changed in the urine within 24 hours. It is removed by haemodialysis and peritoneal dialysis.

#### Cystic fibrosis. References.

- 1. Leeder JS, et al. Ceftazidime disposition in acute and stable cystic fibrosis. Clin Pharmacol Ther 1984; 36: 355–62.
- 2. Hedman A, et al. Influence of the glomerular filtration rate on renal clearance of ceftazidime in cystic fibrosis. Clin Phar cokinet 1988; 15: 57-65.
- 3. Vinks AATMM, et al. Continuous infusion of ceftazidime in cystic fibrosis patients during home treatment: clinical outcome, microbiology and pharmacokinetics. J Antimicrob Chemother 1997; 40: 125-33.

#### The elderly. References.

- 1. LeBel M. et al. Pharmacokinetics of ceftazidime in elderly volnteers. Antimicrob Agents Chemother 1985; 28: 713-15
- 2. Higbee MD, et al. Pharmacokinetics of ceftazidime in elderly patients. Clin Pharm 1989; 8: 59-62.
- Sirgo MA, Norris S. Ceftazidime in the elderly: appropriateness of twice-daily dosing. DICP Ann Pharmacother 1991; 25: 284-8

#### Hepatic impairment. References.

1. El Touny M, et al. Pharmacokinetics of ceftazidime in patients with liver cirrhosis and ascites. J Antimicrob Chemother 1991; **28:** 95–100.

#### Neonates. References.

- 1. van den Anker JN, et al. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. Clin Pharmacol Ther 1995; **58**: 650–9.
- 2. van den Anker JN, et al. Ceftazidime pharmacokinetics in preterm infants: effect of postnatal age and postnatal exposure to indomethacin. *Br J Clin Pharmacol* 1995; **40:** 439–43.
- 3. van den Anker JN, et al. Once-daily versus twice-daily administration of ceftazidime in the preterm infant. Antimicrob Agents Chemother 1995; **39:** 2048–50.

#### Renal impairment. References.

- 1. Welage LS, et al. Pharmacokinetics of ceftazidime in patients with renal insufficiency. Antimicrob Agents Chemother 1984; **25:** 201–4.
- Leroy A, et al. Pharmacokinetics of ceftazidime in normal and uremic subjects. Antimicrob Agents Chemother 1984; 25: 638-42
- 3. Ackerman BH, et al. Effect of decreased renal function on the pharmacokinetics of ceftazidime. Antimicrob Agents Chemother
- Lin N-S, et al. Single- and multiple-dose pharmacokinetics of ceftazidime in infected patients with varying degrees of renal function. J Clin Pharmacol 1989; 29: 331–7.
- 5. Kinowski J-M, et al. Multiple-dose pharmacokinetics of amikacin and ceftazidime in critically ill patients with septic multiple-organ failure during intermittent hemofiltration. Antimicrob Agents Chemother 1993; **37:** 464–73.
- 6. Demotes-Mainard F, et al. Pharmacokinetics of intravenous and intraperitoneal ceftazidime in chronic ambulatory peritoneal dialysis. *J Clin Pharmacol* 1993; **33**: 475–9.

### **Uses and Administration**

Ceftazidime is a third-generation cephalosporin antibacterial with enhanced activity against Pseudomonas aeruginosa. It is used in the treatment of susceptible infections especially those due to Pseudomonas spp. They include biliary-tract infections, bone and joint infections, cystic fibrosis (respiratory-tract infections), endophthalmitis, infections in immunocompromised patients (neutropenic patients), melioidosis, meningitis, peritonitis, pneumonia, upper respiratory-tract infections, septicaemia, skin infections (including burns, ecthyma gangrenosum, and ulceration), and urinarytract infections. It is also used for surgical infection prophylaxis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

Administration and dosage. Ceftazidime is available as the pentahydrate but it is formulated with sodium carbonate, to form the sodium salt in solution, or with arginine. Doses are expressed in terms of anhydrous ceftazidime; ceftazidime pentahydrate 1.16 g is equivalent to about 1 g of anhydrous ceftazidime. It is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes. The usual dose for adults ranges from 1 to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised patients. In adults with cystic fibrosis who have pseudomonal lung infections, high doses of 90 to 150 mg/kg daily in 3 divided doses are used; up to 9 g daily has been given to those with normal renal function. Single doses of more than 1 g should be given intravenously.

Children are usually given ceftazidime 30 to 100 mg/kg daily in 2 or 3 divided doses, but in severely

ill children up to 150 mg/kg daily to a maximum of 6 g daily (9 g in cystic fibrosis with pseudomonal lung infection) may be given in 3 divided doses. Neonates and infants up to 2 months have been given 25 to 60 mg/kg daily in 2 divided doses.

In the elderly the dose should generally not exceed 3 g

Although not licensed for nebulisation in the UK, the BNFC suggests a dose of 1 g inhaled twice daily for the management of chronic Burkholderia cepacia (Pseudomonas cepacia) infection in patients aged 1 month and older with cystic fibrosis.

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

For surgical infection prophylaxis in patients undergoing prostatic surgery, a dose of 1 g may be given at induction of anaesthesia and repeated if necessary when the catheter is removed.

Ceftazidime can be used with an aminoglycoside, another beta lactam such as piperacillin, or vancomycin in patients with severe neutropenia, or, if infection with Bacteroides fragilis is suspected, with an antimicrobial such as clindamycin or metronidazole. The drugs should generally be given separately (see also Incompatibility, above).

#### ◊ References.

1. Rains CP, et al. Ceftazidime: an update of its antibacterial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1995; **49:** 577–617.

Administration in renal impairment. In patients with renal impairment the dosage of ceftazidime may need to be reduced. After a loading dose of 1 g, maintenance doses are based on the creatinine clearance (CC)

• CC 31 to 50 mL/minute: 1 g every 12 hours

· CC 16 to 30 mL/minute: 1 g every 24 hours

· CC 6 to 15 mL/minute: 500 mg every 24 hours

· CC less than 5 mL/minute: 500 mg every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime trough serum concentrations should not exceed 40 micrograms/mL. In patients undergoing peritoneal dialysis a loading dose of 1 g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and then 0.5 to 1 g after each dialysis

# **Preparations**

USP 31: Ceftazidime for Injection; Ceftazidime Injection.

### Proprietary Preparations (details are given in Part 3)

Arg.: Crima; Fortum; Pluseptic, Tinacef; Zidima; Austral.: Fortum; Austria: Fortum; Kefazim; Belg.: Glazidim; Kefadim;† Braz.: Cefazima;†; Cefanorth;† Cefazidon; Ceften; Cetaz; Fortaz; Intracef; Kefadim; Roycefax;† Canad.: Ceptaz;†; Fortaz; Tazidime;†; Chile: Fortum; Kefzim;†; Cz.: Fortum; Kefadim;† Denm.: Fortum; Fin.: Glazidim; Fi:: Fortum; Fortum; Seftum;†; Cortum; Fin.: Glazidim; Fi:: Fortum; Hung.: Cetazime; Fortum; Hung.: Cetazime; Ceftum; Hung.: Cetazime; Ceftum; Cetazum; Edima; Ceftum; Ceftum; Cetazum; Edima; Ceftum; Cef Ceftum; Cetazum; Extimon; Fortum; Lacedim; Pharodime; Sodime; Thicing. Zefdim; Ziba; Zidifee; H.i.: Fortum; Breel: Fortum; Rab.: Cedizim; Ceftim; Dizatec; Etazim; Fribat; Glazidim; Liotixil; Panzid; Spectrum; Starcef; Tazidif; Tottizim; Malgyais: Cef-4; Fortum; Mex.: Fentt; Fortum; Izadima; Leidim; Tagal; Taloken; Taxifur; Zadolina; Zidicef; Neth.: Fortum; Tazidux; Norw.: Fortum; NZ: Fortum; Philipp.: Baxidyme; Dimzef; Fortum; Forzid; Tazicef; Tazidan; Tazidem; Uniranz; Zadim Zeptrigen; Pol.: Biotum; Fortum; Mirocef; Port.: Cefortam; Ceftazim; Zidimox; Rus.: Bestum (Бестум); Fortum; Oppryw); Lorazidime (Лоразидим); S.Afr.: Fortum; Kefam; Taziject; Singapore: Cefazime; Fortum; Spain: Fortam; Kefamin; Swed.: Fortum; Switz.: Fortam; Thali: CEF-4; Cef-Dime; Cefodime; Dimase; Fortadim; Fortum; Taxifect; Geodime; Dimase; Fortadim; Fortum; Taxifect; Fortum; Taxifect; Fortum; Taxifect; Fortum; Fortum; Fortizi; Fortum; Esetum; MZE; Negazef; Fortum; Forzid; Foumox†; Zeffam; **Turk.**: Fortum; lesetum; **UAE**: Negacef; **UK**: Fortum; Kefadim; **USA**: Ceptaz; Fortaz; Tazicef; Tazidime; **Venez.:** Betazidim; Biozidima; Cefgram; Fortum; Kesterina†.

## Cefteram Pivoxil (rINNM)

Ceftéram, Pivoxil de; Cefteram pivoxilo; Cefterami Pivoxil; T-2588. Pivaloyloxymethyl (Z)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-(5-methyl-2H-tetrazol-2-ylmethyl)-3-cephem-4-carboxylic acid.

Цефтерама Пивоксил

 $C_{22}H_{27}N_9O_7S_2 = 593.6.$ 

CAS — 82547-58-8 (cefteram); 82547-81-7 (cefteram pivoxil).

#### Pharmacopoeias. In Jpn.

#### **Profile**

Cefteram is a cephalosporin antibacterial used for the treatment of susceptible infections. It is given orally as the pivaloyloxymethyl ester, cefteram pivoxil, and doses are expressed in terms of cefteram; 186 mg of cefteram pivoxil is equivalent to about 150 mg of cefteram. The usual dose is 150 to 300 mg daily in 3 divided doses after meals. For severe infections, up to 600 mg daily may be given.

For reference to carnitine deficiency occurring after the administration of some pivaloyloxymethyl esters, see Pivampicillin, p.317.

#### **Preparations**

**Proprietary Preparations** (details are given in Part 3) Jpn: Tomiror

#### Ceftezole Sodium (HNNM)

Ceftezol sódico; Ceftézole Sodique; Natrii Ceftezolum. Sodium (7R)-7-[2-(1H-tetrazol-1-yl)acetamido]-3-(1,3,4-thiadiazol-2ylthiomethyl)-3-cephem-4-carboxylate

Натрий I Іефтезол

 $C_{13}H_{11}N_8NaO_4S_3 = 462.5.$ 

- 26973-24-0 (ceftezole); 41136-22-5 (ceftezole sodium).

ATC — JOIDBI2

ATC Vet — QJ01DB12.

### Pharmacopoeias. In Chin.

### Profile

Ceftezole is a cephalosporin antibacterial with properties similar to those of cefalotin (p.219). It is given as the sodium salt but doses are expressed in terms of the base; 1.05 g of ceftezole sodium is equivalent to about 1 g of ceftezole. The usual dose is 2 to 4 g daily by intramuscular injection in 2 or 3 divided doses.

Sodium content. Each g of ceftezole sodium contains about 2.16 mmol of sodium.

# **Preparations**

Proprietary Preparations (details are given in Part 3)

## **Ceftibuten** (BAN, USAN, rINN)

Ceftibutène; Ceftibuteno; Ceftibutenum; Keftibuteeni; 7432-S; Sch-39720. 7-[2-(2-Amino-1,3-thiazol-4-yl)-4-carboxyisocrotonamide]-3-cephem-4-carboxylic acid.

Цефтибутен

 $C_{15}H_{14}N_4O_6S_2 = 410.4.$ 

CAS - 97519-39-6.

ATC — JOIDD14. ATC Vet - QJ01DD14

Pharmacopoeias. Jpn includes the dihydrate.

#### **Adverse Effects and Precautions**

As for Cefalotin Sodium, p.219.

The most frequently reported adverse effects of ceftibuten are gastrointestinal disturbances, especially diarrhoea, and headache.

#### **Antimicrobial Action**

As for Cefixime, p.224. It is less active in vitro against Streptococcus pneumoniae.

♦ References.

- 1. Shawar R, et al. Comparative in vitro activity of ceftibuten (Sch-39720) against bacterial enteropathogens. Antimicrob Agents Chemother 1989; 33: 781-4.
- 2. Bragman SGL, Casewell MW. The in-vitro activity of ceftibuten against 475 clinical isolates of Gram-negative bacilli, compared with cefuroxime and cefadroxil. *J Antimicrob Chemother* 1990; 25: 221-6.
- Wise R, et al. Ceftibuten—in-vitro activity against respiratory pathogens, β-lactamase stability and mechanism of action. J Antimicrob Chemother 1990; 26: 209-13.
- 4. Maioli E, et al. In vitro activity of ceftibuten at sub-inhibitory concentrations in comparison with other antibiotics against res piratory and urinary tract pathogens. *J Chemother* 2007; **19**: 152–60.

#### **Pharmacokinetics**

Ceftibuten is rapidly absorbed from the gastrointestinal tract, although the rate and extent of absorption are somewhat decreased by the presence of food. Peak plasma concentrations of about 17 micrograms/mL are attained about 2 hours after a 400-mg dose. The plasma half-life of ceftibuten is about 2.0 to 2.3 hours and is prolonged in patients with renal impairment. Ceftibuten is 65 to 77% bound to plasma proteins.

Ceftibuten distributes into middle-ear fluid and bronchial secretions. About 10% of a dose is converted to the trans-isomer, which has about one-eighth of the activity of the *cis*-isomer. Ceftibuten is excreted mainly in the urine and also in the faeces. Significant amounts are removed by haemodialysis.

## **Uses and Administration**

Ceftibuten is a third-generation cephalosporin antibacterial used similarly to cefixime (p.225) in the treatment of urinary-tract and respiratory-tract infections. It is given orally as the dihydrate, but doses are expressed in terms of anhydrous ceftibuten; 435 mg of ceftibuten dihydrate is equivalent to about 400 mg of anhydrous ceftibuten. The usual adult dose is 400 mg once daily on an empty stomach. Children over 6 months of age and weighing 45 kg or less may be given 9 mg/kg daily as a single dose. For reduced doses in patients with moderate to severe renal impairment, see below.

Reviews.

- 1. Wiseman LR, Balfour JA, Ceftibuten: review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. *Drugs* 1994; **47**: 784–808.
- 2. Nelson JD, McCracken GH (eds). Ceftibuten: a new orally active cephalosporin for pediatric infections. *Pediatr Infect Dis J* 1995; **14** (suppl): S76–S133.
- Guay DRP. Ceftibuten: a new expanded-spectrum oral cephalosporin. Ann Pharmacother 1997; 31: 1022–33.
- 4. Owens RC, et al. Ceftibuten: an overview. Pharmacotherapy 1997; **17:** 707–20.

Administration in renal impairment. Doses of ceftibuten should be reduced in patients with moderate to severe renal impairment. The following doses based on creatinine clearance (CC) may be used:

. CC 30 to 49 mL/minute: 200 mg once daily

· CC 5 to 29 mL/minute: 100 mg once daily

Patients undergoing haemodialysis 2 or 3 times weekly may be given a dose of  $400~\rm mg$  after each dialysis session.

### **Preparations**

Proprietary Preparations (details are given in Part 3)

Arg.: Cedax†, Sepex†, Austria: Caedax†, Cz.: Cedax†, Ger.: Keimax Gr.: Caedax†, Hong Kong: Cedax; Hung.: Cedax; India: Procadax Israel: Cedax; Hong Kong: Cedax; Hung.: Cedax; India: Procadax Israel: Cedax; Rol.: Cedax; Pol.: Cedax; Port.: Caedax; Mex.: Cedax; Neth.: Cedax; Polipp.: Cedax; Pol.: Cedax; Port.: Caedax; Rus.: Cedax (Lleaex): S.Afr.: Cedax†, Sepexin†, Singapore: Cedax; Spain: Biocef, Cedax; Ce

#### Ceftiofur Hydrochloride (BANM, USAN, rINNM)

Ceftiofur, Chlorhydrate de; Ceftiofuri Hydrochloridum; Hidrocloruro de ceftiofur; U-64279A. (6R,7R)-7-[2-(2-Amino-4-thiazolyl)-glyoxylamido]-3-mercaptomethyl-8-oxo-5-thia-I-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7<sup>2</sup>-(Z)-(O-methyloxime), 2furoate (ester), monohydrochloride.

Цефтиофура Гидрохлорид

 $C_{19}H_{17}N_5O_7S_3.HCI = 560.0.$ 

- 80370-57-6 (ceftiofur); 103980-44-5 (ceftiofur hydrochloride).

#### Ceftiofur Sodium (BANM, USAN, rINNM)

Ceftiofur sódico; Ceftiofur sodique; Ceftiofurum natricum; CM-31-916; Natrii Ceftiofurum; U-64279E

Натрий Цефтиофур

 $C_{19}H_{16}N_5NaO_7S_3 = 545.5.$ CAS — 104010-37-9.

#### **Profile**

Ceftiofur is a cephalosporin antibacterial used as the hydrochloride and sodium salts in veterinary practice.

## Ceftizoxime Sodium (BANM, USAN, rINNM)

Ceftizoxima sódica; Ceftizoxime Sodique; Ceftizoximnatrium; Ceftizoximum Natricum; FK-749; FR-13749; Keftitsoksiiminatrium; Natrii Ceftizoximum; Seftizoksim Sodyum; SKF-88373-Z. Sodium (Z)-7-[2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamidol-3-cephem-4-carboxylate.

Натрий Цефтизоксим

 $C_{13}\dot{H}_{12}N_5\dot{N}_aO_5S_2 = 405.4.$ 

CAS — 68401-81-0 (ceftizoxime); 68401-82-1 (ceftizoxime sodium).

ATC — J01DD07.

ATC Vet - QJ01DD07.

**Pharmacopoeias.** In *Jpn* and *US*.

USP 31 (Ceftizoxime Sodium). A white to pale yellow crystalline powder. Freely soluble in water. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

### Stability. References.

1. Lesko AB, et al. Ceftizoxime stability in iv solutions. DICP Ann Pharmacother 1989; 23: 615–18.

# **Adverse Effects and Precautions**

As for Cefotaxime Sodium, p.228.

Sodium content. Each g of ceftizoxime sodium contains about 2.5 mmol of sodium.

### Interactions

Probenecid reduces the renal clearance of ceftizoxime.

### **Antimicrobial Action**

As for Cefotaxime Sodium, p.228, although ceftizoxime has no active metabolite.

## **Pharmacokinetics**

After intramuscular injection of 0.5 and 1 g of ceftizoxime, mean peak plasma concentrations of about 14 and 39 micrograms/mL respectively have been reported after 1 hour. The plasma half-life of ceftizoxime is about 1.7 hours and is prolonged in neonates and in renal impairment. Ceftizoxime is 30% bound to plasma pro-

Ceftizoxime is widely distributed in body tissues and fluids: therapeutic concentrations are achieved in the CSF when the meninges are inflamed. It crosses the placenta and low concentrations have been detected in breast milk.

Nearly all of a dose is excreted unchanged in the urine within 24 hours of dosage, thus achieving high urinary concentrations. Ceftizoxime is excreted by tubular

secretion as well as glomerular filtration and giving it with probenecid results in higher and more prolonged plasma concentrations. Some ceftizoxime is removed by haemodialysis.

#### Neonates. References.

- 1. Fujii R. Investigation of half-life and clinical effects of ceftizoxime in premature and newborn infants. *Drug Invest* 1990; 2:
- 2. Reed MD, et al. Ceftizoxime disposition in neonates and infants during the first six months of life. DICP Ann Pharmacother 1991; 25: 344-7.

#### **Uses and Administration**

Ceftizoxime is a third-generation cephalosporin antibacterial used similarly to cefotaxime (p.229) for the treatment of susceptible infections.

It is given as the sodium salt by deep intramuscular injection, or intravenously as a slow injection over 3 to 5 minutes or as a continuous or intermittent infusion. If 2 g of ceftizoxime is injected intramuscularly the dose should be divided between sites.

Doses are expressed in terms of the equivalent amount of ceftizoxime; 1.06 g of ceftizoxime sodium is equivalent to about 1 g of ceftizoxime. It is usually given in an adult dose of 1 to 2 g every 8 to 12 hours. In severe infections 2 to 4 g may be given intravenously every 8 hours; doses up to 2 g every 4 hours have been given in life-threatening infections.

Children over 6 months of age may be given 50 mg/kg every 6 to 8 hours.

For the treatment of uncomplicated urinary-tract infections, a dose of 500 mg every 12 hours is used.

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

A single intramuscular dose of 1 g has been given in uncomplicated gonorrhoea.

◊ References

1. Richards DM, Heel RC. Ceftizoxime: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1985; **29:** 281–329.

Administration in renal impairment. Doses of ceftizoxime should be modified in renal impairment; after a loading dose of 0.5 to 1 g, the maintenance dosage should be adjusted according to creatinine clearance (CC) and the severity of the infection:

- · CC 50 to 79 mL/minute: 0.5 to 1.5 g every 8 hours
- · CC 5 to 49 mL/minute: 0.25 to 1 g every 12 hours
- CC less than 5 mL/minute: 250 to 500 mg every 24 hours or  $0.5\ to\ 1\ g$  every 48 hours, after dialysis.

# **Preparations**

USP 31: Ceftizoxime for Injection; Ceftizoxime Injection.

Proprietary Preparations (details are given in Part 3)

Arg.: Ceftix; Ceftizon; Canad.: Ceftixox; Cz.: Ceftixox; Fr.: Ceftizox; India: Ceftixox; India: Ceftixox; India: Eposerin; Jpn: Epocelin; Mex.: Ceftixox; Path.: Ceftixox; Philipp.: Tergecin; Unixox; Port.: Ceftixox; Turk.: Ceftixox; USA: Ceftixox.

### Ceftobiprole Medocaril (USAN, rINN)

BAL-5788; BAL-5788-001; BAL-9141 (ceftobiprole); Ceftobiprol Medocarilo; Ceftobiprole Médocaril; Ceftobiprolum Medocarilum; Ro-65-5788; Ro-63-9141 (ceftobiprole). (6R,7R)-7-[(2Z)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(hydroxyimino)acetamido]-3-((E){(3'R)-1'-[(5-methyl-2-oxo-1,3-dioxol-4-yl)methoxycarbonyl]-2-oxo-(1,3'-bipyrrolidin)-3-ylidene}methyl)-8-oxo-5-thia-I-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Цефтобипрол Медокарил

 $C_{26}H_{26}N_8O_{11}S_2=690.7.$  CAS — 209467-52-7 (ceftobiprole); 376653-43-9 (ceftobiprole medocaril); 252188-71-9 (ceftobiprole medocaril

(ceftobiprole)

### **Profile**

Ceftobiprole is a broad-spectrum cephalosporin that is being tried in the treatment of susceptible infections, including meticil-