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.
3. 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 respiratory 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.
3. 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 mg after each dialysis session.

Preparations
Proprietary Preparations (details are given in Part 3)

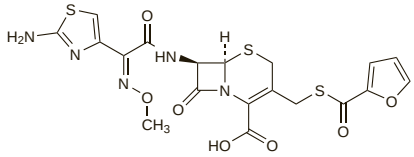
Arg.: Cedax†; Sepex†; ***Austria:*** Caedax†; ***Cz.:*** Cedax†; ***Ger.:*** Keimax; ***Gr.:*** Caedax†; ***Hong Kong:*** Cedax; ***Hung.:*** Cedax; ***India:*** Procadax; ***Israel:*** Cedax; ***Ital.:*** Cedax; Isocef; ***Jpn:*** Seftem; ***Malaysia:*** Cedax; ***Mex.:*** Cedax; ***Neth.:*** Cedax; ***Philipp.:*** Cedax; ***Pol.:*** Cedax; ***Port.:*** Caedax; ***Rus.:*** Cedax (Цедекс); ***S.Afr.:*** Cedax†; Sepexin†; ***Singapore:*** Cedax; ***Spain:*** Biocef; Cedax; Cepifran†; ***Swed.:*** Cedax; ***Switz.:*** Cedax; ***Thai.:*** Cedax; ***USA:*** Cedax; ***Venez.:*** Cedax; Sepexin†.

Ceftiofur Hydrochloride *(BANM, USAN, rINNM)*
Ceftiofur, Chlorhydrate de; Ceftiofuri Hydrochloridum; Hidrocloruro de ceftiofur; U-64279A. (6*R*,7*R*)-7-[2-(2-Amino-4-thiazolyl)-glyoxylamido]-3-mercaptomethyl-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7²-(*Z*)-(*O*-methyloxime), 2-furoate (ester), monohydrochloride.

Цефтиофура Гидрохлорид

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

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



(ceftiofur)

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-methoxyiminoacetamido]-3-cephem-4-carboxylate.

Натрий Цефтизоксим

$C_{13}H_{12}N_5NaO_5S_2$ = 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 proteins.

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:** 143–9.
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)

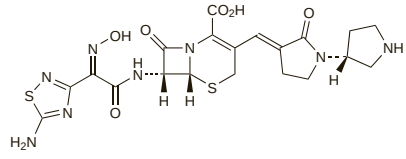
Arg.: Ceftix†; Ceftizon†; ***Canad.:*** Cefizox; ***Cz.:*** Cefizox†; ***Fr.:*** Cefizox†; ***India:*** Cefizox; ***Indon.:*** Cefizox; Tizos; ***Ital.:*** Eposerin; ***Jpn:*** Epocelin†; ***Mex.:*** Cefizox†; ***Neth.:*** Cefizox; ***Philipp.:*** Tergecin; Unizox; ***Port.:*** Cefizox; ***Turk.:*** Cefizox; ***USA:*** Cefizox.

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). (6*R*,7*R*)-7-[(2*Z*)-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-1-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 sodium).



(ceftobiprole)

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

lin-resistant *Staphylococcus aureus*. It is given as the medocaril derivative.

◊ References.

1. Noel GJ. Clinical profile of ceftobiprole, a novel beta-lactam antibiotic. *Clin Microbiol Infect* 2007; **13** (suppl 2): 25–9.
2. Murthy B, Schmitt-Hoffmann A. Pharmacokinetics and pharmacodynamics of ceftobiprole, an anti-MRSA cephalosporin with broad-spectrum activity. *Clin Pharmacokinet* 2008; **47:** 21–33.
3. Zhanel GG, *et al.* Ceftobiprole: a review of a broad-spectrum and anti-MRSA cephalosporin. *Am J Clin Dermatol* 2008; **9:** 245–54.
4. Deresinski SC. The efficacy and safety of ceftobiprole in the treatment of complicated skin and skin structure infections: evidence from 2 clinical trials. *Diagn Microbiol Infect Dis* 2008; **61:** 103–9.
5. Anderson SD, Gums JG. Ceftobiprole: an extended-spectrum anti-methicillin-resistant Staphylococcus aureus cephalosporin. *Ann Pharmacother* 2008; **42:** 806–16.

Ceftriaxone Sodium *(BANM, USAN, rINNM)*

Ceftriakson sodowy; Ceftriaksono natrio druska; Ceftriaxon sodná sůl trihemihydrát; Ceftriaxona sódica; Ceftriaxone sodique; Ceftriaxonnatrium; Ceftriaxon-nátrium; Ceftriaxonum natricum; Ceftriaxonum Natricum Trihemihydricum; Keftriaksoninatrium; Natrii Ceftriaxonum; Ro-13-9904; Ro-13-9904/000 (ceftriaxone); Seftriakson Sodyum. (*Z*)-7-[2-(2-Aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[(2,5-dihydro-6-hydroxy-2-methyl-5-oxo-1,2,4-triazin-3-yl)thiomethyl]-3-cephem-4-carboxylic acid, disodium salt, sesquaterhydrate.

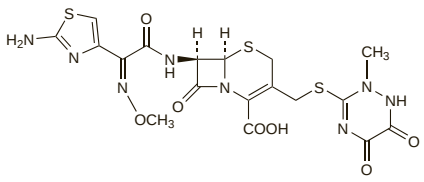
Натрий Цефтриаксон

$C_{18}H_{16}N_8Na_2O_7S_3,3H_2O$ = 661.6.

CAS — 73384-59-5 (ceftriaxone); 74578-69-1 (anhydrous ceftriaxone sodium); 104376-79-6 (ceftriaxone sodium sesquaterhydrate).

ATC — J01DD04.

ATC Vet — QJ01DD04.



(ceftriaxone)

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

Ph. Eur. 6.2 (Ceftriaxone Sodium). A semi-synthetic product derived from a fermentation product. An almost white to yellowish, slightly hygroscopic, crystalline powder. Freely soluble in water; very slightly soluble in dehydrated alcohol; sparingly soluble in methyl alcohol. A 12% solution in water has a pH of 6.0 to 8.0. Store in airtight containers. Protect from light.

USP 31 (Ceftriaxone Sodium). A white to yellowish-orange crystalline powder. Freely soluble in water; very slightly soluble in alcohol; sparingly soluble in methyl alcohol. pH of a 10% solution in water is between 6.0 and 8.0. Store in airtight containers.

Incompatibility. UK licensed product information warns of incompatibility if ceftriaxone sodium is mixed with calcium-containing solutions or with aminoglycosides, amsacrine, fluconazole, labetalol, or vancomycin. Published reports of incompatibility have included that between ceftriaxone and vancomycin[1] or pentamidine.[2]

1. Pritts D, Hancock D. Incompatibility of ceftriaxone with vancomycin. *Am J Hosp Pharm* 1991; **48:** 77.
2. Lewis JD, El-Gendy A. Cephalosporin-pentamidine isethionate incompatibilities. *Am J Health-Syst Pharm* 1996; **53:** 1461–2.

Stability. References.

1. Nahata MC. Stability of ceftriaxone sodium in peritoneal dialysis solutions. *DICP Ann Pharmacother* 1991; **25:** 741–2.
2. Canton E, Esteban MJ. Stability of ceftriaxone solution. *J Antimicrob Chemother* 1992; **30:** 397–8.
3. Bailey LC, *et al.* Stability of ceftriaxone sodium in injectable solutions stored frozen in syringes. *Am J Hosp Pharm* 1994; **51:** 2159–61.
4. Plumridge RJ, *et al.* Stability of ceftriaxone sodium in polypropylene syringes at −20, 4, and 20°C. *Am J Health-Syst Pharm* 1996; **53:** 2320–3.

Adverse Effects and Precautions

As for Cefotaxime Sodium, p.228.

Changes in bowel flora may be more marked than with cefotaxime because of the greater biliary excretion of ceftriaxone; diarrhoea may occur more often, especially in children. Biliary sludge or pseudolithiasis due to a precipitate of calcium ceftriaxone has been seen occasionally in patients given ceftriaxone. Similarly, deposition of the calcium salt has occurred rarely in the urine. Isolated cases of death in term or premature neonates have been associated with precipitation of calcium ceftriaxone in lungs and kidneys, and in some of these cases a calcium-containing product has been given by a different route or line, or at a different time. US licensed product information therefore contra-indicates the use of ceftriaxone within 48 hours of products or solutions containing calcium, particularly in neonates. Ceftriaxone is highly protein bound and is able to displace bilirubin from albumin binding sites, causing hyperbilirubinaemia; its use should be avoided in jaundiced neonates.

Neutropenia has been reported with most cephalosporins; a complex mechanism has been attributed to that associated with ceftriaxone. There have been rare reports of fatal haemolysis associated with ceftriaxone.

Although ceftriaxone has an *N*-methylthiotriazine ring rather than an *N*-methylthiotetrazole side-chain, it might still have the potential to cause hypoprothrombinaemia.

Breast feeding. A study of drug distribution and protein binding between maternal blood and breast milk post partum in a 26-year-old woman given ceftriaxone 2 g daily by intravenous infusion for 10 days found that penetration of ceftriaxone into breast milk increased at these doses as protein binding capacity was saturated, although no adverse effects occurred in the infant.[1] The authors advised caution in breast-feeding mothers given acidic drugs which also have high protein binding such as ceftriaxone[1] although, on the basis that no adverse effects have been observed in breast-fed infants whose mothers were receiving ceftriaxone, the American Academy of Pediatrics considers[2] that it is therefore usually compatible with breast feeding.

1. Bourget P, *et al.* Ceftriaxone distribution and protein binding between maternal blood and milk postpartum. *Ann Pharmacother* 1993; **27:** 294–7.
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 biliary tract. Using abdominal ultrasonography, biliary sludge or pseudolithiasis was found in about 40% of severely ill children being treated with high doses of ceftriaxone[1] and was later reported in adults.[2-4] The sludge has been identified as a calcium salt of ceftriaxone.[5] Patients are often asymptomatic and the sludge usually dissolves once ceftriaxone is stopped. Gallstones with ceftriaxone as a major component have been identified in a patient given long-term high-dose treatment.[6] Similarly, a bile-duct stone composed of ceftriaxone occurred with high-dose ceftriaxone in a child.[7] In another report, intractable hiccups were associated with ceftriaxone-related pseudolithiasis in a 10-year-old boy.[8]

1. Schaad UB, *et al.* Reversible ceftriaxone-associated biliary pseudolithiasis in children. *Lancet* 1988; **ii:** 1411–13.
2. Pigrau C, *et al.* Ceftriaxone-associated biliary pseudolithiasis in adults. *Lancet* 1989; **ii:** 165.
3. Heim-Duthoy KL, *et al.* Apparent biliary pseudolithiasis during ceftriaxone therapy. *Antimicrob Agents Chemother* 1990; **34:** 1146–9.
4. Bickford CL, Spencer AP. Biliary sludge and hyperbilirubinemia associated with ceftriaxone in an adult: case report and review of the literature. *Pharmacotherapy* 2005; **25:** 1389–95.
5. Park HZ, *et al.* Ceftriaxone-associated gallbladder sludge: identification of calcium-ceftriaxone salt as a major component of gallbladder precipitate. *Gastroenterology* 1991; **100:** 1665–70.
6. Lopez AJ, *et al.* Ceftriaxone-induced cholelithiasis. *Ann Intern Med* 1991; **115:** 712–14.
7. Robertson FM, *et al.* Ceftriaxone choledocholithiasis. *Pediatrics* 1996; **98:** 133–5.
8. Bonioli E, *et al.* Pseudolithiasis and intractable hiccups in a boy receiving ceftriaxone. *N Engl J Med* 1994; **331:** 1532.

Effects on the blood. References.

1. Haubenstock A, *et al.* Hypoprothrombinaemic bleeding associated with ceftriaxone. *Lancet* 1983; **i:** 1215–16.
2. Rey D, *et al.* Ceftriaxone-induced granulopenia related to a peculiar mechanism of granulopoiesis inhibition. *Am J Med* 1989; **87:** 591–2.
3. Bernini JC, *et al.* Fatal hemolysis induced by ceftriaxone in a child with sickle cell anemia. *J Pediatr* 1995; **126:** 813–15.
4. Lascari AD, Amyot K. Fatal hemolysis caused by ceftriaxone. *J Pediatr* 1995; **126:** 816–17.
5. Scimeca PG, *et al.* Hemolysis after treatment with ceftriaxone. *J Pediatr* 1996; **128:** 163.
6. Moallem HJ, *et al.* Ceftriaxone-related fatal hemolysis in an adolescent with perinatally acquired human immunodeficiency virus infection. *J Pediatr* 1998; **133:** 279–81.
7. Meyer O, *et al.* Fatal immune haemolysis due to a degradation product of ceftriaxone. *Br J Haematol* 1999; **105:** 1084–5.
8. Viner Y, *et al.* Severe hemolysis induced by ceftriaxone in a child with sickle-cell anemia. *Pediatr Infect Dis J* 2000; **19:** 83–5.
9. Seltsam A, Salama A. Ceftriaxone-induced immune haemolysis: two case reports and a concise review of the literature. *Intensive Care Med* 2000; **26:** 1390–4.
10. Citak A, *et al.* Ceftriaxone-induced haemolytic anaemia in a child with no immune deficiency or haematological disease. *J Paediatr Child Health* 2002; **38:** 209–10.

Effects on the pancreas. References.

1. Zimmermann AE, *et al.* Ceftriaxone-induced acute pancreatitis. *Ann Pharmacother* 1993; **27:** 36–7.
2. Maranan MC, *et al.* Gallstone pancreatitis caused by ceftriaxone. *Pediatr Infect Dis J* 1998; **17:** 662–3.

Neonates. References to the displacement of bilirubin by ceftriaxone in neonates.

1. Gulian J-M, *et al.* Bilirubin displacement by ceftriaxone in neonates: evaluation by determination of 'free' bilirubin and erythrocyte-bound bilirubin. *J Antimicrob Chemother* 1987; **19:** 823–9.
2. Fink S, *et al.* Ceftriaxone effect on bilirubin-albumin binding. *Pediatrics* 1987; **80:** 873–5.

Sodium content. Each g of ceftriaxone sodium contains about 3.0 mmol of sodium.

Interactions

Ceftriaxone has an *N*-methylthiotriazine side-chain and may have the potential to increase the effects of anticoagulants and to cause a disulfiram-like reaction with alcohol.

Unlike many cephalosporins, probenecid does not affect the renal excretion of ceftriaxone.

Antimicrobial Action

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

◊ References.

1. Goldstein FW, *et al.* Resistance to ceftriaxone and other β-lactams in bacteria isolated in the community. *Antimicrob Agents Chemother* 1995; **39:** 2516–19.

Pharmacokinetics

Ceftriaxone demonstrates nonlinear dose-dependent pharmacokinetics because of its protein binding; about 85 to 95% is bound to plasma proteins depending on the concentration of ceftriaxone.

Mean peak plasma concentrations of about 40 and 80 micrograms/mL have been reported 2 hours after intramuscular injection of 0.5 and 1 g of ceftriaxone respectively. The plasma half-life of ceftriaxone is not dependent on the dose and varies between 6 and 9 hours; it may be prolonged in neonates. The half-life does not change appreciably in patients with moderate renal impairment, but it may be prolonged in severe impairment especially when there is also hepatic impairment.

Ceftriaxone is widely distributed in body tissues and fluids. It crosses both inflamed and non-inflamed meninges, generally achieving therapeutic concentrations in the CSF. It crosses the placenta and low concentrations have been detected in breast milk. High concentrations are achieved in bile.

About 40 to 65% of a dose of ceftriaxone is excreted unchanged in the urine, principally by glomerular filtration; the remainder is excreted in the bile and is ultimately found in the faeces as unchanged drug and microbiologically inactive compounds.

◊ Reviews.

1. Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986; **11:** 76–86.
2. Yuk JH, *et al.* Clinical pharmacokinetics of ceftriaxone. *Clin Pharmacokinet* 1989; **17:** 223–35.
3. Perry TR, Schentag JJ. Clinical use of ceftriaxone: a pharmacokinetic-pharmacodynamic perspective on the impact of minimum inhibitory concentration and serum protein binding. *Clin Pharmacokinet* 2001; **40:** 685–94.

Hepatic impairment. References.

1. Stoeckel K, *et al.* Single-dose ceftriaxone kinetics in liver insufficiency. *Clin Pharmacol Ther* 1984; **36:** 500–9.
2. Hary L, *et al.* The pharmacokinetics of ceftriaxone and cefotaxime in cirrhotic patients with ascites. *Eur J Clin Pharmacol* 1989; **36:** 613–16.
3. Toth A, *et al.* Pharmacokinetics of ceftriaxone in liver-transplant recipients. *J Clin Pharmacol* 1991; **31:** 722–8.

Pregnancy. References.

1. Bourget P, *et al.* Pharmacokinetics and protein binding of ceftriaxone during pregnancy. *Antimicrob Agents Chemother* 1993; **37:** 54–9.

Renal impairment. The pharmacokinetics of ceftriaxone are not markedly altered in mild to moderate renal impairment,[1] but the half-life can be prolonged in severe or end-stage renal disease.[1-4] Ceftriaxone is generally not removed by peritoneal dialysis[4] or by haemodialysis[1-3] although a decrease in half-life has been reported during haemodialysis.[5] In many patients no alteration in dosage is necessary, but some individuals have reduced non-renal clearance despite apparently normal hepatic function.[2,3] It is advisable to monitor plasma ceftriaxone in