other drugs. When the pH of a solution exceeds 8.5 there may be hydrolysis and when it is below 4.5 insoluble cefazolin may be precipitated.

References.

- Nahata MC, Ahalt PA. Stability of cefazolin sodium in peritoneal dialysis solutions. *Am J Hosp Pharm* 1991; **48**: 291-2.
- Wu C-C, et al. Stability of cefazolin in heparinized and non-heparinized peritoneal dialysis solutions. *Am J Health-Syst Pharm* 2002; **59**: 1537-8.
- Lin Y-F, et al. Stability of cefazolin sodium in icodextrin-containing peritoneal dialysis solution. *Am J Health-Syst Pharm* 2002; **59**: 2362, 2364.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219. Stevens-Johnson syndrome has occurred.

Like cephalosporins with an *N*-methylthiotetrazole side-chain, cefazolin has been associated with hypoprothrombinaemia.

Breast feeding. In a study¹ of 20 lactating women receiving cefazolin, the amount of cefazolin in breast milk was found to be extremely small (equivalent to less than 0.075% of the dose). No adverse effects have been seen in breast-fed infants whose mothers were receiving cefazolin, and the American Academy of Pediatrics considers² that it is therefore usually compatible with breast feeding.

- Yoshioka H, et al. Transfer of cefazolin into human milk. *J Pediatr* 1979; **94**: 151-2.
- American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108**: 776-89. Correction. *ibid.*; 1029. Also available at: <http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776> (accessed 25/05/04)

Effects on the nervous system. References.

- Manzella JP, et al. CNS toxicity associated with intraventricular injection of cefazolin: report of three cases. *J Neurosurg* 1988; **68**: 970-1.
- Martin ES, et al. Seizures after intraventricular cefazolin administration. *Clin Pharm* 1992; **11**: 104-5.

Sodium content. Each g of cefazolin sodium contains about 2.1 mmol of sodium.

Interactions

Cefazolin contains a methylthiadiazolethiol side-chain; like cephalosporins containing the related *N*-methylthiotetrazole side-chain (see Cefamandole, p.221), it may have the potential to cause a disulfiram-like reaction with alcohol, and enhance the effects of warfarin.

The renal excretion of cefazolin and many other cephalosporins is delayed by probenecid.

Antimicrobial Action

As for Cefalotin Sodium, p.220, although cefazolin is more sensitive to staphylococcal beta-lactamase.

Pharmacokinetics

Cefazolin is poorly absorbed from the gastrointestinal tract and is given by the intramuscular or intravenous routes. After a 500-mg dose given intramuscularly, peak plasma concentrations of 30 micrograms or more per mL are obtained after 1 hour. About 85% of cefazolin is bound to plasma proteins. The plasma half-life of cefazolin is about 1.8 hours, and is increased in patients with renal impairment. Cefazolin diffuses into bone and into ascitic, pleural, and synovial fluid but not appreciably into the CSF. It crosses the placenta; only low concentrations are detected in breast milk.

Cefazolin is excreted unchanged in the urine, mainly by glomerular filtration with some renal tubular secretion, at least 80% of a dose given intramuscularly being excreted within 24 hours. Peak urine concentrations of more than 2 and 4 mg/mL have been reported after intramuscular doses of 0.5 and 1 g respectively. Probenecid delays excretion. Cefazolin is removed to some extent by haemodialysis.

High biliary concentrations have been reported, although the amount excreted by this route is small.

Uses and Administration

Cefazolin is a first-generation cephalosporin antibacterial used to treat infections due to susceptible organisms, including biliary-tract infections, endocarditis (staphylococcal), and peritonitis (associated with continuous ambulatory peritoneal dialysis). It is also used for surgical infection prophylaxis, including prophylaxis of endometritis at caesarean section. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefazolin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intravenous infusion. Doses are expressed in terms of the equivalent amount of cefazolin; 1.05 g of cefazolin sodium is equivalent to about 1 g of cefazolin. The usual adult dose is the equivalent of 0.5 to 1 g of cefazolin every 6 to 12 hours. The usual maximum daily dose is 6 g, although up to 12 g has been used in severe life-threatening infections. Children over 1 month of age may be given 25 to 50 mg/kg daily in 3 or 4 divided doses, increased in severe infections to a maximum of 100 mg/kg daily.

For the prophylaxis of infection during surgery, a 1-g dose is given half to one hour before the operation, followed by 0.5 to 1 g during surgery for lengthy procedures. A dose of 0.5 to 1 g is given every 6 to 8 hours postoperatively for 24 hours, or up to 5 days in certain cases.

For details of reduced doses of cefazolin in patients with renal impairment, see below.

Other routes used for cefazolin sodium include intraperitoneal use in peritoneal dialysis solutions, and intra-ocular injection.

In some countries a modified-release intramuscular formulation of cefazolin sodium with the less soluble dibenzylamine salt of cefazolin, in the ratio of 1:4, has been used.

Administration in renal impairment. Dosage of cefazolin should be reduced in patients with renal impairment and various modifications have been recommended. After a loading dose the licensed product information suggests the following doses based on creatinine clearance (CC):

Adults

- CC 55 mL or more per minute: usual doses
- CC 35 to 54 mL/minute: usual doses but at intervals of at least 8 hours
- CC 11 to 34 mL/minute: half the usual dose every 12 hours
- CC 10 mL or less per minute: half the usual dose every 18 to 24 hours

Children

- CC 40 to 70 mL/minute: 60% of the normal daily dose in 2 divided doses
- CC 20 to 40 mL/minute: 25% of the normal daily dose in 2 divided doses
- CC 5 to 20 mL/minute: 10% of the normal daily dose every 24 hours.

One report¹ indicated that, for patients on long-term haemodialysis, a dose of 20 mg/kg given 3 times weekly after dialysis maintained therapeutic cefazolin concentrations.

- Ahern JW, et al. Cefazolin dosing protocol for patients receiving long-term hemodialysis. *Am J Health-Syst Pharm* 2003; **60**: 178-81.

Preparations

BP 2008: Cefazolin Injection;

USP 31: Cefazolin for Injection; Cefazolin Injection; Cefazolin Ophthalmic Solution.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefalomicina; Cefamezin; **Austral.:** Kefzol; **Austria:** Kefzol; Servazolin; **Belg.:** Cefacidal; Kefzol; **Braz.:** Ceftrat; Cezolin; Duocel; Fazolon; Kefazol; Zolin; **Canad.:** Kefzol; **Chile:** Kefzol; **Cz.:** Kefzol; Ori-zolin; Vulmizolin; **Fr.:** Cefacidal; **Ger.:** Basocel; Elzogram; **Gr.:** Biozolin; Vifazolin; **Hong Kong:** Cefamezin; **Hung.:** Totacef; **India:** Azolin; Reflin; Zolin; **Indon.:** Biozolin; Cefazol; **Israel:** Cefamezin; Kefazin; Kefzol; Totacef; **Ital.:** Acef; Cefabiozim; Cefamezin; Cefazil; Cromezin; Nefazolin; Re-cef; Sicef; Silzolin; Totacef; **Jpn:** Cefamezin; Otsuka Cez; **Mex.:** Cefacidal; **Neth.:** Cefacidal; Cefamezin; Kefazin; Kefzol; **NZ:** Kefzol; Zepilen; **Philipp.:** Cefoxin; Cizo; Cloviz; Fazol; Fonvicol; Illoze; Lupec; Maxcep; Megacef; Oryant; Samarial; Stancef; Zofadep; Zolival; **Pol.:** Biofazolin; Tarfazolin; **Port.:** Cefamezin; Kurgan; **Rus.:** Cefamezin (Цефамезин); Ifizol (Ифизол); Intrazoline (Интразолин); Kefzol (Кефзол); Orizolin (Оризолин); Reflin (Рефин); **S.Afr.:** Cefacidal; Izacef; Kefzol; Ranzol; **Spain:** Areuzolin; Brizolina; Camil; Cancef; Cefa Resan; Cefacene; Cefadrex; Dacovor; Fazoplex; Filoklin; Gencefal; Intrazolin; Kefol; Kurgan; Neofazolin; Tasep; Tecfazolin; Zolival; **Switz.:** Kefzol; **Thai.:** Cefalin; Cefamezin; Cefazillin; Cefazol; Cefzolin; Fazolin; Zefa; Zepilen; Zolicef; Zolimed; **Turk.:** Cefamezin; Cefozin; Equizolin; Ilespor; Maksiporin; Sefamax; Sefazol; **USA:** Ancef; Zolicef; **Venez.:** Cefacidal; Cefarizon; Cellozina; Kefzol.

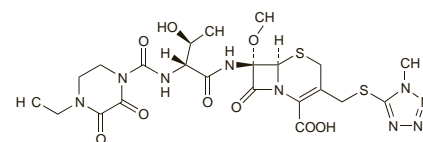
Cefbuperazone (USAN, rINN)

BMV-25182; Cefbuperazona; Cefbupérazone; Cefbuperazonum; T-1982. 7-[(2R,3S)-2-(4-ethyl-2,3-dioxopiperazin-1-ylcarboxamido)-3-hydroxybutylamido]-7-methoxy-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефбуперазон

$C_{27}H_{29}N_9O_9S_2 = 627.7$.

CAS — 76610-84-9.



Cefbuperazone Sodium (rINN)

Cefbuperazona de sodio; Cefbupérazone Sodique; Natrii Cefbuperazonum.

Натрий Цефбуперазон

$C_{27}H_{28}N_9NaO_9S_2 = 649.6$.

Pharmacopoeias. In Jpn.

Profile

Cefbuperazone is a cephamycin antibiotic similar to cefoxitin (p.230) but with an *N*-methylthiotetrazole side-chain like cefamandole (p.220). It is given by injection as the sodium salt. Its spectrum of activity includes Enterobacteriaceae, but more especially anaerobic bacteria such as *Bacteroides fragilis*. Cefbuperazone does not appear to be active against cefoxitin-resistant strains of *B. fragilis*.

Preparations

Proprietary Preparations (details are given in Part 3)

Jpn: Tomiporan.