cefaclor, 6 of which proved fatal, they had received 12 reports of probable or confirmed cases with cefuroxime axetil and 15 with cefixime, one of them fatal. In clinical trials of cefuroxime axetil and cefixime, diarrhoea and pseudomembranous colitis appeared to be dose-related and therefore the CSM recommended that higher doses should be reserved for severe infections. In any event they advised that treatment should be stopped if symptoms suggestive of pseudomembranous colitis arose.

For further discussion of the management of this condition, see p.171.

1. de Lalla F, *et al.* Third generation cephalosporins as a risk factor for Clostridium difficile-associated disease: a four-year survey in a general hospital. *J Antimicrob Chemother* 1989; **23:** 623–31.
2. Golledge CL, *et al.* Extended spectrum cephalosporins and Clostridium difficile. *J Antimicrob Chemother* 1989; **23:** 929–31.
3. Freiman JP, *et al.* Pseudomembranous colitis associated with single-dose cephalosporin prophylaxis. *JAMA* 1989; **262:** 902.
4. Committee on Safety of Medicines. Pseudomembranous (antibiotic-associated) colitis and diarrhoea with cephalosporins. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the blood. References.

1. Lipsky JJ. Antibiotic-associated hypoprothrombinaemia. *J Antimicrob Chemother* 1988; **21:** 281–300.
2. Shearer MJ, *et al.* Mechanism of cephalosporin-induced hypoprothrombinemia: relation to cephalosporin side chain, vitamin K metabolism, and vitamin K status. *J Clin Pharmacol* 1988; **28:** 88–95.
3. Welage LS, *et al.* Comparative evaluation of the pharmacokinetics of N-methylthiotetrazole following administration of cefoperazone, cefotetan, and cefmetazole. *Antimicrob Agents Chemother* 1990; **34:** 2369–74.

Effects on the kidneys. References.

1. Zhanel GG. Cephalosporin-induced nephrotoxicity: does it exist? *DICP Ann Pharmacother* 1990; **24:** 262–5.
2. Tune BM. Nephrotoxicity of beta-lactam antibiotics: mechanisms and strategies for prevention. *Pediatr Nephrol* 1997; **11:** 768–72.

Precautions

Cefalotin should not be given to patients who are hypersensitive to it or to other cephalosporins. Immunological studies have suggested that up to 20% of penicillin-sensitive patients may also be allergic to cephalosporins although clinical studies indicate a lower frequency and the true incidence is uncertain; great care should be taken if cefalotin is to be given to such patients. Care is also necessary in patients with a history of allergy.

Cefalotin should be given with caution to patients with renal impairment; dosage reduction may be necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy. Cefalotin and some other cephalosporins and cephamycins (ceforanide, cefotetan, cefoxitin, and cefpirome) may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function. Positive results to the direct Coombs' test have been found during treatment with cefalotin and these can interfere with blood cross-matching. The urine of patients being treated with cefalotin may give false-positive reactions for glucose using copper-reduction reactions.

Porphyria. Cephalosporins are considered to be unsafe in patients with porphyria although there is conflicting experimental evidence of porphyrinogenicity.

Sodium content. Each g of cefalotin sodium contains about 2.39 mmol of sodium.

Interactions

The use of nephrotoxic drugs such as the aminoglycosides gentamicin and tobramycin may increase the risk of kidney damage with cefalotin. There is also some evidence for enhanced nephrotoxicity with the loop diuretic furosemide, but this is less certain than for furosemide with cefaloridine. As with penicillins, the renal excretion of cefalotin and many other cephalosporins is inhibited by probenecid. There may be antagonism between cefalotin and bacteriostatic antibacterials.

Antimicrobial Action

Cefalotin is a beta-lactam antibacterial. It is bactericidal and acts similarly to benzylpenicillin (p.214) by inhibiting synthesis of the bacterial cell wall. It is most active against Gram-positive cocci, and has moderate activity against some Gram-negative bacilli.

Sensitive Gram-positive cocci include both penicillinase- and non-penicillinase-producing staphylococci, although meticillin-resistant staphylococci are resistant; most streptococci are also sensitive, but not penicillin-resistant *Streptococcus pneumoniae;* enterococci are usually resistant. Some Gram-positive anaerobes are also susceptible. Cefalotin is usually inactive against *Listeria monocytogenes*.

Among Gram-negative bacteria cefalotin has activity against some Enterobacteriaceae including strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Salmonella*, and *Shigella* spp., but not against *Enterobacter*, indole-positive *Proteus*, or *Serratia* spp. It is also active against *Moraxella catarrhalis* (*Branhamella catarrhalis*) and *Neisseria* spp., though *Haemophilus influenzae* is moderately resistant. *Bacteroides fragilis* and *Pseudomonas aeruginosa* are not sensitive and neither are mycobacteria, mycoplasma, and fungi.

Resistance of bacteria to cefalotin may be due to several mechanisms: the drug may be prevented from reaching its site of action, for example in some Gram-negative organisms the cell wall may be a potential barrier; the target penicillin-binding proteins may be altered so that cefalotin cannot bind with these proteins; or, most importantly, the organism may produce beta-lactamases (cephalosporinases). Cefalotin is relatively resistant to hydrolysis by staphylococcal beta-lactamase, but is inactivated by a variety of beta-lactamases produced by Gram-negative organisms; resistance of Gram-negative organisms often depends on more than one factor. Resistance can be chromosomally or plasmid-mediated and may sometimes be inducible by cephalosporins.

Certain strains of bacteria may be inhibited but not killed by cephalosporins or penicillins and in such cases the minimum bactericidal concentration is much greater than the minimum inhibitory concentration; this is known as tolerance.

As well as with other cephalosporins, some cross-resistance may occur between cefalotin and the penicillinase-resistant penicillins.

Pharmacokinetics

Cefalotin is poorly absorbed from the gastrointestinal tract. After intramuscular injection peak plasma concentrations of about 10 and 20 micrograms/mL are achieved within 30 minutes of doses of 0.5 and 1 g, respectively. A concentration of 30 micrograms/mL has been reported 15 minutes after the intravenous injection of a 1-g dose; a range of 14 to 20 micrograms/mL has been achieved by the continuous intravenous infusion of 500 mg/hour.

Cefalotin is widely distributed in body tissues and fluids except the brain and CSF where the concentrations achieved are low and unpredictable. It crosses the placenta and low concentrations have been detected in breast milk. The plasma half-life varies from about 30 to 50 minutes, but may be longer in patients with renal impairment, especially that of the metabolite. About 70% of cefalotin is bound to plasma proteins.

About 20 to 30% of cefalotin is rapidly deacetylated in the liver and about 60 to 70% of a dose is excreted in the urine by the renal tubules within 6 hours as cefalotin and the less active metabolite, desacetylcefalotin. High urine concentrations of 0.8 and 2.5 mg/mL have been observed after intramuscular doses of 0.5 and 1 g, respectively. Probenecid blocks the renal excretion of cefalotin. A very small amount is excreted in bile.

Uses and Administration

Cefalotin is a first-generation cephalosporin antibacterial that has been used in the treatment of infections due to susceptible bacteria, particularly staphylococci, but has generally been replaced by newer cephalosporins.

Cefalotin is given as the sodium salt by slow intravenous injection over 3 to 5 minutes or by intermittent or continuous infusion. It may be given intramuscularly but this route is painful. Doses are expressed in terms of the equivalent amount of cefalotin; 1.06 g of cefalotin sodium is equivalent to about 1 g of cefalotin. The usual dose is 0.5 to 1 g of cefalotin every 4 to 6 hours; up to 12 g daily has been given in severe infections.

Administration in renal impairment. Reduced doses are recommended if cefalotin is given to patients with renal impairment. After an intravenous loading dose of 1 to 2 g patients may be given the following maximum doses according to their creatinine clearance (CC):

- CC 50 to 80 mL/minute: 2 g every 6 hours
- CC 25 to 50 mL/minute: 1.5 g every 6 hours
- CC 10 to 25 mL/minute: 1 g every 6 hours
- CC 2 to 10 mL/minute: 500 mg every 6 hours
- CC less than 2 mL/minute: 500 mg every 8 hours

Preparations

USP 31: Cephalothin for Injection; Cephalothin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Arecamin; Cefade†; Dasuglor; Keflin; Rupecef†; ***Austral.:*** Keflin Neutral; ***Braz.:*** Cefalin; Cefalot†; Cefalotil; Cefariston; Kefalotin†; Keflin; ***Canad.:*** Ceporacin†; ***Denm.:*** Keflin†; ***Fin.:*** Keflin†; ***Indon.:*** Cephation; Moraxine; ***Israel:*** Keflin†; ***Ital.:*** Keflin†; ***Mex.:*** Cefelen; Ceftina; Falot; Keflin; Liroken I; Loriken†; Lotin; ***Neth.:*** Keflin; ***Norw.:*** Keflin; ***Philipp.:*** Fezef; ***S.Afr.:*** Keflin†; ***Singapore:*** Cefadin; ***Thai.:*** Cefadin†; Keflin†; ***Venez.:*** Cefaciclina†; Ceflen; Keflin†.

Cefamandole *(BAN, USAN, rINN)*

83405; Cefamandol; Céfamandole; Cefamandolum; Cephamandole; Compound 83405; Kefamandoli. (7*R*)-7-D-Mandelamido-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylic acid; {6*R*-[6α,7β(R^*)]}-7-[(hydroxyphenylacetyl)amino]-3-{[(1-methyl-1*H*-tetrazol-5-yl)thio]methyl}-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

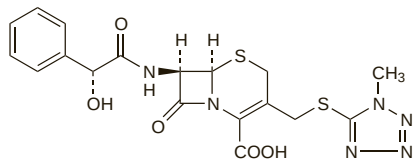
Цефамандол

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

CAS — 34444-01-4.

ATC — J01DC03.

ATC Vet — QJ01DC03.



Cefamandole Nafate *(BAN, USAN, rINNM)*

106223; Cefamandole Formate Sodium; Céfamandole, nafate de; Cefamandoli nafas; Cefamandoli Nafatum; Cefamandolio nafatas; Cefamandolnafat; Cefamandol-nafát; Cefamandolu nafan; Cefmandoli Nafas; Cephamandole Nafate; Kefamandolinafaatti; Nafato de cefamandol. Sodium (7*R*)-7-[(2*R*)-2-formyloxy-2-phenylacetamido]-3-(1-methyl-1*H*-tetrazol-5-ylthiomethyl)-3-cephem-4-carboxylate.

Цефамандола Нафат

$C_{19}H_{17}N_6NaO_6S_2$ = 512.5.

CAS — 42540-40-9.

ATC — J01DC03.

ATC Vet — QJ01DC03.

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

Ph. Eur. 6.2 (Cefamandole Nafate). A white, or almost white powder. Freely soluble in water; sparingly soluble in methyl alcohol. A 10% solution in water has a pH, measured after 30 minutes, of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Cefamandole Nafate). A white, odourless, crystalline solid. Soluble in water and in methyl alcohol; practically insoluble in chloroform, in cyclohexane, in ether, and in benzene. pH of a 10% solution in water is between 3.5 and 7.0. Store in airtight containers.

Incompatibility and stability. Cefamandole nafate has been reported to be incompatible with aminoglycosides and with metronidazole. Formulations of cefamandole nafate available for injection contain sodium carbonate and are incompatible with solutions containing calcium or magnesium salts. When reconstituted with water the sodium carbonate rapidly hydrolyses about 30% of the ester to cefamandole sodium; during storage of the reconstituted solution at room temperature carbon dioxide is produced.

References.

1. Frable RA, *et al.* Stability of cefamandole nafate injection with parenteral solutions and additives. *Am J Hosp Pharm* 1982; **39:** 622–7. Correction. *ibid.*; 1479.

Cefamandole Sodium *(BANM, rINNM)*

Cefamandol sódico; Céfamandole 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 hypoprothrombinaemia and/or platelet disorders.

Sodium content. 1.05 g of cefamandole sodium and 1.11g 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 hypoprothrombinaemic response to anticoagulants as discussed under Warfarin (p.1428).

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

◊ References.

1. Portier H, *et al.* Interaction between cephalosporins and alcohol. *Lancet* 1980; **ii:** 263.
2. 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.

1. 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.

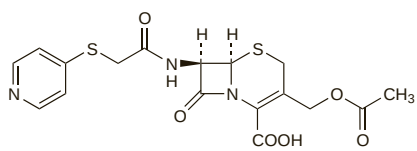
Proprietary Preparations (details are given in Part 3)
Austral.: Mandol; ***Austria:*** Mandokef; ***Belg.:*** Mandol; ***Cz.:*** Mandol†; ***Gr.:*** Acemycin; Cefadin; Mandokef; ***Hong Kong:*** Mandol†; ***Hung.:*** Cefam; Mandokef†; ***Indon.:*** Dardokef; Dofacef; ***Irl.:*** Kefadol†; ***Ital.:*** Cefam; Cemado; Lampomandol; Mancef; Mandokef†; Mandolsan†; Septomandolo†; ***Neth.:*** Mandol; ***NZ:*** Mandol; ***Pol.:*** Tarcefandol; ***Port.:*** Mandokef†; ***Rus.:*** Cefat (Цефат); Mandol (Мандол); ***S.Afr.:*** Kefdole†; Mandokef; ***Switz.:*** Mandokef; ***Thai.:*** Cefadol; Cefmandol; Mandol†.

Cefapirin Sodium *(BANM, plNNM)*

BL-P-1322; Cefapirin sodná sůl; Cefapirina sódica; Céfapirine sodique; Cefapirinnatrium; Cefapirin-nátrium; Cefapirino natrio druska; Cefapirinum natricum; Cephapirin Sodium *(USAN)*; Kefapiriininatrium; Natrii Cefapirinum. Sodium (7*R*)-7-[2-(4-pyridylthio)acetamido]cephalosporanate; Sodium (7*R*)-3-acetoxymethyl-7-[2-(4-pyridylthio)acetamido]-3-cephem-4-carboxylate.

Натрий Цефапирин

$C_{17}H_{16}N_3NaO_6S_2$ = 445.4.
CAS — 21593-23-7 (cefapirin); 24356-60-3 (cefapirin sodium).
ATC — J01DB08.
ATC Vet — QJ01DB08.



(cefapirin)

Pharmacopoeias. In *Eur.* (see p.vii), *Jpn*, and *US*.
US also includes Cephapirin 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 (Cephapirin 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: Cephapirin for Injection.

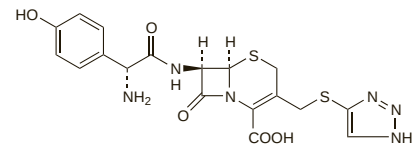
Proprietary Preparations (details are given in Part 3)
Cz.: Cefatrexyl†; ***Fr.:*** Cefaloject; ***Gr.:*** Cefatrex†; ***Spain:*** Brisfirina.

Cefatrizine *(BAN, USAN, plNN)*

BL-S640; Cefatrizina; Céfatrizine; Cefatrizinum; SKF-60771; S-640P. (7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-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, plNNM)*

Cefatrizina propilenglicol; Cefatrizinas propilenglikolis; Céfatrizine propylèneglycol; Cefatrizin-propilénglikol; Cefatrizinpropylenglykol; Cefatrizin-propylenglykol; Cefatrizinum propylen glycolum; Cefatrizinum Propylenglycolum; Kefatritsiinipropyleeniglykoli. (7*R*)-7-(α-D-4-Hydroxyphenylglycylamino)-3-(1*H*-1,2,3-triazol-4-ylthiomethyl)-3-cephem-4-carboxylate propylene glycol.

Цефатризин Пропиленгликол

$C_{18}H_{18}N_6O_5S_2$, $(C_3H_8O_2)_n$.
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.: Cefaperos; ***Fr.:*** Cefaperos†; ***Gr.:*** Anfagladin; Axelorax; Banadroxin†; Ceftazin; Cetrizin; Clomin†; Fica-F; Gertemycin; Izerin; Kentacef; Klevasin; Liamycin; Liferost; Lingopen; Mekan†; Nibocin; Northiron; Phacobiotic†; Relyovix; Specicef-N; Trixilan; ***Ital.:*** Biotrixina†; Cefatrix†; Cetrazil†; Cetrinox†; Faretrizin; Ipatrizina†; Ketrizin; Miracef†; Novacef†; Tamyl†; Tricef†; Trizina; ***Port.:*** Macropen; Supracefa.