- Ferrara N, et al. Neurotoxicity induced by cefepime in a very old hemodialysis patient. Clin Nephrol 2003; 59: 388–90.
 Dakdouki GK, Al-Awar GN. Cefepime-induced encephalopa-thy. Int J Infect Dis 2004; 8: 59–61.
- 4. Alpay H, et al. Cefepime-induced non-convulsive status epilepticus in a peritoneal dialysis patient. Pediatr Nephrol 2004; 19:
- 5. Abanades S, et al. Reversible coma secondary to cefepime neurotoxicity. *Ann Pharmacother* 2004; **38**: 606–8.
 6. Capparelli FJ, *et al.* Cefepime- and cefixime-induced encepha
- lopathy in a patient with normal renal function. Neurology 2005; **65**: 1840.
- 7. Maganti R, et al. Nonconvulsive status epilepticus due to cefepime in a patient with normal renal function. Epilepsy Behav 2006; 8: 312-4.
- 8. Lam S, Gomolin IH. Cefepime neurotoxicity: case report, pharmacokinetic considerations, and literature review. *Pharmacotherapy* 2006; **26**: 1169–74.
- 9. Sonck J, et al. The neurotoxicity and safety of treatment with cefepime in patients with renal failure. Nephrol Dial Transplant 2008; 23: 966-70.
- 10. Garces EO, et al. Renal failure is a risk factor for cefepimeinduced encephalopathy. J Nephrol 2008; 21: 526-34

Antimicrobial Action

Cefepime is a fourth-generation cephalosporin and is active against a wide range of Gram-positive and Gram-negative aerobic organisms. Against Gram-positive cocci, its activity is similar to that of cefotaxime (p.228) and includes staphylococci (but not meticillinresistant Staphylococcus aureus) and streptococci. Against Enterobacteriaceae, it has a broader spectrum of activity than other cephalosporins, including activity against organisms producing chromosomally mediated beta-lactamases such as Enterobacter spp. and Proteus vulgaris. Against Pseudomonas aeruginosa, it has similar or slightly less activity than ceftazidime (p.234), although it may be active against some strains resistant to ceftazidime.

Pharmacokinetics

Cefepime is given by injection as the hydrochloride. It is rapidly and almost completely absorbed on intramuscular injection and mean peak plasma concentrations of about 14 and 30 micrograms/mL have been reported about 1.5 hours after doses of 500 mg and 1 g respectively. Within 30 minutes of similar intravenous doses, peak plasma concentrations of about 40 and 80 micrograms/mL are achieved. The plasma half-life of cefepime is about 2 hours and is prolonged in patients with renal impairment. About 20% of cefepime is bound to plasma proteins.

Cefepime is widely distributed in body tissues and fluids. High concentrations are achieved in bile. Low concentrations have been detected in breast milk

Cefepime is eliminated principally by the kidneys and about 85% of a dose is recovered unchanged in the urine. Cefepime is substantially removed by haemodialysis.

♦ References.

- Okamoto MP, et al. Cefepime clinical pharmacokinetics. Clin Pharmacokinet 1993; 25: 88–102.
- Rybak M. The pharmacokinetic profile of a new generation of parenteral cephalosporin. Am J Med 1996; 100 (suppl 6A): 39S-44S.
- 3. Reed MD. et al. Pharmacokinetics of intravenously and intramuscularly administered cefepime in infants and children. Anti-microb Agents Chemother 1997; 41: 1783–7.
- Allaouchiche B, et al. Pharmacokinetics of cefepime during continuous venovenous hemodiafiltration. Antimicrob Agents Chemother 1997; 41: 2424-7.
- Blumer JL, et al. Review of the pharmacokinetics of cefepime in children. Pediatr Infect Dis J 2001; 20: 337–42.
- Capparelli E, et al. Population pharmacokinetics of cefepime in the neonate. Antimicrob Agents Chemother 2005; 49: 2760–6.

Uses and Administration

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

Cefepime is given as the hydrochloride by deep intramuscular injection, or intravenously by infusion over at least 30 minutes. Doses are expressed in terms of the equivalent amount of cefepime; 1.19 g of cefepime hydrochloride is equivalent to about 1 g of cefepime. The usual adult dose is 1 to 2 g daily in 2 divided doses for mild to moderate infections, increased to 4 g daily in 2 divided doses in severe infections, although up to 6 g daily in 3 divided doses has been given for febrile neutropenia. Children aged over 2 months and weighing up to 40 kg may be given 50 mg/kg twice daily; this dose may be given 3 times daily for febrile neutrope-

For details of reduced doses to be used in renal impairment, see below.

◊ Reviews

- 1. Various. Cefepime: a β-lactamase-stable extended-spectrum cephalosporin. J Antimicrob Chemother 1993; 32 (suppl B):
- 2. Barradell LB, Bryson HM, Cefepime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1994; **47:** 471–505.
- Okamoto MP, et al. Cefepime: a new fourth-generation cephalosporin. Am J Hosp Pharm 1994; 51: 463–77.
- Wynd MA, Paladino JA. Cefepime: a fourth-generation parenteral cephalosporin. Ann Pharmacother 1996; 30:
- 1414–24.
 S. Wong-Beringer A. Treating serious infections: focus on cefepime. *Pharmacotherapy* 2004; 24: 2168–23S.
 Roberts JA, et al. Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. *Int J Antimicrob Agents* 2007; 29: 117–28.

Administration in renal impairment. Dosage of cefepime should be modified in renal impairment. After a normal first dose the maintenance dosage should be adjusted according to the patient's creatinine clearance (CC) and the severity of the infection:

- CC 30 to 60 mL/minute: 0.5 to 2 g every 24 hours (2 g every 12 hours for febrile neutropenia)
- · CC 11 to 29 mL/minute: 0.5 to 1 g every 24 hours (2 g every 24 hours for febrile neutropenia)
- CC 10 mL/minute or less: 250 to 500 mg every 24 hours (1 g every 24 hours for febrile neutropenia)

Patients undergoing haemodialysis should be given a dose of 1 g on the first day of treatment, followed by 500 mg daily; the dose should be given after haemodialysis on those days. A dose of 1 g daily should be used for febrile neutropenia. Patients undergoing continuous ambulatory peritoneal dialysis should receive normal recommended doses at intervals of 48 hours. A dose of 2 g every 48 hours is used for febrile neutropenia.

Preparations

USP 31: Cefepime for Injection.

USP 31: Cefepime for Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Cefimen-K; Maxcef; Rwepime; Austral.: Maxipime; Austria: Maxipime; Belg.: Maxipime; Braz.: Cefepenț; Cemaxț; Clocef; Maxcef; Maxipime; Braz.: Carefepenț; Cemaxț; Clocef; Maxcef; Maxipime; Braz.: Maxipime; Genz.: Maxipime; Denn.: Maxipime; Fin.: Maxipime; Genz.: Maxipime; Denn.: Maxipime; Fin.: Maxipime; Genz.: Maxipime; Maxipime; Werapime; Zefipime; Hong.: Maxipime; Singabore; Maxipime; Sbain: Maxipime (Maксипим); S.Afr.: Maxipime; Singapore: Maxipime; Spain: Maxipime; Swed.: Maxipime; Swed.: Maxipime; Switz.: Maxipime; Thai.: Maxipime; Turk.: Maxipime; USA: Maxipime; Venez.: Maxipime.

Cefetamet (USAN, rINN)

Céfétamet; Cefetametum; LY-097964; Ro-15-8074. (Z)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-methyl-3-cephem-4-carboxylic acid.

Пефетамет

 $C_{14}H_{15}N_5O_5S_2 = 397.4.$ CAS - 65052-63-3 (cefetamet). ATC - JOIDDIO. ATC Vet — QJ01DD10.

Cefetamet Pivoxil Hydrochloride (MNNM)

Céfétamet Pivoxil, Chlorhydrate de; Cefetameti Pivoxili Hydrochloridum: Cefetametpivoxilhydroklorid: Cefetametum Pivoxili Hydrochloridum; Hidrocloruro de cefetamet pivoxilo; Kefetameettipivoksiilihydrokloridi; Ro-15-8075 (cefetamet pivoxil). Cefetamet pivaloyloxymethyl hydrochloride.

Цефетамета Пивоксила Гидрохлорид

 $C_{20}H_{25}N_5O_7S_2$,HCI = 548.0. CAS = 65243-33-6 (cefetamet pivoxil); | | | 696-23-2 (cefetamet pivoxil hydrochloride). ATC — J01DD10. ATC Vet — QJ01DD10.

Cefetamet is a third-generation cephalosporin antibacterial similar to cefixime (below). It has been given orally as the hydrochloride of the pivaloyloxymethyl ester, cefetamet pivoxil hydro-chloride, which is hydrolysed to cefetamet *in vivo*. The usual dose is 500 mg twice daily.

For reference to carnitine deficiency occurring with some pivaloyloxymethyl esters, see Pivampicillin, p.317.

◊ Reviews.

- 1. Bryson HM, Brogden RN. Cefetamet pivoxil: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1993; **45:** 589–621.
- Blouin RA, Stoeckel K. Cefetamet pivoxil clinical pharmacokinetics. Clin Pharmacokinet 1993; 25: 172–88.

Preparations

Proprietary Preparations (details are given in Part 3)

Braz.: Globocef†; Ger.: Globocef†; Hong Kong: Globocef†; Ital.: Globocef†; Pol.: Tarcevis†; Port.: Cefec†; Globocef†; Switz.: Globocef†.

Cefixime (BAN, USAN, rINN)

Cefiksimas; Cefixim; Cefixim trihydrát; Cefixima; Céfixime; Cefiximum; Cefiximum Trihydricum; CL-284635; FK-027; FR-17027; Sefiksim. (Z)-7-[2-(2-Aminothiazol-4-yl)-2-(carboxymethoxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid trihydrate.

Пефиксим

 $C_{16}H_{15}N_5O_7S_2,3H_2O = 507.5.$ CAS — 79350-37-1. ATC - J01DD08. ATC Vet — QJ0 I DD08.

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

Ph. Eur. 6.2 (Cefixime). A white or almost white, slightly hygroscopic, powder. Slightly soluble in water; sparingly soluble in dehydrated alcohol; practically insoluble in ethyl acetate; freely soluble in methyl alcohol. A 5% suspension in water has a pH of 2.6 to 4.1. Store in airtight containers. Protect from light.

USP 31 (Cefixime). A white to light yellow crystalline powder. Practically insoluble in water, in ether, in ethyl acetate, and in hexane; slightly soluble in alcohol, in acetone, and in glycerol; soluble in methyl alcohol and in propylene glycol; very slightly soluble in 70% sorbitol and in octanol. pH of a solution in water containing the equivalent of cefixime 0.07% is between 2.6 and 4.1. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

The most frequently reported adverse effects of cefixime are gastrointestinal disturbances, especially diarrhoea. Cefixime should be stopped if diarrhoea is severe.

Although cefixime does not have the N-methylthiotetrazole side-chain usually associated with hypoprothrombinaemia increases in prothrombin times have occurred in a few patients.

Antibiotic-associated colitis. For reports of diarrhoea and pseudomembranous colitis associated with cefixime, see Cefalotin, p.219.

Interactions

Care should be exercised in patients receiving anticoagulants and cefixime due to the possibility that cefixime may increase prothrombin times (see above).

Antimicrobial Action

Cefixime is bactericidal and is stable to hydrolysis by many beta-lactamases. It has a mode of action and spectrum of activity similar to those of the third-generation cephalosporin cefotaxime (p.228), but some Enterobacteriaceae are less susceptible to cefixime. Haemophilus influenzae, Moraxella catarrhalis (Branhamella catarrhalis), and Neisseria gonorrhoeae are sensitive, including penicillinase-producing strains. Of the Gram-positive bacteria, streptococci are

sensitive to cefixime but most strains of staphylococci, enterococci, and Listeria spp. are not.

Enterobacter spp., Pseudomonas aeruginosa, and Bacteroides spp. are resistant to cefixime.

Pharmacokinetics

Only 40 to 50% of an oral dose of cefixime is absorbed from the gastrointestinal tract, whether taken before or after meals, although the rate of absorption may be decreased in the presence of food. Cefixime is better absorbed from oral suspension than from tablets. Absorption is fairly slow; peak plasma concentrations of 2 to 3 micrograms/mL and 3.7 to 4.6 micrograms/mL have been reported between 2 and 6 hours after single doses of 200 and 400 mg, respectively. The plasma half-life is usually about 3 to 4 hours and may be prolonged when there is renal impairment. About 65% of cefixime is bound to plasma proteins.

Information on the distribution of cefixime in body tissues and fluids is limited. It crosses the placenta. Relatively high concentrations may be achieved in bile and urine. About 20% of an oral dose (or 50% of an absorbed dose) is excreted unchanged in the urine within 24 hours. Up to 60% may be eliminated by nonrenal mechanisms; there is no evidence of metabolism but some is probably excreted into the faeces from bile. It is not substantially removed by dialysis.

◊ References.

- 1. Brittain DC, et al. The pharmacokinetic and bactericidal characteristics of oral cefixime. Clin Pharmacol Ther 1985; 38: 590-4.
- 2. Guay DRP, et al. Pharmacokinetics of cefixime (CL-284,635; FK027) in healthy subjects and patients with renal insufficiency. Antimicrob Agents Chemother 1986; **30:** 485–90.
- 3. Faulkner RD, et al. Pharmacokinetics of cefixime in the young and elderly. J Antimicrob Chemother 1988; 21: 787-94.
- Stone JW, et al. Cefixime, in-vitro activity, pharmacokinetics and tissue penetration. J Antimicrob Chemother 1989; 23: 221-8.
- Westphal JF, et al. Biliary excretion of cefixime: assessment in patients provided with T-tube drainage. Antimicrob Agents Chemother 1993; 37: 1488–91.
- 6. Somekh E, et al. Penetration and bactericidal activity of cefixime in synovial fluid. Antimicrob Agents Chemother 1996; 40: 1198–1200.

Uses and Administration

Cefixime is generally classified as a third-generation cephalosporin antibacterial and is given orally in the treatment of susceptible infections including gonorrhoea, otitis media, pharyngitis, lower respiratory-tract infections such as bronchitis, and urinary-tract infections. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefixime is available as the trihydrate and doses are expressed in terms of anhydrous cefixime; 1.12 g of cefixime trihydrate is equivalent to about 1 g of anhydrous cefixime. It is given orally in adult doses of 200 to 400 mg daily as a single dose or in two divided doses. Children over 6 months and under 50 kg may be given 8 mg/kg daily as an oral suspension, again as a single dose or in two divided doses. For details of reduced dosage of cefixime in patients with moderate to severe renal impairment, see below.

For uncomplicated gonorrhoea, a single oral dose of 400 mg is given.

♦ General references.

- Leggett NJ, et al. Cefixime. DICP Ann Pharmacother 1990; 24: 489–95.
- 2. Adam D, Wallace RJ, eds. Symposium on cefixime. Drugs 1991; 42 (suppl 4): 1-32.
- 3. Markham A, Brogden RN. Cefixime: a review of its therapeutic efficacy in lower respiratory tract infections. *Drugs* 1995; **49:** 1007–22.

Administration in renal impairment. Doses of cefixime should be reduced in patients with moderate to severe renal impairment. A dose of 200 mg daily should not be exceeded in patients with a creatinine clearance of less than 20 mL/minute.

Preparations

USP 31: Cefixime for Oral Suspension; Cefixime Tablets.

Proprietary Preparations (details are given in Part 3)

Arg.: Cetaxim†; Novacef; Vixcef; Austria: Aerocef; Enzine; Exciol; Tricef; Xefotil; Xetinol; Braz.: Cefnax†; Neo Cefix; Plenax†, Canad.: Suprax; Chile: Cefspan†; Tricef; Urotricef; Cz.: Suprax; Fr.: Oroken; Ger.: Cefixdu-

ra; Cephoral; InfectoOpticef; Suprax; Uro-Cephoral; **Gr.:** Ceftoral; Covocef-N; **Hung.:** Suprax; **India:** Biotax-O; Ceftx; Cefocef-LB; Fixx; Si-Fixim†; Xim; Ziprax; **Indon.:** Cefspan; Ceptik; Comsporin; Ethifix; Fixacep; Fixxef Fixiphar; Lanfix; Maxpro; Opixime; Simcef; Sofix; Spancef; Spaxim; Sporetik; Starcef; Tocefi **Irl.:** Suprax; **Israel:** Supran; **Ital.:** Cefixoral; Suprax; Unixime; **Jpn:** Cefspan; **Malaysia:** Minixime; **Mex.:** Denvar; Novacef†; **Neth.:** Fixin; Philipp:. Tergecef; Ultraxime; Zefra; Port.: Bonoceff; Ceffine; Ceffton; Cefize; Neocef; Tricef; Rus.: Suprax (Cyrpaxc); S.Afr.: Fixime; Spain: Denvar; Necopen; Swed.: Triceff; Switz.: Cephoral; That.: Cefspan; Turk.: Suprax; Zimaks; UK: Suprax; USA: Suprax; Venez.: Longacef.

Multi-ingredient: India: Cefix LB.

Cefmenoxime Hydrochloride (USAN, rINNM)

Abbott-50192; Cefménoxime, Chlorhydrate de; Cefmenoxime Hemihydrochloride; Cefmenoximi Hydrochloridum; Hidrocloruro de cefmenoxima; SCE-1365 (cefmenoxime). (Z)-(7R)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(I-methyl-IH-tetrazol-5-yl)thiomethyl]-3-cephem-4-carboxylic hydrochloride.

Цефменоксима Гидрохлорид

 $(C_{16}H_{17}N_9O_5S_3)_2$, HCI = 1059.6.

65085-01-0 (cefmenoxime); 75738-58-8 (cefmenoxime hydrochloride).

ATC — J0 I DD05. ATC Vet - QJ01DD05.

(cefmenoxime)

Pharmacopoeias. In Jpn and US.

USP 31 (Cefmenoxime Hydrochloride). White to light orangeyellow crystals or crystalline powder. Very slightly soluble in water; practically insoluble in dehydrated alcohol and in ether; freely soluble in formamide; slightly soluble in methyl alcohol.

Profile

Cefmenoxime is a third-generation cephalosporin antibacterial with actions and uses similar to those of cefotaxime (p.228). It has been given as the hydrochloride by intramuscular injection, or intravenously by injection or infusion in the treatment of susceptible infections.

Like cefamandole (p.220), cefmenoxime has an N-methylthiotetrazole side-chain and coagulopathy and a disulfiram-like interaction with alcohol have been reported rarely.

Cefmenoxime hydrochloride is also given as eve drops for the treatment of eye infections.

1. Campoli-Richards DM, Todd PA. Cefmenoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1987; **34:** 188–221.

Preparations

USP 31: Cefmenoxime for Injection.

Proprietary Preparations (details are given in Part 3) Gr.: Tacef†; Jpn: Bestcall; Bestron

Cefmetazole (USAN, rINN)

Cefmetazol; Cefmétazole; Cefmetazolum; U-72791. (6R,7S)-7-{2-[(Cyanomethyl)thio]acetamido}-7-methoxy-3-{[(I-methyl-IH-tetrazol-5-yl)thio]methyl}-8-oxo-5-thia-I-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid.

Цефметазол

 $C_{15}H_{17}N_7O_5S_3 = 471.5.$ CAS — 56796-20-4.

ATC - JOIDCO9. ATC Vet - QI0 I DC09

Pharmacopoeias. In US.

USP 31 (Cefmetazole). Store in airtight containers.

Cefmetazole Sodium (USAN, rINNM)

Cefmetazol sódico; Cefmétazole Sodique; Cefmetazolnatrium; Cefmetazolum Natricum; CS-1170; Kefmetatsolinatrium; Natrii Cefmetazolum; SKF-83088; U-72791A.

Натрий Цефметазол

 $C_{15}H_{16}N_7NaO_5S_3 = 493.5.$

CAS - 56796-39-5.

ATC — J01DC09.

ATC Vet - QJ0 I DC09

Pharmacopoeias. In Jpn and US.

USP 31 (Cefmetazole Sodium). A white solid. Very soluble in water and in methyl alcohol; soluble in acetone; practically insoluble in chloroform. pH of a 10% solution in water is between 4.2 and 6.2. Store in airtight containers.

Adverse Effects and Precautions

As for Cefalotin Sodium, p.219.

Cefmetazole contains an N-methylthiotetrazole side-chain and has the potential to cause hypoprothrombinaemia and bleeding.

Effects on the blood. References

1. Breen GA, St Peter WL. Hypoprothrombinemia associated with cefmetazole. *Ann Pharmacother* 1997; **31:** 180–4.

Sodium content. Each g of cefmetazole sodium contains about 2 mmol of sodium

Interactions

As for Cefamandole, p.221.

Antimicrobial Action

Cefmetazole is a cephamycin antibacterial with a similar spectrum of antibacterial activity to that of cefoxitin (p.230), including the anaerobe Bacteroides fragilis.

Cornick NA, et al. Activity of cefmetazole against anaerobic bacteria. Antimicrob Agents Chemother 1987; 31: 2010–12.

Pharmacokinetics

After cefmetazole sodium 2 g intravenously every 6 hours, peak and trough plasma concentrations of 138 and 6 micrograms/mL have been achieved. Cefmetazole is 65 to 85% bound to plasma proteins, depending on the plasma concentration. A plasma halflife of about 1.1 to 1.5 hours has been reported; it is prolonged in patients with renal impairment. Small amounts have been detected in breast milk. Relatively high concentrations have been achieved in bile.

The majority of a dose is excreted unchanged in the urine resulting in high concentrations; up to 85% of a dose has been recovered within 12 hours. Cefmetazole is partly excreted by renal tubular secretion and probenecid prolongs elimination

Cefmetazole is removed to some extent by haemodialysis.

Uses and Administration

Cefmetazole is a cephamycin antibacterial generally classified with the second-generation cephalosporins and used similarly to cefoxitin (p.230) in the treatment and prophylaxis of anaerobic and mixed bacterial infections, especially intra-abdominal and pelvic infections. It may also be used in the treatment of gonorrhoea. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Cefmetazole is given intravenously as the sodium salt by infusion over 10 to 60 minutes or by slow injection over 3 to 5 minutes. Cefmetazole sodium is also used intramuscularly in some countries. Doses are expressed in terms of the equivalent amount of cefmetazole; 1.05 g of cefmetazole sodium is equivalent to about 1 g of cefmetazole.

The usual dose is 0.5 to 1 g intramuscularly or intravenously every 12 hours. For severe infections the dose may be increased to 3 to 4 g daily, given in divided doses every 6 to 8 hours.

For details of reduced dosage of cefmetazole in patients with renal impairment, see below.

♦ References.

Finch R, et al. eds. Cefimetazole: a clinical appraisal. J Antimi-crob Chemother 1989; 23 (suppl D): 1–142.

Administration in renal impairment. Doses of cefmetazole should be reduced in patients with renal impairment. It has been suggested that the interval between doses should be 12, 16, or 24 hours in patients with mild, moderate, or severe renal impairment, respectively; patients with virtually no renal function might be given cefmetazole every 48 hours, after haemodialysis.

Preparations

USP 31: Cefmetazole for Injection; Cefmetazole Injection.

Proprietary Preparations (details are given in Part 3)

Hong Kong: Cefmetazon†; *Ital.*: Metacaf†; Metafar; Metasal†; Metax; Metazol†; *Ipn*: Cefmetazon†; **USA:** Zefazone†.

The symbol † denotes a preparation no longer actively marketed