For infection prophylaxis during surgical procedures, an intravenous dose of 1 or 2 g is given 30 to 60 minutes before surgery or, in caesarean section, as soon as the umbilical cord is clamped.

Administration in renal impairment. Dosage of cefotetan should be reduced in patients with moderate to severe renal impairment. US licensed product information gives the following dosing guidelines based on creatinine clearance (CC):

- CC 10 to 30 mL/minute: the usual dose every 24 hours or one-half the usual dose every 12 hours
- CC less than 10 mL/minute: the usual dose every 48 hours or one-quarter the usual dose every 12 hours

In patients undergoing haemodialysis, one-quarter the usual dose may be given every 24 hours on days between dialysis and one-half the usual dose on the day of dialysis.

Preparations

USP 31: Cefotetan for Injection; Cefotetan Injection.

Proprietary Preparations (details are given in Part 3)

Austral.: Apatef†; ***Belg.:*** Apacef†; ***Canad.:*** Cefotan†; ***Fr.:*** Apacef†; ***Ital.:*** Apatef†; ***Jpn:*** Yamatetan†; ***NZ:*** Apatef†; ***Port.:*** Apatef†; ***USA:*** Cefotan.

Cefotiam Hydrochloride *(BANM, USAN, rINNM)*

Abbott-48999; Céfotiam, Chlorhydrate de; Cefotiami Hydrochloridum; CGP-14221E (cefotiam or cefotiam hydrochloride); Hidrocloruro de cefotiam; SCE-963. 7-[2-(2-Amino-1,3-thiazol-4-yl)acetamido]-3-[1-(2-dimethylaminoethyl)-1*H*-tetrazol-5-ylthiomethyl]-3-cephem-4-carboxylic acid dihydrochloride.

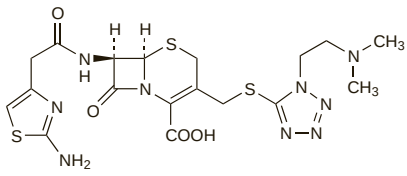
Цефотиама Гидрохлорид

$C_{18}H_{23}N_9O_4S_3,2HCl$ = 598.6.

CAS — 61622-34-2 (cefotiam); 66309-69-1 (cefotiam hydrochloride).

ATC — J01DC07.

ATC Vet — QJ01DC07.



(cefotiam)

Pharmacopoeias. In *Jpn* and *US*. *Jpn* also includes cefotiam hexetil hydrochloride.
USP 31 (Cefotiam Hydrochloride). Store in airtight containers.

Profile

Cefotiam is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefamandole (p.220). It is given intravenously or intramuscularly as the hydrochloride but doses are expressed in terms of the base; 1.14 g of cefotiam hydrochloride is equivalent to about 1 g of cefotiam. The usual dose is the equivalent of up to 6 g of cefotiam daily in divided doses, according to the severity of the infection.

Cefotiam hexetil hydrochloride, a prodrug of cefotiam, is given orally in doses equivalent to 200 to 400 mg of cefotiam twice daily.

◊ References.

1. Brogard JM, *et al.* Clinical pharmacokinetics of cefotiam. *Clin Pharmacokinet* 1989; **17:** 163–74.

Preparations

USP 31: Cefotiam for Injection.

Proprietary Preparations (details are given in Part 3)

Austria: Spizef; ***Fr.:*** Taketiam; Texodil; ***Ger.:*** Spizef; ***Indon.:*** Aspil; Cefradol; Ceradolan; Ethidol; Fodiclo; Fotaram; ***Jpn:*** Pansporin; ***Philipp.:*** Ceradolan; ***Singapore:*** Ceradolan; ***Thai.:*** Ceradolan.

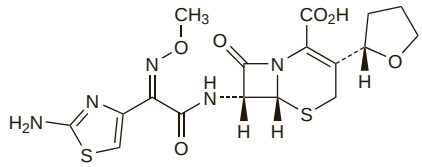
Cefovecin Sodium *(USAN, rINNM)*

Cefovecina sódica; Céfovécine Sodique; Natrii Cefovecinum; UK-287074-02. Sodium (6*R*,7*R*)-7-{[(2*Z*)-(2-aminothiazol-4-yl)(methoxyimino)acetyl]amino}-8-oxo-3-[(2*S*)-tetrahydrofuran-2-yl]-5-thia-1-azabicyclo[4.4.0]oct-2-ene-2-carboxylate.

Натрий Цефовецин

$C_{17}H_{18}N_5NaO_6S_2$ = 475.5.

CAS — 234096-34-5 (cefovecin); 141195-77-9 (cefovecin sodium).



(cefovecin)

Profile

Cefovecin sodium is a third-generation cephalosporin antibacterial used in veterinary medicine.

Cefoxitin Sodium *(BANM, USAN, rINNM)*

Cefoksitino natrio druska; Cefoksytyna sodowa; Cefoxitin sodná sůl; Cefoxitina sódica; Céfoxitine sodique; Cefoxitinnatrium; Cefoxitin-nátrium; Cefoxitinum natricum; Kefoksitiininatrium; L-620388; MK-306; Natrii Cefoxitinum. Sodium 3-carbamoyloxymethyl-7-methoxy-7-[2-(2-thienyl)acetamido]-3-cephem-4-carboxylate.

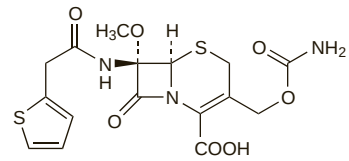
Натрий Цефокситин

$C_{16}H_{16}N_3NaO_7S_2$ = 449.4.

CAS — 35607-66-0 (cefoxitin); 33564-30-6 (cefoxitin sodium).

ATC — J01DC01.

ATC Vet — QJ01DC01.



(cefoxitin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Cefoxitin Sodium). A white or almost white, very hygroscopic, powder. Very soluble in water; sparingly soluble in alcohol. A 1% solution in water has a pH between 4.2 and 7.0. Store in airtight containers.
USP 31 (Cefoxitin Sodium). White to off-white, somewhat hygroscopic, granules or powder, having a slight characteristic odour. Very soluble in water; slightly soluble in acetone; insoluble in chloroform and in ether; sparingly soluble in dimethylformamide; soluble in methyl alcohol. pH of a 10% solution in water is between 4.2 and 7.0. Store in airtight containers at a temperature not exceeding 8°.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefoxitin may interfere with the Jaffé method of measuring creatinine concentrations to produce falsely high values; this should be borne in mind when measuring renal function.

Breast feeding. Cefoxitin is distributed into breast milk but is detectable only in low concentrations. In a study[1] in which cefoxitin was given prophylactically in doses of 2 to 4 g to 18 women undergoing caesarean section, only one sample of breast milk contained measurable concentrations of cefoxitin, 19 hours after the last dose. No adverse effects have been observed in breast-fed infants whose mothers were receiving cefoxitin, and the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Roex AJM, *et al.* Secretion of cefoxitin in breast milk following short-term prophylactic administration in caesarean section. *Eur J Obstet Gynecol Reprod Biol* 1987; **25:** 299–302.
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 gastrointestinal tract. Marked changes in anaerobic, facultative, and aerobic faecal flora have been noted with cefoxitin.[1]

1. Mulligan ME, *et al.* Alterations in human fecal flora, including ingrowth of Clostridium difficile, related to cefoxitin therapy. *Antimicrob Agents Chemother* 1984; **26:** 343–6.

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

Interactions

Probenecid reduces the renal clearance of cefoxitin.

Antimicrobial Action

Cefoxitin is a cephamycin antibacterial which, like the other beta lactams, is bactericidal and is considered to act through the inhibition of bacterial cell wall synthesis.

It has a similar spectrum of activity to cefamandole (p.221) but is more active against anaerobic bacteria, especially *Bacteroides fragilis*.

Cefoxitin can induce the production of beta-lactamases by some bacteria, and use of cefoxitin with other beta lactams have been shown to be antagonistic *in vitro*.

Cefoxitin itself is considered to be resistant to a wide range of beta-lactamases, including those produced by *Bacteroides* spp. However, acquired resistance to cefoxitin has been reported in *B. fragilis* (see Anaerobic Bacterial Infections, p.163) and has been attributed to beta-lactamase as well as to alterations in penicillin-binding proteins or to outer membrane proteins; there may be cross-resistance to other antibacterials.

◊ References.

1. Cuchural GJ, *et al.* Transfer of β-lactamase-associated cefoxitin resistance in Bacteroides fragilis. *Antimicrob Agents Chemother* 1986; **29:** 918–20.
2. Piddock LJV, Wise R. Cefoxitin resistance in Bacteroides species: evidence indicating two mechanisms causing decreased susceptibility. *J Antimicrob Chemother* 1987; **19:** 161–70.
3. Brogan O, *et al.* Bacteroides fragilis resistant to metronidazole, clindamycin and cefoxitin. *J Antimicrob Chemother* 1989; **23:** 660–2.
4. Wexler HM, Halebian S. Alterations to the penicillin-binding proteins in the Bacteroides fragilis group: a mechanism for non-β-lactamase mediated cefoxitin resistance. *J Antimicrob Chemother* 1990; **26:** 7–20.
5. Cherubin CE, Appleman MD. Susceptibility of cefoxitin-resistant isolates of bacteroides to other agents including β-lactamase inhibitor/β-lactam combinations. *J Antimicrob Chemother* 1993; **32:** 168–70.

Pharmacokinetics

Cefoxitin is not absorbed from the gastrointestinal tract; it is given parenterally as the sodium salt. After 1 g by intramuscular injection a peak plasma concentration of up to 30 micrograms/mL at 20 to 30 minutes has been reported whereas concentrations of 125, 72, and 25 micrograms/mL have been achieved after intravenous doses of 1 g over 3, 30, and 120 minutes respectively. Cefoxitin is about 70% bound to plasma proteins. It has a plasma half-life of 45 to 60 minutes which is prolonged in renal impairment. Cefoxitin is widely distributed in the body but there is normally little penetration into the CSF, even when the meninges are inflamed. It crosses the placenta and has been detected in breast milk. Relatively high concentrations are achieved in bile.

The majority of a dose is excreted unchanged by the kidneys, up to about 2% being metabolised to descarbamylcefoxitin which is virtually inactive. Cefoxitin is excreted in the urine by glomerular filtration and tubular secretion and about 85% of a dose is recovered within 6 hours; probenecid slows this excretion. After an intramuscular dose of 1 g, peak concentrations in the urine are usually greater than 3 mg/mL.

Cefoxitin is removed to some extent by haemodialysis.

Uses and Administration

Cefoxitin is a cephamycin antibacterial that differs structurally from the cephalosporins by the addition of a 7-α-methoxy group to the 7-β-aminocephalosporanic acid nucleus.

It is generally classified with the second-generation cephalosporins and can be used similarly to cefamandole (p.221) for the treatment of susceptible infections. However, because of its activity against *Bacteroides fragilis* and other anaerobic bacteria, it is used principally in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. Indications include endometritis (prophylaxis at caesarean section), pelvic inflammatory disease, and surgical infection (prophylaxis). It may also be used in the treatment of gonorrhoea and

urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Cefoxitin is given as the sodium salt by deep intramuscular injection, by slow intravenous injection over 3 to 5 minutes, or by intermittent or continuous intravenous infusion.

Doses are expressed in terms of the equivalent amount of cefoxitin; 1.05 g of cefoxitin sodium is equivalent to about 1 g of cefoxitin. The usual adult dose is 1 or 2 g every 8 hours although it may be given more frequently (every 4 or 6 hours). In severe infections up to 12 g daily has been recommended. Children and neonates may be given 20 to 40 mg/kg, every 12 hours for neonates up to 1 week old, every 8 hours for those aged 1 to 4 weeks, and every 6 to 8 hours for older infants and children; in severe infections, up to 200 mg/kg daily may be given, to a maximum of 12 g daily.

For the treatment of uncomplicated urinary-tract infections, cefoxitin 1 g twice daily has been given intramuscularly.

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

For the treatment of uncomplicated gonorrhoea, a single dose of 2 g intramuscularly has been given with probenecid 1 g orally.

For surgical infection prophylaxis, the usual adult dose is cefoxitin 2 g intramuscularly or intravenously 30 to 60 minutes before the procedure and then every 6 hours, not usually for more than 24 hours. Infants and children undergoing surgical procedures can be given doses of 30 to 40 mg/kg, at the same time intervals as adults; neonates may be given 30 to 40 mg/kg, but at intervals of 8 to 12 hours.

At caesarean section a single 2-g dose may be given intravenously to the mother as soon as the umbilical cord is clamped. If necessary, a 3-dose regimen, with further 2-g doses 4 and 8 hours after the initial dose, may be used.

◊ Reviews.

1. DiPiro JT, May JR. Use of cephalosporins with enhanced antianaerobic activity for treatment and prevention of anaerobic and mixed infections. *Clin Pharm* 1988; **7:** 285–302.
2. Goodwin CS. Cefoxitin 20 years on: is it still useful? *Rev Med Microbiol* 1995; **6:** 146–53.

Administration in renal impairment. In renal impairment, dosage of cefoxitin should be reduced according to creatinine clearance (CC). After an initial loading dose of 1 to 2 g, maintenance doses are:

- CC 30 to 50 mL/minute: 1 to 2 g every 8 to 12 hours
- CC 10 to 29 mL/minute: 1 to 2 g every 12 to 24 hours
- CC 5 to 9 mL/minute: 0.5 to 1 g every 12 to 24 hours
- CC below 5 mL/minute: 0.5 to 1 g every 24 to 48 hours

In patients undergoing haemodialysis, the loading dose should be repeated after each dialysis session.

Preparations

BP 2008: Cefoxitin Injection;
USP 31: Cefoxitin for Injection; Cefoxitin Injection.

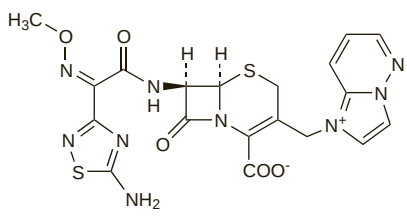
Proprietary Preparations (details are given in Part 3)
Arg.: Mefoxin†; Pluricefo†; ***Austral.:*** Mefoxin; ***Austria:*** Mefoxitin; ***Belg.:*** Mefoxin†; ***Braz.:*** Cefoxan; Cefoxin; Cefton; Foxtil†; Gamacef; Mefoxin; Propoten†; ***Canad.:*** Mefoxin†; ***Cz.:*** Mefoxin†; ***Fin.:*** Mefoxin†; ***Fr.:*** Mefoxin†; ***Ger.:*** Mefoxitin; ***Gr.:*** Destrepen†; Mefoxil; Metaptyl; ***Hong Kong:*** Mefoxin; ***Ital.:*** Cefociclin; Mefoxin; Tifox†; ***Neth.:*** Mefoxin†; ***Norw.:*** Mefoxitin†; ***NZ:*** Mefoxin; ***Philipp.:*** Monowel; Panafox; Zepax; ***Port.:*** Atralxitina; Mefoxin†; Niacef; ***S.Afr.:*** Mefoxin; ***Spain:*** Mefoxitin†; ***Swed.:*** Mefoxitin†; ***Switz.:*** Mefoxitin†; ***Thai.:*** Cefoxin; Cefxitin; Maxotin; Zefin; ***UK:*** Mefoxin†; ***USA:*** Mefoxin; ***Venez.:*** Mefoxitin†.

Cefozopran Hydrochloride *(rINNM)*

Céfozopran, Chlorhydrate de; Cefozoprani Hydrochloridum; Hidrocloruro de cefozoprán. (–)-1-{[(6*R*,7*R*)-7-[2-(5-Amino-1,2,4-thiadiazol-3-yl)glyoxylamido]-2-carboxy-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-en-3-yl]methyl}-1*H*-imidazo[1,2-*b*]pyridazin-4-ium hydroxide inner salt, 7²-(*Z*)-(*O*-methyloxime), hydrochloride.

Цефозопрана Гидрохлорид

$C_{19}H_{17}N_9O_5S_2,HCl$ = 552.0.
CAS — 113359-04-9 (cefozopran); 113981-44-5 (cefozopran hydrochloride).



(cefozopran)

Pharmacopoeias. In *Jpn.*

Profile
Cefozopran is a cephalosporin antibacterial used parenterally as the hydrochloride.

◊ References.

1. Iwahi T, *et al.* In vitro and in vivo activities of SCE-2787, a new parenteral cephalosporin with a broad antibacterial spectrum. *Antimicrob Agents Chemother* 1992; **36:** 1358–66.
2. Paulfeuerborn W, *et al.* Comparative pharmacokinetics and serum bactericidal activities of SCE-2787 and ceftazidime. *Antimicrob Agents Chemother* 1993; **37:** 1835–41.
3. Fujii R, *et al.* Pharmacokinetics and clinical effects of cefozopran in pediatric patients. *Jpn J Antibiot* 1996; **49:** 17–33.

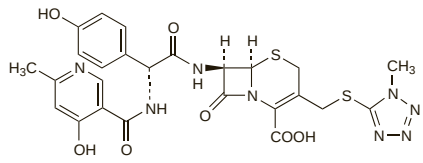
Preparations
Proprietary Preparations (details are given in Part 3)
Jpn: Firstcin.

Cefpiramide *(USAN, rINN)*

Cefpiramida; Cefpiramidum; SM-1652; Wy-44635. (7*R*)-7-[(*R*)-2-(4-Hydroxy-6-methylnicotinamido)-2-(4-hydroxyphenyl)acetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid.

Цефпирамид

$C_{25}H_{24}N_8O_7S_2$ = 612.6.
CAS — 70797-11-4.
ATC — J01DD11.
ATC Vet — QJ01DD11.



Pharmacopoeias. In *US.*
USP 31 (Cefpiramide). Store in airtight containers. pH of a 0.5% suspension in water is between 3.0 and 5.0.

Cefpiramide Sodium *(USAN, rINNM)*

Cefpiramida sódica; Cefpiramide Sodique; Natrii Cefpiramidum.

Натрий Цефпирамид

$C_{25}H_{23}N_8NaO_7S_2$ = 634.6.
CAS — 74849-93-7.
ATC — J01DD11.
ATC Vet — QJ01DD11.

Pharmacopoeias. In *Jpn.*

Profile
Cefpiramide is a third-generation cephalosporin antibacterial related to cefoperazone (p.227) and with similar activity against *Pseudomonas aeruginosa*, but possibly less active against Enterobacteriaceae. Cefpiramide is also active against staphylococci and streptococci and marginal activity against enterococci *in vitro* has been reported. Like cefamandole (p.220), cefpiramide contains an *N*-methylthiotetrazole side-chain, a structure associated with hypoprothrombinaemia, alcohol intolerance, and potentiation of anticoagulants.

Cefpiramide is given by intravenous injection or infusion as the sodium salt in the treatment of susceptible infections but doses are expressed in terms of cefpiramide; 1.04 g of cefpiramide sodium is equivalent to about 1 g of cefpiramide. The usual dose is 1 to 2 g daily in 2 divided doses.

◊ References.

1. Wang H, *et al.* In-vitro antibacterial activities of cefpiramide and other broad-spectrum antibiotics against 440 clinical isolates in China. *J Infect Chemother* 2000; **6:** 81–5.

Sodium content. Each g of cefpiramide sodium contains about 1.6 mmol of sodium.

Preparations
USP 31: Cefpiramide for Injection.

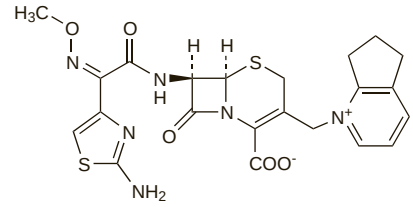
Proprietary Preparations (details are given in Part 3)
Jpn: Sepatren.

Cefpirome Sulfate *(USAN, rINNM)*

Cefpirome, sulfate de; Cefpirome Sulphate *(BANM)*; Cefpiromi sulfas; Cefpiromsulfat; HR-810 (cefpirome or cefpirome sulfate); Kefpiromisulfaatti; Sulfato de cefpiroma. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(1-pyrindiniomethyl)-3-cephem-4-carboxylate sulphate.

Цефпирома Сульфат

$C_{22}H_{22}N_6O_5S_2,H_2SO_4$ = 612.7.
CAS — 84957-29-9 (cefpirome); 98753-19-6 (cefpirome sulfate).
ATC — J01DE02.
ATC Vet — QJ01DE02.



(cefpirome)

Pharmacopoeias. In *Jpn.*

Adverse Effects and Precautions
As for Cefalotin, p.219.

Cefpirome is reported to interfere with the Jaffé method of measuring creatinine concentrations to determine renal function.

◊ References.

1. Rubinstein E, *et al.* A review of the adverse events profile of cefpirome. *Drug Safety* 1993; **9:** 340–5.

Interactions
Probenecid reduces the renal clearance of cefpirome.

Antimicrobial Action
Cefpirome is a fourth-generation cephalosporin that is stable to a wide range of beta-lactamases. It has a spectrum of activity similar to that of the third-generation cephalosporin cefotaxime (p.228), but it appears to be more active *in vitro* against staphylococci, some enterococci, some Enterobacteriaceae, and *Pseudomonas aeruginosa*. Cefpirome may be less active than ceftazidime (p.234) against *Ps. aeruginosa*.

Pharmacokinetics
Cefpirome is given by injection as the sulfate. Mean peak serum concentrations of 80 to 90 micrograms/mL are attained after a single intravenous 1-g dose. The elimination half-life is about 2 hours and is prolonged in patients with renal impairment. Cefpirome is less than 10% bound to plasma proteins.

Cefpirome is widely distributed into body tissues and fluids and appears in breast milk. It is mainly excreted by the kidneys and 80 to 90% of a dose is recovered unchanged in the urine. Significant amounts are removed by haemodialysis.

Uses and Administration
Cefpirome is a fourth-generation cephalosporin antibacterial used in the treatment of infections due to susceptible organisms. They include infections of the urinary tract, respiratory tract, and skin, and also septicaemia and infections in immunocompromised patients. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefpirome is given by intravenous injection over 3 to 5 minutes or infusion over 20 to 30 minutes as the sulfate, but doses are expressed in terms of the base; 1.19 g of cefpirome sulfate is equivalent to about 1 g of cefpirome. The usual dose is the equivalent of 1 or 2 g of cefpirome every 12 hours. For details of reduced doses to be used in renal impairment, see below.

◊ References.

1. Brown EM, *et al.* eds. Cefpirome: a novel extended spectrum cephalosporin. *J Antimicrob Chemother* 1992; **29** (suppl A): 1–104.
2. Wiseman LR, Lamb HM. Cefpirome: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy in the treatment of severe nosocomial infections and febrile neutropenia. *Drugs* 1997; **54:** 117–40.

Administration in renal impairment. Dosage of cefpirome should be modified in renal impairment; after a loading dose of 1 or 2 g depending on the severity of infection, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of infection:

- CC 20 to 50 mL/minute: 0.5 or 1 g twice daily
- CC 5 to 20 mL/minute: 0.5 or 1 g once daily
- CC 5 mL/minute or less (in haemodialysis patients): 0.5 or 1 g once daily plus a half-dose after each dialysis session.