Chlortetracycline Hydrochloride *(BANM, rINNM)*

Chlorotetracykliny chlorowodorek; Chlortetraciklino hidrochloridas; Chlortétracycline, chlorhydrate de; Chlortetracyclini hydrochloridum; Chlortetracyklin-hydrochlorid; Hidrocloruro de clortetraciclina; Klooritetrasykliinihydrokloridi; Klórtetraciklin-hidroklorid; Klortetracyklinhydroklorid.

Хлортетрациклина Гидрохлорид

$C_{22}H_{23}ClN_2O_8,HCl = 515.3$.

CAS — 64-72-2.

ATC — A01AB21; D06AA02; J01AA03; S01AA02.

ATC Vet — QA01AB21; QD06AA02; QJ01AA03; QS01AA02.

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

Ph. Eur. 6.2 (Chlortetracycline Hydrochloride). The hydrochloride of a substance produced by the growth of certain strains of *Streptomyces aureofaciens* or by any other means. A yellow powder. Slightly soluble in water and in alcohol; it dissolves in solutions of alkali hydroxides and carbonates. A 1% solution in water has a pH of 2.3 to 3.3. Protect from light.

USP 31 (Chlortetracycline Hydrochloride). A yellow, odourless crystalline powder. Soluble 1 in 75 of water and 1 in 560 of alcohol; practically insoluble in acetone, in chloroform, in dioxan, and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a 1% solution in water is between 2.3 and 3.3. Store in airtight containers. Protect from light.

Profile

Chlortetracycline is a tetracycline derivative with general properties similar to those of tetracycline (p.347) and is used as the hydrochloride, more often topically than orally. It is used as a 1% ophthalmic ointment and as a 3% ointment for application to the skin. It is poorly absorbed from the gastrointestinal tract compared with other tetracyclines but is sometimes given orally with other tetracycline derivatives.

Preparations

BP 2008: Chlortetracycline Eye Ointment; Chlortetracycline Ointment; ***USP 31:*** Chlortetracycline Hydrochloride Ointment; Chlortetracycline Hydrochloride Ophthalmic Ointment.

Proprietary Preparations (details are given in Part 3)
Austria: Aureomycin; ***Belg.:*** Aureomycin; Aureomycine; ***Fr.:*** Aureomycine; ***Ger.:*** Aureomycin; ***Hong Kong:*** Aureomycin†; Chlortralim; ***Ital.:*** Aureomicina; ***Malaysia:*** Chlortralim; ***Norw.:*** Aureomycin†; ***Pol.:*** Chlorocyclinum; ***Port.:*** Aurecil†; Aureodermil†; ***Singapore:*** Chlortralim; ***Spain:*** Aureomicina; Dermosa Aureomicina; ***Thai.:*** Aureomycin; Chlortralim.

Multi-ingredient: ***Austria:*** Aureocort; ***Braz.:*** Corciclen; ***Ger.:*** Aureodelf†; Aureomycin N†; ***Ital.:*** Aureocort; Aureomix; ***S.Afr.:*** Tritet; ***UK:*** Aureocort; Deteclo†.

Ciclacillin *(BAN, rINN)*

Ciclacilina; Ciclacilline; Ciclacillinum; Ciklacillin; Cyclacillin *(USAN)*; Siklasilliini; Wy-4508. (6*R*)-6-(1-Aminocyclohexanecarboxamido)penicillanic acid.

Циклациллин

$C_{15}H_{23}N_3O_4S = 341.4$.

CAS — 3485-14-1.

Pharmacopoeias. In *Jpn.*

Profile

Ciclacillin is an aminopenicillin with properties similar to those of ampicillin (p.204), although it is generally less active *in vitro*.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Cilinase†.

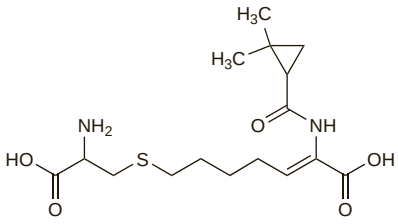
Cilastatin Sodium *(BANM, USAN, rINNM)*

Cilastatin sodná sůl; Cilastatina sódica; Cilastatine sodique; Cilastatinnatrium; Cilastatino natrio druska; Cilastatinum natricum; Cilasztatin-nátrium; L-642957; MK-791; Natrii Cilastatinas; Natrii Cilastatinum; Natriumsilastatinaatti; Natriumsilastatinat; Silastatininatrium; Silastatin Sodyum. (*Z*)-(*S*)-6-Carboxy-6-[(*S*)-2,2-dimethylcyclopropanecarboxamido]hex-5-enyl-L-cysteine, monosodium salt.

Натрий Циластатин

$C_{16}H_{25}N_2NaO_5S = 380.4$.

CAS — 82009-34-5 (cilastatin); 81129-83-1 (cilastatin sodium).



(cilastatin)

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

Ph. Eur. 6.2 (Cilastatin Sodium). A white or light yellow, hygroscopic, amorphous powder. Very soluble in water and in methyl alcohol; slightly soluble in dehydrated alcohol; practically insoluble in acetone and in dichloromethane; very slightly soluble in dimethyl sulfoxide. A 1% solution in water has a pH of 6.5 to 7.5. Store at a temperature not exceeding 8° in airtight containers.

USP 31 (Cilastatin Sodium). A white to tan-coloured powder. Soluble in water and in methyl alcohol. pH of a 1% solution in water is between 6.5 and 7.5. Store at a temperature less than 8°.

Profile

Cilastatin is an inhibitor of dehydropeptidase I, an enzyme found in the brush border of the renal tubules. It is given as the sodium salt with the antibacterial imipenem (p.286) to prevent its renal metabolism to microbiologically inactive and potentially nephrotoxic products. This increases the concentrations of imipenem achieved in the urine and protects against any nephrotoxic effects, which were seen with high doses of imipenem given experimentally to *animals*.

Cilastatin has no antibacterial activity itself, and does not affect the antibacterial activity of imipenem.

Preparations

USP 31: Imipenem and Cilastatin for Injectable Suspension; Imipenem and Cilastatin for Injection.

Proprietary Preparations (details are given in Part 3)
Pol.: Tienam.

Multi-ingredient: ***Arg.:*** Dixabiox; Imipecil; Imistatin; Klonam†; Zienam; ***Austral.:*** Primaxin; ***Austria:*** Zienam; ***Belg.:*** Tienam; ***Braz.:*** Penexil†; Tienam; ***Canad.:*** Primaxin; ***Chile:*** Inem; Tienam; ***Cz.:*** Tienam; ***Denm.:*** Tienam; ***Fin.:*** Tienam; ***Fr.:*** Tienam; ***Ger.:*** Zienam; ***Gr.:*** Primaxin; ***Hong Kong:*** Prepenem; Tienam; ***Hung.:*** Tienam; ***India:*** Cilanem; ***Indon.:*** Pelastin; Tienam; ***Israel:*** Tienam; ***Ital.:*** Imipem; Tenacid; Tienam; ***Malaysia:*** Bacqure; Tienam; ***Mex.:*** Arzomeba; Iminen; Tienam; ***Neth.:*** Tienam; ***Norw.:*** Tienam; ***NZ:*** Primaxin; ***Philipp.:*** Anipen; Tienam; ***Port.:*** Tienam; ***Rus.:*** Tienam (Тиенам); ***S.Afr.:*** Tienam; ***Singapore:*** Tienam; ***Spain:*** Tienam; ***Swed.:*** Tienam; ***Switz.:*** Tienam; ***Thai.:*** Tienam; ***Turk.:*** Tienam; ***UK:*** Primaxin; ***USA:*** Primaxin; ***Venez.:*** Zienam.

Cinoxacin *(BAN, USAN, rINN)*

64716; Azolinic Acid; Cinoxacine; Cinoxacino; Cinoxacinum; Compound 64716; Sinoksasiini. 1-Ethyl-1,4-dihydro-4-oxo-1,3-dioxolo[4,5-*g*]cinnoline-3-carboxylic acid.

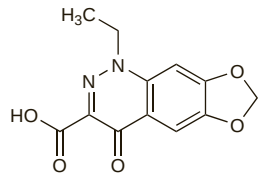
Циноксацин

$C_{12}H_{10}N_2O_5 = 262.2$.

CAS — 28657-80-9.

ATC — J01MB06.

ATC Vet — QJ01MB06.



Pharmacopoeias. In *US*.

USP 31 (Cinoxacin). A white to yellowish-white, odourless crystalline solid. Insoluble in water and in most common organic solvents; soluble in alkaline solution. Store in airtight containers.

Adverse Effects and Precautions

As for Nalidixic Acid, p.304.

Cinoxacin should be used in reduced dosage, or not at all, in patients with renal impairment.

◊ References.

1. Stricker BHC, *et al.* Anaphylactic reactions to cinoxacin. *BMJ* 1988; **297:** 1434–5.

Interactions

As for Nalidixic Acid, p.304.

Antimicrobial Action

As for Nalidixic Acid, p.304. Cross-resistance with nalidixic acid has been shown.

Pharmacokinetics

Cinoxacin is rapidly and almost completely absorbed after oral doses. Peak serum concentrations of about 15 micrograms/mL occur 2 to 3 hours after a 500-mg dose. The plasma half-life is about 1 to 2 hours. Cinoxacin is more than 60% bound to plasma proteins.

Cinoxacin appears to be metabolised in the liver and is excreted via the kidney. Over 95% of a dose appears in the urine within 24 hours, over half as unaltered drug and the remainder as inactive metabolites. Mean urinary concentrations of about 300 micrograms/mL have been achieved during the first 4 hours after a 500-mg oral dose. Urinary excretion is reduced by probenecid and in patients with renal impairment.

Uses and Administration

Cinoxacin is a 4-quinolone antibacterial with actions and uses similar to those of nalidixic acid (p.304). In the treatment of urinary-tract infections the usual oral dose is 500 mg twice daily; for prophylaxis 500 mg is given at bedtime.

For advice on use in renal impairment, see below.

Administration in renal impairment. Cinoxacin should be used in reduced dosage, or not used at all, in patients with renal impairment.

Preparations

USP 31: Cinoxacin Capsules.

Proprietary Preparations (details are given in Part 3)
Gr.: Cinobactin†; ***Ital.:*** Cinobac; Cinocil; Cinoxen; Nossacin; Noxigram†; Uroc; Uronorm†; Uroxacin†; ***Mex.:*** Gugecin†; ***USA:*** Cinobac†.

Ciprofloxacin *(BAN, USAN, rINN)*

Bay-q-3939; Ciprofloksacinas; Ciprofloxacine; Ciprofloxacino; Ciprofloxacinum; Siprofloksasiini; Siprofloksasin; Siprofloxacin. 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazin-1-ylquinoline-3-carboxylic acid.

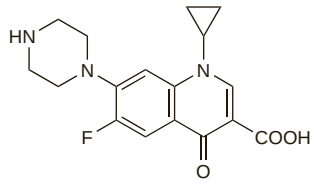
Ципрофлоксацин

$C_{17}H_{18}FN_3O_3 = 331.3$.

CAS — 85721-33-1.

ATC — J01MA02; S01AX13; S02AA15; S03AA07.

ATC Vet — QJ01MA02; QS01AX13; QS02AA15; QS03AA07.



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

Ph. Eur. 6.2 (Ciprofloxacin). An almost white or pale yellow, slightly hygroscopic, crystalline powder. Practically insoluble in water; very slightly soluble in dehydrated alcohol and in dichloromethane. Store in airtight containers. Protect from light.

USP 31 (Ciprofloxacin). Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Avoid temperatures above 40°. Protect from light.

Ciprofloxacin Hydrochloride *(BANM, USAN, rINNM)*

Bay-o-9867; Ciprofloksacino hidrochloridas; Ciprofloxacine, chlorhydrate de; Ciprofloxacin-hidroklorid; Ciprofloxacin-hydrochlorid; Ciprofloxacinhydroklorid; Ciprofloxacini hydrochloridum; Cyprofloksacyny chlorowodorek; Hidrocloruro de ciprofloxacino; Siprofloksasiinihydrokloridi; Siprofloksasin Hidroklorür. Ciprofloxacin hydrochloride monohydrate.

Ципрофлоксацина Гидрохлорид

$C_{17}H_{18}FN_3O_3,HCl,H_2O = 385.8$.

CAS — 86483-48-9 (anhydrous ciprofloxacin hydrochloride); 86393-32-0 (ciprofloxacin hydrochloride monohydrate).

ATC — S02AA15.

ATC Vet — QS02AA15.

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

Ph. Eur. 6.2 (Ciprofloxacin Hydrochloride). A pale yellow, slightly hygroscopic, crystalline powder. Soluble in water; very slightly soluble in dehydrated alcohol; practically insoluble in acetone, in dichloromethane, and in ethyl acetate; slightly soluble in methyl alcohol. A 2.5% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Ciprofloxacin Hydrochloride). Faintly yellowish to light yellow crystals. Sparingly soluble in water; very slightly soluble in dehydrated alcohol; slightly soluble in acetic acid and in methyl alcohol; practically insoluble in acetone, in acetonitrile, in dichloromethane, in ethyl acetate, and in hexane. pH of a 2.5% solution in water is between 3.0 and 4.5. Store in airtight containers at a temperature of 25°, excursions permitted between 15° and 30°. Protect from light.

Ciprofloxacin Lactate *(BANM, rINNM)*

Ciprofloxacine, Lactate de; Ciprofloxacini Lactas; Lactato de ciprofloxacino.

Ципрофлоксацина Лактат

$C_{17}H_{18}FN_3O_3,C_3H_6O_3 = 421.4$.

CAS — 97867-33-9.

ATC — S02AA15.

ATC Vet — QS02AA15.

Incompatibility. Ciprofloxacin infusion is stated in UK licensed product information to have a pH of 3.9 to 4.5 and to be incompatible with injections chemically or physically unstable at this pH range. Incompatibility has been reported between ciprofloxacin and other drugs including some antibacterials.[1-5]

1. Lyall D, Blythe J. Ciprofloxacin lactate infusion. *Pharm J* 1987; **238:** 290.

2. Janknegt R, *et al.* Quinolones and penicillins incompatibility. *DICP Ann Pharmacother* 1989; **23:** 91–2.
3. Goodwin SD, *et al.* Compatibility of ciprofloxacin injection with selected drugs and solutions. *Am J Hosp Pharm* 1991; **48:** 2166–71.
4. Jim LK. Physical and chemical compatibility of intravenous ciprofloxacin with other drugs. *Ann Pharmacother* 1993; **27:** 704–7.
5. Elmore RL, *et al.* Stability and compatibility of admixtures of intravenous ciprofloxacin and selected drugs. *Clin Ther* 1996; **18:** 246–55.

Stability. For mention of loss of activity in ciprofloxacin solutions exposed to ultraviolet light see under Precautions, below.

Adverse Effects

Ciprofloxacin is generally well tolerated. The range of adverse effects associated with ciprofloxacin and the other fluoroquinolones is broadly similar to that of earlier quinolones such as nalidixic acid (p.304). They most often involve the gastrointestinal tract, CNS, or skin.

Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia and are the most frequent adverse effects. Pseudomembranous colitis, pancreatitis, and dysphagia have been reported rarely.

Headache, dizziness, confusion, insomnia, and restlessness are among the commonest effects on the CNS. Others include tremor, drowsiness, nightmares, visual and other sensory disturbances, hallucinations, psychotic reactions, depression, convulsions, and intracranial hypertension. Paraesthesia and peripheral neuropathy have also been reported.

In addition to rash and pruritus, hypersensitivity-type reactions affecting the skin have included, rarely, vasculitis, erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Photosensitivity has occurred, although it may be more frequent with some other fluoroquinolones such as lomefloxacin and sparfloxacin. Anaphylaxis has been associated with ciprofloxacin and some other quinolones. As with other quinolones, reversible arthralgia or myalgia has sometimes occurred and joint erosions have been documented in immature *animals*. Tendon damage has also been reported.

Other adverse effects reported with ciprofloxacin include crystalluria, transient increases in serum creatinine or blood urea nitrogen and, rarely, acute renal failure secondary to interstitial nephritis. Elevated liver enzyme values, jaundice, and hepatitis have occurred, as have haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and, very rarely, pancytopenia, haemolytic anaemia or agranulocytosis. Cardiovascular adverse effects include tachycardia, hypotension, oedema, syncope, hot flushes, and sweating. Some fluoroquinolones may rarely cause prolongation of the QT interval and ventricular arrhythmias, including torsade de pointes (see below).

As with other antibacterials, superinfection with organisms not very susceptible to ciprofloxacin is possible. Such organisms include *Candida*, *Clostridium difficile*, and *Streptococcus pneumoniae*. There is some evidence that fluoroquinolone use may be associated with an increased risk of colonisation by MRSA.

Pain and irritation may occur at the site of infusion accompanied rarely by phlebitis or thrombophlebitis.

Adverse effects reported after ocular use of ciprofloxacin include local burning or discomfort, keratopathy, corneal staining, corneal precipitates or infiltrates, and photophobia.

Local discomfort, pain, or pruritus have occurred after use of ear drops containing ciprofloxacin.

◊ General reviews of the adverse effects of fluoroquinolones[1-7] and ciprofloxacin specifically.[8,9]

1. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin Infect Dis* 1999; **28:** 352–64.
2. Ball P, *et al.* Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* 1999; **21:** 407–21.
3. Rubinstein E. History of quinolones and their side effects. *Chemotherapy* 2001; **47** (suppl 3): 3–8.
4. Leone R, *et al.* Adverse drug reactions related to the use of fluoroquinolone antimicrobials: an analysis of spontaneous reports and fluoroquinolone consumption data from three Italian regions. *Drug Safety* 2003; **26:** 109–20.
5. Stahlmann R, Lode H. Fluoroquinolones in the elderly: safety considerations. *Drugs Aging* 2003; **20:** 289–302.
6. Owens RC, Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S144–S157.
7. Mehlhorn AJ, Brown DA. Safety concerns with fluoroquinolones. *Ann Pharmacother* 2007; **41:** 1859–66.
8. Segev S, *et al.* Safety of long-term therapy with ciprofloxacin: data analysis of controlled clinical trials and review. *Clin Infect Dis* 1999; **28:** 299–308.
9. Heyd A, Haverstock D. Retrospective analysis of the safety profile of oral and intravenous ciprofloxacin in a geriatric population. *Clin Ther* 2000; **22:** 1239–50.

Effects on the blood. Haematological disturbances including thrombocytopenia,[1] eosinophilia,[2] leucopenia, and, very rarely, pancytopenia,[3] haemolytic anaemia,[4] or agranulocytosis have been reported with ciprofloxacin and some other fluoroquinolones. There has also been a case report[5] of haemolytic-uraemic syndrome associated with ciprofloxacin therapy; the patient recovered with routine supportive treatment (haemodialysis and plasma exchange) after the drug was stopped. In addition, transient reductions in factor VIII and von Willebrand's factor leading to bleeding in 2 patients receiving ciprofloxacin has been reported.[6] Neutropenia that developed in an elderly patient a few days after starting treatment with intravenous moxifloxacin resolved on stopping the drug.[7]

1. Starr JA, Ragucci KR. Thrombocytopenia associated with intravenous ciprofloxacin. *Pharmacotherapy* 2005; **25:** 1030–4.
2. Mofredj A, *et al.* Norfloxacin-induced eosinophilia in a cirrhotic patient. *Ann Pharmacother* 2002; **36:** 1107–8.
3. Deng JY, Tovar JM. Pancytopenia with levofloxacin therapy for pelvic inflammatory disease in an otherwise healthy young patient. *Ann Pharmacother* 2006; **40:** 1692–3.
4. Oh YR, *et al.* Levofloxacin-induced autoimmune hemolytic anemia. *Ann Pharmacother* 2003; **37:** 1010–13.
5. Allan DS, *et al.* Ciprofloxacin-associated hemolytic-uremic syndrome. *Ann Pharmacother* 2002; **36:** 1000–1002.
6. Castaman G, Rodeghiero F. Acquired transitory von Willebrand syndrome with ciprofloxacin. *Lancet* 1994; **343:** 492.
7. Chang C-M, *et al.* Moxifloxacin-associated neutropenia in a cirrhotic elderly woman with lower extremity cellulitis. *Ann Pharmacother* 2008; **42:** 580–3.

Effects on the cardiovascular system. Prolongation of the QT interval,[1,2] sometimes progressing to torsade de pointes,[3-8] has been associated with ciprofloxacin and other fluoroquinolones although a review[9] considered that ciprofloxacin was least likely to produce this effect. Licensed product information recommends that gatifloxacin, gemifloxacin, levofloxacin, lomefloxacin, moxifloxacin, ofloxacin, and sparfloxacin should be avoided in patients with predisposing factors or who are also receiving other drugs that are known to cause this effect and that norfloxacin should be used with caution in such situations.

1. Noel GJ, *et al.* Effects of three fluoroquinolones on QT interval in healthy adults after single doses. *Clin Pharmacol Ther* 2003; **73:** 292–303.
2. Nykamp DL, *et al.* QTc prolongation associated with combination therapy of levofloxacin, imipramine, and fluoxetine. *Ann Pharmacother* 2005; **39:** 543–6.
3. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy* 2001; **21:** 1468–72.
4. Owens RC, Ambrose PG. Torsades de pointes associated with fluoroquinolones. *Pharmacotherapy* 2002; **22:** 663–8.
5. Bertino JS, *et al.* Gatifloxacin-associated corrected QT interval prolongation, torsades de pointes, and ventricular fibrillation in patients with known risk factors. *Clin Infect Dis* 2002; **34:** 861–3.
6. Amankwa K, *et al.* Torsades de pointes associated with fluoroquinolones: importance of concomitant risk factors. *Clin Pharmacol Ther* 2004; **75:** 242–7.
7. Dale KM, *et al.* Moxifloxacin and torsade de pointes. *Ann Pharmacother* 2007; **41:** 336–40.
8. Knorr JP, *et al.* Ciprofloxacin-induced Q-T interval prolongation. *Am J Health-Syst Pharm* 2008; **65:** 547–51.
9. Owens RC. QT prolongation with antimicrobial agents: understanding the significance. *Drugs* 2004; **64:** 1091–1124.

Effects on the gastrointestinal tract. There have been case reports and studies of pseudomembranous colitis or superinfection with *Clostridium difficile* in patients given ciprofloxacin[1-6] and other fluoroquinolones[7-10] although some commentators have questioned this association and pointed out that other circumstances, such as poor infection control, may be significant contributory factors.

1. Cain DB, O'Connor ME. Pseudomembranous colitis associated with ciprofloxacin. *Lancet* 1990; **336:** 946.
2. Bates CJ, *et al.* Ciprofloxacin and Clostridium difficile infection. *Lancet* 1990; **336:** 1193.
3. Low N, Harries A. Ciprofloxacin and pseudomembranous colitis. *Lancet* 1990; **336:** 1510.
4. Hillman RJ, *et al.* Ciprofloxacin as a cause of Clostridium difficile-associated diarrhoea in an HIV antibody-positive patient. *J Infect* 1990; **21:** 205–7.
5. McFarland LV, *et al.* Ciprofloxacin-associated Clostridium difficile disease. *Lancet* 1995; **346:** 977–8.
6. Angel CA, *et al.* Severe ciprofloxacin-associated pseudomembranous colitis in an eight-year-old child. *J Pediatr Surg* 2004; **39:** 1590–2.
7. Dan M, Samra Z. Clostridium difficile colitis associated with ofloxacin therapy. *Am J Med* 1989; **87:** 479.
8. Ortiz-de-Saracho J, *et al.* Moxifloxacin-induced Clostridium difficile diarrhea. *Ann Pharmacother* 2003; **37:** 452–3.
9. Gaynes R, *et al.* Outbreak of Clostridium difficile infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis* 2004; **38:** 640–5.
10. Pépin J, *et al.* Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis* 2005; **41:** 1254–60.

Effects on glucose metabolism. For the effects of fluoroquinolones, and in particular gatifloxacin, on blood glucose see under Gatifloxacin, p.281.

Effects on the kidneys. A review[1] of case reports of renal toxicity (including interstitial nephritis, acute renal failure, acute tubular necrosis, and crystalluria) associated with ciprofloxacin and other fluoroquinolones indicated that such toxicity, although potentially serious, was rare. It was also noted that nearly all patients developing acute renal failure were over 50 years of age. Another review,[2] confirming that the problem remained rare, noted that risk factors for quinolone-induced nephrotoxicity seemed to include the particular quinolone chosen, with ciprofloxacin the most often involved, as well as the use of high doses, patient age, inadequate hydration, and use of other nephrotoxic drugs or the presence of other processes likely to contribute to renal damage such as diabetes.

1. Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Safety* 2000; **22:** 479–85.
2. Montagnac R, *et al.* Les insuffisances rénales aiguës aux quinolones: revue générale à propos d'une observation avec cristallisation liée à la ciprofloxacine. *Nephrol Ther* 2005; **1:** 44–51.

Effects on the liver. Fluoroquinolones, including ciprofloxacin, may cause elevated liver enzyme values. In most patients this effect is transient and reversible without stopping the drug.

More serious cases of hepatotoxicity, including fatalities, have been reported both with ciprofloxacin[1-5] and with other fluoroquinolones[4,6-14] but they are rare. In many cases the patients were elderly and had co-morbid conditions.

1. Grassmick BK, *et al.* Fulminant hepatic failure possibly related to ciprofloxacin. *Ann Pharmacother* 1992; **26:** 636–9.
2. Sherman O, Beizer JL. Possible ciprofloxacin-induced acute cholestatic jaundice. *Ann Pharmacother* 1994; **28:** 1162–4.
3. Villeneuve J-P, *et al.* Suspected ciprofloxacin-induced hepatotoxicity. *Ann Pharmacother* 1995; **29:** 257–9.
4. Jones SE, Smith RH. Quinolones may induce hepatitis. *BMJ* 1997; **314:** 869.
5. Contreras MA, *et al.* Severe ciprofloxacin-induced acute hepatitis. *Eur J Clin Microbiol Infect Dis* 2001; **20:** 434–5.
6. González Carro P, *et al.* Fatal subfulminant hepatic failure with ofloxacin. *Am J Gastroenterol* 2000; **95:** 1606.
7. Björnsson E, *et al.* Norfloxacin-induced eosinophilic necrotizing granulomatous hepatitis. *Am J Gastroenterol* 2000; **95:** 3662–4.
8. Spahr L, *et al.* Acute fatal hepatitis related to levofloxacin. *J Hepatol* 2001; **35:** 308–9.
9. Karim A, *et al.* Possible levofloxacin-induced acute hepatocellular injury in a patient with chronic obstructive lung disease. *Clin Infect Dis* 2001; **33:** 2088–90.
10. Soto S, *et al.* Moxifloxacin-induced acute liver injury. *Am J Gastroenterol* 2002; **97:** 1853–4.
11. Coleman CI, *et al.* Possible gatifloxacin-induced fulminant hepatic failure. *Ann Pharmacother* 2002; **36:** 1162–7.
12. Schwalm J-D, Lee CH. Acute hepatitis associated with oral levofloxacin therapy in a hemodialysis patient. *CMAJ* 2003; **168:** 847–8.
13. Cheung O, *et al.* Gatifloxacin-induced hepatotoxicity and acute pancreatitis. *Ann Intern Med* 2004; **140:** 73–4.
14. Çoban Ş, *et al.* Levofloxacin-induced acute fulminant hepatic failure in a patient with chronic hepatitis B infection. *Ann Pharmacother* 2005; **39:** 1737–40.

Effects on the musculoskeletal system. Reversible arthralgia has sometimes occurred with the fluoroquinolones;[1] joint erosions have been documented in immature *animals*. In a report,[2] treatment with pefloxacin may have contributed to the destructive arthropathy that occurred in a 17-year-old youth. For a discussion of the use of fluoroquinolones in children and adolescents, see Administration in Children, under Precautions, below.

There have been reports[3-7] of tendinitis and tendon rupture associated with fluoroquinolones. By July 1995, the UK CSM[5] had received 21 reports of tendon damage, often of the Achilles tendon, associated with these antibacterials—11 with ciprofloxacin and 10 with ofloxacin. In a later case-control study[8] of a cohort of 46 776 users of fluoroquinolones between July 1992 to June 1998, 704 had Achilles tendinitis and 38 had Achilles tendon rupture; the adjusted relative risk of Achilles tendon disorders with current use was 1.9. The risk of tendon damage is increased by use with corticosteroids and is more common with increasing age:[5] the case-control study[8] found that the relative risk for current users rose to 3.2 among those aged 60 and over, and to 6.2 in those in this age group also using corticosteroids. Another case-control study[9] using data from 1988 to 1998 held on a different UK general practice database reported similar findings and concluded that ofloxacin was associated with a higher risk of tendon damage than other fluoroquinolones. A review[10] of the literature between 1966 and 2001 revealed 98 case reports of fluoroquinolone-associated tendon damage. Of these, 36 were associated with pefloxacin therapy and 25 with ciprofloxacin; ofloxacin was associated with 6 cases. Renal disease or impairment was also considered as a risk factor.

Onset may be rapid: rupture has occurred within 48 hours of starting therapy.[11] The CSM[5] warned that at the first sign of pain or inflammation the fluoroquinolone should be withdrawn and the affected limb rested until the tendon symptoms had resolved.

Similar warnings have been issued in other countries, but some cases have continued to be reported.[12] In the USA the FDA has required a warning to be added to prescribing information for the fluoroquinolones stating that there is an increased risk in patients over 60, in kidney, heart, and lung transplant recipients, and with use of concomitant corticosteroid therapy.[13]

There have been reports[14,15] of rhabdomyolysis in patients given fluoroquinolones, including one fatality associated with levofloxacin therapy.[14]

1. Alfaham M, *et al.* Arthropathy in a patient with cystic fibrosis taking ciprofloxacin. *BMJ* 1987; **295:** 699.
2. Chevalier X, *et al.* A case of destructive polyarthropathy in a 17-year-old youth following pefloxacin treatment. *Drug Safety* 1992; **7:** 310–14.
3. Huston KA. Achilles tendinitis and tendon rupture due to fluoroquinolone antibiotics. *N Engl J Med* 1994; **331:** 748.
4. Szarfman A, *et al.* More on fluoroquinolone antibiotics and tendon rupture. *N Engl J Med* 1995; **332:** 193.
5. Committee on Safety of Medicines/Medicines Control Agency. Tendon damage associated with quinolone antibiotics. *Current Problems* 1995; **21:** 8. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015619&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
6. Carrasco JM, *et al.* Tendinitis associated with ciprofloxacin. *Ann Pharmacother* 1997; **31:** 120.
7. Mathis AS, *et al.* Levofloxacin-associated Achilles tendon rupture. *Ann Pharmacother* 2003; **37:** 1014–17.
8. van der Linden PD, *et al.* Fluoroquinolones and risk of Achilles tendon disorders: case-control study. *BMJ* 2002; **324:** 1306–7.
9. van der Linden PD, *et al.* Increased risk of Achilles tendon rupture with quinolone antibacterial use, especially in elderly patients taking oral corticosteroids. *Arch Intern Med* 2003; **163:** 1801–7.
10. Khaliq Y, Zhanel GG. Fluoroquinolone-associated tendinopathy: a critical review of the literature. *Clin Infect Dis* 2003; **36:** 1404–10.
11. Committee on Safety of Medicines/Medicines Control Agency. Reminder: fluoroquinolone antibiotics and tendon disorders. *Current Problems* 2002; **28:** 3–4. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007454&RevisionSelectionMethod=LatestReleased (accessed 12/07/06)
12. Adverse Drug Reactions Advisory Committee (ADRAC). Fluoroquinolone antibiotics: remember tendon disorders. *Aust Adverse Drug React Bull* 2006; **25:** 3. Also available at: http://www.tga.health.gov.au/adr/aadrb/aadr0602.pdf (accessed 12/07/06)
13. FDA. Fluoroquinolone Antimicrobial Drugs [ciprofloxacin (marketed as Cipro and generic ciprofloxacin), ciprofloxacin extended release (marketed as Cipro XR and Proquin XR), gemifloxacin (marketed as Factive), levofloxacin (marketed as Levaquin), moxifloxacin (marketed as Avelox), norfloxacin (marketed as Noroxin), and ofloxacin (marketed as Floxin and generic ofloxacin)] (issued 8th July, 2008). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/fluoroquinolonesHCP.htm (accessed 12/08/08)
14. Petitjeans F, *et al.* A case of rhabdomyolysis with fatal outcome after a treatment with levofloxacin. *Eur J Clin Pharmacol* 2003; **59:** 779–80.
15. Hsiao S-H, *et al.* Acute rhabdomyolysis associated with ofloxacin/levofloxacin therapy. *Ann Pharmacother* 2005; **39:** 146–9.

Effects on the nervous system. By 1991 the UK CSM[1] had received 26 reports of convulsions associated with ciprofloxacin, 1 with norfloxacin, and 1 with ofloxacin. It was noted that convulsions could occur both in patients with epilepsy and in those with no history of convulsions. Generalised seizures have been reported in patients given gatifloxacin[2] and levofloxacin.[3,4] Seizures have also been associated with the use of ear drops containing ciprofloxacin.[5] All 5 case reports[2-5] involved patients aged 65 years and over; of these, 1 had a history (although unclear) of seizures,[2] 3 had chronic renal impairment,[3-5] and 1 had neither.[3]

Other reports of CNS toxicity associated with ciprofloxacin have included eosinophilic meningitis,[6] delirium,[7] and acute psychoses.[8,9] Peripheral neuropathy,[10] dysaesthesia,[11] catatonia,[12] hemiparesis,[13] and tinnitus[14] have also been reported. Acute psychosis occurred[15] in a patient using ciprofloxacin eye drops. A review[16] of published and spontaneous reports found an association between adverse manic reactions and the use of certain antibacterials including ciprofloxacin and ofloxacin.

There have also been reports of sleep disturbances[17] and of a Tourette-like syndrome[18] associated with ofloxacin. Ataxia[19] and hallucinations[20] have been reported with the use of gatifloxacin.

1. Committee on Safety of Medicines. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
2. Quigley CA, Lederman JR. Possible gatifloxacin-induced seizure. *Ann Pharmacother* 2004; **38:** 235–7.
3. Kushner JM, *et al.* Seizures associated with fluoroquinolones. *Ann Pharmacother* 2001; **35:** 1194–8.
4. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
5. Orr CF, Rowe DB. Eardrop attacks: seizures triggered by ciprofloxacin eardrops. *Med J Aust* 2003; **178:** 343.
6. Asperilla MO, *et al.* Eosinophilic meningitis associated with ciprofloxacin. *Am J Med* 1989; **87:** 589–90.
7. Jay GT, Fitzgerald JM. Ciprofloxacin-induced delirium. *Ann Pharmacother* 1997; **31:** 252.
8. McCue JD, Zandt JR. Acute psychoses associated with the use of ciprofloxacin and trimethoprim-sulfamethoxazole. *Am J Med* 1991; **90:** 528–9.
9. Reeves RR. Ciprofloxacin-induced psychosis. *Ann Pharmacother* 1992; **26:** 930–1.
10. Aoun M, *et al.* Peripheral neuropathy associated with fluoroquinolones. *Lancet* 1992; **340:** 127.
11. Zehnder D, *et al.* Painful dysaesthesia with ciprofloxacin. *BMJ* 1995; **311:** 1204.
12. Akhtar S, Ahmad H. Ciprofloxacin-induced catatonia. *J Clin Psychiatry* 1993; **54:** 115–16.
13. Rosolen A, *et al.* Acute hemiparesis associated with ciprofloxacin. *BMJ* 1994; **309:** 1411.
14. Paul J, Brown NM. Tinnitus and ciprofloxacin. *BMJ* 1995; **311:** 232.
15. Tripathi A, *et al.* Acute psychosis following the use of topical ciprofloxacin. *Arch Ophthalmol* 2002; **120:** 665–6.
16. Abouesh A, *et al.* Antimicrobial-induced mania (antibiomania): a review of spontaneous reports. *J Clin Psychopharmacol* 2002; **22:** 71–81.
17. Upton C. Sleep disturbance in children treated with ofloxacin. *BMJ* 1994; **309:** 1411.
18. Thomas RJ, Reagan DR. Association of a Tourette-like syndrome with ofloxacin. *Ann Pharmacother* 1996; **30:** 138–41.
19. Mohan N, *et al.* Oral gatifloxacin-induced ataxia. *Am J Health-Syst Pharm* 2002; **59:** 1894.
20. Adams M, Tavakoli H. Gatifloxacin-induced hallucinations in a 19-year-old man. *Psychosomatics* 2006; **47:** 360.

Hypersensitivity. Hypersensitivity and skin reactions have been associated with ciprofloxacin and other fluoroquinolones. Reports have included anaphylaxis (which has sometimes been fatal, and may occur after the first dose),[1-7] serum sickness,[8] Stevens-Johnson syndrome,[9] toxic epidermal necrolysis (sometimes fatal),[10-17] laryngeal oedema,[18] and vasculitis.[19-21] Fatal vasculitis has been reported with ofloxacin.[22]

1. Davis H, *et al.* Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989; **111:** 1041–3.
2. Peters B, Pinching AJ. Fatal anaphylaxis associated with ciprofloxacin in a patient with AIDS related complex. *BMJ* 1989; **298:** 605.
3. Wurtz RM, *et al.* Anaphylactoid drug reactions to ciprofloxacin and rifampicin in HIV-infected patients. *Lancet* 1989; **i:** 955–6.
4. Assouad M, *et al.* Anaphylactoid reactions to ciprofloxacin. *Ann Intern Med* 1995; **122:** 396–7.
5. Smythe MA, Cappelletty DM. Anaphylactoid reaction to levofloxacin. *Pharmacotherapy* 2000; **20:** 1520–3.
6. Ho DY, *et al.* Anaphylactoid reaction to ciprofloxacin. *Ann Pharmacother* 2003; **37:** 1018–23.
7. Sachs B, *et al.* Fluoroquinolone-associated anaphylaxis in spontaneous adverse drug reaction reports in Germany: differences in reporting rates between individual fluoroquinolones and occurrence after first-ever use. *Drug Safety* 2006; **29:** 1087–1100.
8. Slama TG. Serum sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother* 1990; **34:** 904–5.
9. Hällgren J, *et al.* Stevens-Johnson syndrome associated with ciprofloxacin: a review of adverse cutaneous events reported in Sweden as associated with this drug. *J Am Acad Dermatol* 2003; **49** (suppl): S267–S269.
10. Tham TCK, *et al.* Possible association between toxic epidermal necrolysis and ciprofloxacin. *Lancet* 1991; **338:** 522.
11. Moshfeghi M, Mandler HD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1993; **27:** 1467–9.
12. Yerasi AB, Oertel MD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 1996; **30:** 297.
13. Livasy CA, Kaplan AM. Ciprofloxacin-induced toxic epidermal necrolysis: a case report. *Dermatology* 1997; **195:** 173–5.
14. Melde SL. Ofloxacin: a probable cause of toxic epidermal necrolysis. *Ann Pharmacother* 2001; **35:** 1388–90.
15. Sahin MT, *et al.* Norfloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 768–70.
16. Christie MJ, *et al.* Generalized seizure and toxic epidermal necrolysis following levofloxacin exposure. *Ann Pharmacother* 2005; **39:** 953–5.
17. Islam AFMS, Rahman MS. Levofloxacin-induced fatal toxic epidermal necrolysis. *Ann Pharmacother* 2005; **39:** 1136–7.
18. Baciewicz AM, *et al.* Laryngeal edema related to ciprofloxacin therapy. *Ann Pharmacother* 1992; **26:** 1456.
19. Choe U, *et al.* Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; **320:** 257–8.
20. Stubbings J, *et al.* Cutaneous vasculitis due to ciprofloxacin. *BMJ* 1992; **305:** 29.
21. Drago F, *et al.* Henoch-Schönlein purpura induced by fluoroquinolones. *Br J Dermatol* 1994; **131:** 448.
22. Pace JL, Gatt P. Fatal vasculitis associated with ofloxacin. *BMJ* 1989; **299:** 658.

Superinfection. Superinfection with *Streptococcus pneumoniae* has been reported in patients receiving ciprofloxacin.[1-3] For references to superinfection with *Clostridium difficile* and associated pseudomembranous colitis, see under Effects on the Gastrointestinal Tract, above.

Fungal otitis externa is also associated with the use of ear drops containing fluoroquinolones.[4]

1. Righter J. Pneumococcal meningitis during intravenous ciprofloxacin therapy. *Am J Med* 1990; **88:** 548.
2. Gordon JJ, Kauffman CA. Superinfection with Streptococcus pneumoniae during therapy with ciprofloxacin. *Am J Med* 1990; **89:** 383–4.
3. Lee BL, *et al.* Infectious complications with respiratory pathogens despite ciprofloxacin therapy. *N Engl J Med* 1991; **325:** 520–1.
4. Schrader N, Isaacson G. Fungal otitis externa: its association with fluoroquinolone eardrops. *Pediatrics* 2003; **111:** 1123.

Precautions

Ciprofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders. Care is also necessary in those with renal impairment, G6PD deficiency, or myasthenia gravis. An adequate fluid intake should be maintained during treatment with ciprofloxacin and excessive alkalinity of the urine avoided because of the risk of crystalluria.

Since ciprofloxacin and related fluoroquinolones have, like nalidixic acid, been shown to cause degenerative changes in weight-bearing joints of young *animals*, it has been suggested that these drugs should not generally be used in patients aged under 18 years (see also below), pregnant women, or breast-feeding mothers (but see also below) unless the benefits outweigh the risks. Tendon damage may occur rarely with fluoroquinolones (see Effects on the Musculoskeletal System, above) and treatment should be stopped if patients experience tendon pain, inflammation, or rupture; subsequent use of fluoroquinolones is contra-indicated in these patients.

Exposure to strong sunlight or sunlamps should be avoided during treatment with ciprofloxacin. The ability to drive or operate machinery may be impaired, especially when alcohol is also taken.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, above) and should be avoided or used with caution in patients with QT prolongation or relevant risk factors such as uncorrected electrolyte disturbances, bradycardia, or pre-existing cardiac disease. Certain drugs may also increase the risk (see Interactions, below).

Ciprofloxacin and other fluoroquinolones should be avoided in MRSA infections because of the high level of resistance.

Administration in children. Since ciprofloxacin and other fluoroquinolones can cause degenerative changes in weight-bearing joints of young *animals* they should only be used in children and adolescents where their use may be justified if the benefits outweigh the risks.[1-3] For example, ciprofloxacin is licensed in some countries for use in the prophylaxis and treatment of inhalational anthrax and also in the treatment of certain infections in those under 18 years of age (see under Uses and Administration, below).

A comparative cohort study[2] involving about 500 children and adolescents found that the incidence of musculoskeletal adverse effects was higher (10 cases out of 264 patients) in those taking fluoroquinolones (ciprofloxacin, ofloxacin, or pefloxacin) than in those taking other antibacterials (1 out of 237). In the former group of patients, these adverse effects, mainly arthralgias, were reversible and were most frequent with pefloxacin therapy.

1. Burstein GR, *et al.* Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002; **35** (suppl 2): S191–S199.
2. Chalumeau M, *et al.* Fluoroquinolone safety in pediatric patients: a prospective, multicenter, comparative cohort study in France. Abstract: *Pediatrics* 2003; **111:** 1427–8. Full version: http://pediatrics.aappublications.org/cgi/reprint/111/6/e714 (accessed 01/11/06)
3. American Academy of Pediatrics Committee on Infectious Diseases. The use of systemic fluoroquinolones. *Pediatrics* 2006; **118:** 1287–92.

Breast feeding. Ciprofloxacin was found to be undetectable in the serum of a breast-fed infant whose mother took ciprofloxacin 500 mg daily for 10 days.[1] In another study[2] involving 30 women who underwent termination of pregnancy, 10 each were given ciprofloxacin, ofloxacin, or pefloxacin respectively, and all 3 drugs were found to be highly concentrated in breast milk with ratios exceeding 75% of the simultaneous serum concentrations 2 hours after a dose. It was concluded that, because fluoroquinolones had been shown to cause arthropathy in young *animals*, their potential benefits should be weighed against the risk to the infant before they were considered for use in breast-feeding women. The American Academy of Pediatrics[3] considers that the use of ciprofloxacin is usually compatible with breast feeding.

1. Gardner DK, *et al.* Simultaneous concentrations of ciprofloxacin in breast milk and in serum in mother and breast-fed infant. *Clin Pharm* 1992; **11:** 352–4.
2. Giamarellou H, *et al.* Pharmacokinetics of three newer quinolones in pregnant and lactating women. *Am J Med* 1989; **87** (suppl 5A): 49S–51S.
3. 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)

Exposure to UV light. Loss of antibacterial activity has been reported after irradiation of ciprofloxacin solutions by UV light.[1] In addition to the possible hazard of photosensitivity reactions, a reduction in both cutaneous and circulating levels of ciprofloxacin was predicted in patients exposed to sunlight through window glass or the longer wavelength UVA radiation from sunbeds.[1]

1. Phillips G, *et al.* The loss of antibiotic activity of ciprofloxacin by photodegradation. *J Antimicrob Chemother* 1990; **26:** 783–9.

Interference with diagnostic tests. Ciprofloxacin did not interfere with determination of urinary-glucose concentrations carried out with *Clinitest*, *Diastix*, or *Tes-Tape*,[1] but pseudoglycosuria, a false-positive reaction for glucose in urine, has been

reported with *BM-Test-7* in elderly patients given ciprofloxacin for urinary-tract infections.[2]

1. Tartaglione TA, Flint NB. Effect of imipenem-cilastatin and ciprofloxacin on tests for glycosuria. *Am J Hosp Pharm* 1985; **42:** 602–5.
2. Drysdale L, *et al.* Pseudoglycosuria and ciprofloxacin. *Lancet* 1988; **ii:** 961.

Myasthenia gravis. Caution is advised in patients with myasthenia gravis given fluoroquinolones after reports of the possible exacerbation of symptoms in a patient,[1] and unmasking of subclinical myasthenia gravis in another,[2] by ciprofloxacin. Exacerbation of myasthenia gravis has also been reported with other fluoroquinolones including norfloxacin,[3] ofloxacin,[4] and pefloxacin.[5]

1. Moore B, *et al.* Possible exacerbation of myasthenia gravis by ciprofloxacin. *Lancet* 1988; **i:** 882.
2. Mumford CJ, Ginsberg L. Ciprofloxacin and myasthenia gravis. *BMJ* 1990; **301:** 818.
3. Rauser EH, *et al.* Exacerbation of myasthenia gravis by norfloxacin. *DICP Ann Pharmacother* 1990; **24:** 207–8.
4. Azevedo E, *et al.* Probable exacerbation of myasthenia gravis by ofloxacin. *J Neurol* 1993; **240:** 508.
5. Vial T, *et al.* Aggravation d'une myasthénie sous péfloxacine. *Rev Neurol (Paris)* 1995; **151:** 286–7.

Interactions

Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as theophylline and tizanidine, that are metabolised by this isoenzyme. Use of ciprofloxacin with tizanidine is contra-indicated, although theophylline may be used providing its dose is reduced and concentrations monitored.

Ciprofloxacin is reported to enhance the effect of oral anticoagulants such as warfarin and the oral antidiabetic glibenclamide. Severe hypoglycaemia, sometimes fatal, has occurred in patients also taking glibenclamide. Renal tubular secretion of methotrexate may be inhibited by ciprofloxacin, potentially increasing its toxicity.

The excretion of ciprofloxacin or related drugs is reduced and plasma concentrations may be increased by probenecid. Cations such as aluminium, calcium, magnesium, or iron reduce the absorption of oral ciprofloxacin or related drugs when given together. Changes in the pharmacokinetics of fluoroquinolones have been reported when given with histamine H_2 antagonists, possibly due to changes in gastric pH, but do not seem to be of much clinical significance.

Transient increases in serum creatinine have occurred when ciprofloxacin is given with ciclosporin; monitoring of serum creatinine concentrations is recommended. Altered serum concentrations of phenytoin have been reported in patients also receiving ciprofloxacin.

Further details concerning some of these interactions, and others, are given below.

Some fluoroquinolones have the potential to prolong the QT interval (see Effects on the Cardiovascular System, above) and should be avoided in patients also receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmics (such as amiodarone and sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).

For physical or chemical incompatibilities with ciprofloxacin, see above.

Analgesics. Use of *fenbufen* with fluoroquinolones may increase the incidence of fluoroquinolone CNS adverse effects. Reviews[1,2] have noted cases of convulsions associated with the use of fenbufen and enoxacin reported to the Japanese regulatory authorities. The UK CSM[3] has recognised that convulsions may occur due to an interaction between the fluoroquinolones and *NSAIDs*; by 1991, 3 such interactions had been reported to them. Adverse neurological effects have also been reported in a patient receiving *naproxen* and chloroquine when ciprofloxacin was given, which abated when the antirheumatic drugs were stopped.[4]

Ciprofloxacin also interacts with *opioid analgesics*; peak serum concentrations of ciprofloxacin given by mouth pre-operatively were significantly reduced when intramuscular *papaveretum* was injected.[5] In the UK, licensed product information for ciprofloxacin tablets recommends that opioid premedication should not be used if ciprofloxacin is given for surgical infection prophylaxis.

1. Janknegt R. Drug interactions with quinolones. *J Antimicrob Chemother* 1990; **26** (suppl D): 7–29.
2. Christ W. Central nervous system toxicity of quinolones: human and animal findings. *J Antimicrob Chemother* 1990; **26** (suppl B): 219–25.
3. Committee on Safety of Medicines. Convulsions due to quinolone antimicrobial agents. *Current Problems 32* 1991. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024450&RevisionSelectionMethod=LatestReleased (accessed 02/03/07)
4. Rollof J, Vinge E. Neurologic adverse effects during concomitant treatment with ciprofloxacin, NSAIDs, and chloroquine: possible drug interaction. *Ann Pharmacother* 1993; **27:** 1058–9.
5. Morran C, *et al.* Brief report: pharmacokinetics of orally administered ciprofloxacin in abdominal surgery. *Am J Med* 1989; **87** (suppl 5A): 86S–88S.

Antacids and metal ions. The absorption of ciprofloxacin and other fluoroquinolones is reduced by *antacids* containing *aluminium* or *magnesium* and also by *calcium*, *iron*, and *zinc* salts.[1] *Sucralfate* releases aluminium ions in the stomach and thereby reduces the absorption of ciprofloxacin[2,3] and other fluoroquinolones, including norfloxacin,[4] ofloxacin, and sparfloxacin.[5] In addition, antacids or oral iron preparations might antagonise the antibacterial activity of fluoroquinolones within the gut lumen.[6] *Dairy products* with a high calcium content may also interfere with the absorption of some fluoroquinolones.[7-9] *Enteral feeds*, which contain cations, have also been found to reduce absorption of ciprofloxacin.[10] A reduction in ciprofloxacin bioavailability has also been reported after *chewable tablets* of didanosine which contain aluminium and magnesium ion buffering agents.[11]

It is recommended that oral ciprofloxacin should be given at least 2 hours before or 6 hours after such products; similar advice also applies to other fluoroquinolones.

1. Lomaestro BM, Bailie GR. Absorption interactions with fluoroquinolones: 1995 update. *Drug Safety* 1995; **12:** 314–33.
2. Garrelts JC, *et al.* Sucralfate significantly reduces ciprofloxacin concentrations in serum. *Antimicrob Agents Chemother* 1990; **34:** 931–3.
3. Van Slooten AD, *et al.* Combined use of ciprofloxacin and sucralfate. *DICP Ann Pharmacother* 1991; **25:** 578–82.
4. Parpia SH, *et al.* Sucralfate reduces the gastrointestinal absorption of norfloxacin. *Antimicrob Agents Chemother* 1989; **33:** 99–102.
5. Kamberi M, *et al.* The effect of staggered dosing of sucralfate on oral bioavailability of sparfloxacin. *Br J Clin Pharmacol* 2000; **49:** 98–103.
6. Lewin CS, Smith JT. 4-Quinolones and multivalent ions. *J Antimicrob Chemother* 1990; **26:** 149.
7. Neuvonen PJ, *et al.* Interference of dairy products with the absorption of ciprofloxacin. *Clin Pharmacol Ther* 1991; **50:** 498–502.
8. Kivistö KT, *et al.* Inhibition of norfloxacin absorption by dairy products. *Antimicrob Agents Chemother* 1992; **36:** 489–91.
9. Neuvonen PJ, Kivistö KT. Milk and yoghurt do not impair the absorption of ofloxacin. *Br J Clin Pharmacol* 1992; **33:** 346–8.
10. Healy DP, *et al.* Ciprofloxacin absorption is impaired in patients given enteral feedings orally and via gastrostomy and jejunostomy tubes. *Antimicrob Agents Chemother* 1996; **40:** 6–10.
11. Sahai J, *et al.* Cations in the didanosine tablet reduce ciprofloxacin bioavailability. *Clin Pharmacol Ther* 1993; **53:** 292–7.

Antibacterials. The simultaneous use of parenteral ciprofloxacin and *azlocillin* has resulted in higher and more prolonged serum concentrations of ciprofloxacin.[1] Steady-state plasma concentrations of moxifloxacin are significantly reduced when given with *rifampicin* and *isoniazid* for the treatment of tuberculosis.[2]

1. Barriere SL, *et al.* Alteration in the pharmacokinetic disposition of ciprofloxacin by simultaneous administration of azlocillin. *Antimicrob Agents Chemother* 1990; **34:** 823–6.
2. Nijland HMJ, *et al.* Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clin Infect Dis* 2007; **45:** 1001–7.

Anticoagulants. For reports of ciprofloxacin and other fluoroquinolones enhancing the effect of oral anticoagulants, see under *Warfarin*, p.1428.

Antidiabetics. For reference to elevated *glibenclamide* concentrations in patients who were also given ciprofloxacin, see p.462.

Antiepileptics. For conflicting reports of the effect of ciprofloxacin on serum-*phenytoin* concentrations, see p.498.

Antifungals. Both *fluconazole* and levofloxacin can prolong the QT interval. The simultaneous use of intravenous levofloxacin and fluconazole resulted in an episode of torsade de pointes in a patient on haemodialysis.[1]

1. Gandhi PJ, *et al.* Fluconazole- and levofloxacin-induced torsades de pointes in an intensive care unit patient. *Am J Health-Syst Pharm* 2003; **60:** 2479–83.

Antimigraine drugs. For a recommendation to reduce the dosage of *zolmitriptan* when given with ciprofloxacin, see p.628.

Antineoplastics. Absorption of oral ciprofloxacin appears to be reduced after cytotoxic chemotherapy.[1]

For reference to the effect of ciprofloxacin on the pharmacokinetics of *cyclophosphamide*, see p.703.

1. Johnson EJ, *et al.* Reduced absorption of oral ciprofloxacin after chemotherapy for haematological malignancy. *J Antimicrob Chemother* 1990; **25:** 837–42.

Antivirals. Both ciprofloxacin and *foscarnet* can cause convulsions and 2 patients developed generalised tonic-clonic seizures while receiving the drugs together.[1]

For reference to reduction of ciprofloxacin bioavailability due to the antacid content of chewable *didanosine* tablets, see under Antacids and Metal Ions, above.

1. Fan-Havard P, *et al.* Concurrent use of foscarnet and ciprofloxacin may increase the propensity for seizures. *Ann Pharmacother* 1994; **28:** 869–72.

Anxiolytics. For reference to the effect of ciprofloxacin on the pharmacokinetics of *diazepam*, *midazolam*, and *temazepam*, see under Diazepam, p.989.

Immunosuppressants. For reference to possible interaction between fluoroquinolones and *ciclosporin*, see Quinolones, p.1825. For a pharmacokinetic study reporting reduced exposure to *mycophenolate mofetil* when given with norfloxacin or norfloxacin plus metronidazole, see p.1837.

Muscle relaxants. For a report of ciprofloxacin increasing the plasma concentrations of *tizanidine*, see p.1898.

Xanthines. Ciprofloxacin and other fluoroquinolones (to a greater or lesser extent) decrease the clearance of *theophylline* (p.1143) and *caffeine* (p.1117) from the body. Seizures have occurred in patients given ciprofloxacin and theophylline and in one such report[1] serum-theophylline concentrations were normal.

1. Bader MB. Role of ciprofloxacin in fatal seizures. *Chest* 1992; **101:** 883–4.

Antimicrobial Action

Ciprofloxacin is bactericidal and acts by inhibiting DNA gyrase and topoisomerase IV, which are essential enzymes in the reproduction of bacterial DNA. It has a broader spectrum of activity and is more potent *in vitro* than the non-fluorinated quinolone nalidixic acid although resistance to many species or strains previously sensitive is emerging. Activity may be reduced in acid media and in the presence of urine but not of serum.

Spectrum of activity. Among Gram-negative aerobic bacteria, ciprofloxacin may be active *in vitro* against Enterobacteriaceae, including *Escherichia coli* and *Citrobacter*, *Enterobacter*, *Klebsiella*, *Proteus*, *Providencia*, *Salmonella*, *Serratia*, *Shigella*, and *Yersinia* spp. It may also exhibit activity against *Pseudomonas aeruginosa* and *Neisseria gonorrhoeae*. *H. influenzae*, *Moraxella catarrhalis* (*Branhamella catarrhalis*), and *N. meningitidis* are all sensitive. Other Gram-negative aerobic bacteria reported to be sensitive to ciprofloxacin have included *Gardnerella vaginalis*, *Helicobacter pylori*, *Legionella* spp., *Pasteurella multocida*, and *Vibrio* spp. Variable activity has been reported against *Acinetobacter* spp., *Brucella melitensis*, and *Campylobacter* spp.

Among Gram-positive aerobic bacteria, ciprofloxacin is active against staphylococci, including penicillinase-producing and penicillinase-nonproducing strains, and against some MRSA. Streptococci, in particular *Streptococcus pneumoniae* and enterococci, are less susceptible. Other Gram-positive bacteria sensitive to ciprofloxacin *in vitro* are *Bacillus* spp.; variable activity has been noted for *Corynebacterium* spp.

Most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*, are resistant to ciprofloxacin, although some other *Clostridium* spp. may be susceptible.

Ciprofloxacin has some activity against mycobacteria, mycoplasmas, rickettsias, *Chlamydia trachomatis*, and *Ureaplasma urealyticum*.

Acquired resistance. Resistant strains, particularly of MRSA, *Ps. aeruginosa*, *E. coli*, *Klebsiella pneumoniae*, *C. jejuni*, *N. gonorrhoeae*, and *Str. pneumoniae* have emerged during treatment with ciprofloxacin although there are widely differing patterns of resistance geographically. Resistance to ciprofloxacin has usually been chromosomally mediated although plasma-mediated resistance has recently been noted.

Pharmacokinetics

Ciprofloxacin is rapidly and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70 to 80% and a peak serum concentration of about 2.4 micrograms/mL occurs 1 to 2 hours after a 500-mg oral dose. Absorption of ciprofloxacin tablets may be

delayed by the presence of food, but is not substantially affected overall.

Plasma protein binding ranges from 20 to 40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. It appears in the CSF, but concentrations are only about 10% of those in serum when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed into breast milk. High concentrations are achieved in bile.

The elimination half-life is about 3 to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. However, no dose adjustment is usually necessary in patients with renal impairment unless it is severe; similarly, usual doses can be given to the elderly except in those with severe renal impairment. There is limited information on the effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of the liver. With one or two exceptions, most studies have shown that the pharmacokinetics of ciprofloxacin are not markedly affected by cystic fibrosis.

Ciprofloxacin is eliminated principally by urinary excretion, but non-renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified. Oxociprofloxacin appears to be the major urinary metabolite and sulfociprofloxacin the primary faecal metabolite. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid; it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as metabolites. Up to 70% of a parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 20 to 35% of an oral dose and 15% of an intravenous dose.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

General pharmacokinetics. Reviews of the pharmacokinetics of ciprofloxacin[1] and the fluoroquinolones in general.[2,3]

1. Vance-Bryan K, *et al.* Clinical pharmacokinetics of ciprofloxacin. *Clin Pharmacokinet* 1990; **19:** 434–61.
2. Aminimanizani A, *et al.* Comparative pharmacokinetics and pharmacodynamics of the newer fluoroquinolone antibacterials. *Clin Pharmacokinet* 2001; **40:** 169–187.
3. Wispelwey B. Clinical implications of pharmacokinetics and pharmacodynamics of fluoroquinolones. *Clin Infect Dis* 2005; **41** (suppl 2): S127–S135.

Uses and Administration

Ciprofloxacin is a fluorinated 4-quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid (see Antimicrobial Action, above) and more favourable pharmacokinetics allowing its use in systemic infections. It has been used in the treatment of infections including anthrax, biliary-tract infections, infected bites and stings, bone and joint infections, cat scratch disease, chancroid, exacerbations of cystic fibrosis, ear, nose, and throat infections (including otitis externa, otitis media, and sinusitis), HACEK endocarditis, gastro-enteritis (including travellers' diarrhoea and campylobacter enteritis, cholera, salmonella enteritis, shigellosis, and yersinia enteritis), gonorrhoea, granuloma inguinale, infections in immunocompromised patients (neutropenia), legionnaires' disease, pelvic inflammatory disease, peritonitis, plague, lower respiratory-tract infections (including pseudomonal infections in cystic fibrosis, but excluding infections due to *Streptococcus pneumoniae* such as pneumococcal pneumonia), rickettsial infections (including Q fever, spotted fevers, and typhus), septicaemia, skin infections (including soft-tissue infections), typhoid and paratyphoid fever, and urinary-tract infections including chronic bacterial prostatitis. Ciprofloxacin is used for meningococcal meningitis prophylaxis. It is also used for surgical infection prophylaxis and in the treatment of nontuberculous mycobacterial infections and tuberculosis. Ciprofloxacin is used topically in the treatment of eye and ear infections.

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

Administration and dosage. Ciprofloxacin is given orally as the hydrochloride or base, by intravenous infusion as the lactate, and in eye drops, eye ointment, or ear drops as the hydrochloride. Doses and strengths are expressed in terms of the base. Ciprofloxacin hydrochloride 291.1 mg is equivalent to about 250 mg of ciprofloxacin. Ciprofloxacin lactate 127 mg is equivalent to about 100 mg of ciprofloxacin.

The usual adult oral dose of ciprofloxacin ranges from 250 to 750 mg twice daily depending on the severity and nature of the infection. Modified-release preparations for once-daily dosage are available in some countries. The usual adult intravenous dose is 200 to 400 mg twice daily, given over 30 to 60 minutes as a solution containing the equivalent of 1 to 2 mg/mL.

Women with acute uncomplicated cystitis may be given an oral dose of 100 to 250 mg twice daily for 3 days or 100 mg twice daily by intravenous infusion. A 28-day course of treatment with an oral dose of 500 mg twice daily or an intravenous dose of 400 mg twice daily should be given for chronic bacterial prostatitis. Bone and joint infections should be treated with an oral dose of 500 to 750 mg twice daily or an intravenous dose of 400 mg two or three times daily for 4 to 6 weeks. Intravenous infusions of 400 mg three times daily have also been recommended in severe or complicated lower respiratory tract or skin infections, nosocomial pneumonia, and with piperacillin for empirical treatment of febrile neutropenic patients.

For treatment and postexposure prophylaxis of inhalation anthrax, a 60-day course of treatment with initial intravenous doses of 400 mg twice daily followed by oral doses of 500 mg twice daily is recommended; although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of 500 to 750 mg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

Doses should be reduced in patients with severe renal impairment (see below).

Single oral doses of 250 or 500 mg or single intravenous doses of 100 mg are used for the treatment of gonorrhoea, depending upon patterns of resistance. A single oral dose of 750 mg is used for surgical infection prophylaxis, given 60 to 90 minutes before the procedure. Although unlicensed in the UK, the *BNF* suggests a single oral dose of 500 mg for meningococcal meningitis prophylaxis.

For details of doses in children, including infants and adolescents, see below.

For corneal ulcers and superficial ocular infections caused by susceptible strains of bacteria ciprofloxacin is given as the hydrochloride in eye drops and eye ointment containing the equivalent of 0.3% of ciprofloxacin.

Ciprofloxacin is also used topically as the hydrochloride in ear drops containing the equivalent of 0.2 or 0.3% of ciprofloxacin, usually with a corticosteroid such as dexamethasone or hydrocortisone, for the treatment of otitis externa and chronic suppurative otitis media caused by susceptible strains of bacteria.

◊ General references to fluoroquinolones[1-9] including ciprofloxacin specifically.[10-13]

1. von Rosenstiel N, Adam D. Quinolone antibacterials: an update of their pharmacology and therapeutic use. *Drugs* 1994; **47:** 872–901.
2. Balfour JA, Goa KL, eds. Proceedings of the 5th International symposium on new quinolones. *Drugs* 1995; **49** (suppl 2): 1–505.
3. Walker RC. The fluoroquinolones. *Mayo Clin Proc* 1999; **74:** 1030–7.
4. Smith A, *et al.* Fluoroquinolones: place in ocular therapy. *Drugs* 2001; **61:** 747–61.
5. Schaeffer AJ. The expanding role of fluoroquinolones. *Am J Med* 2002; **113** (suppl 1A): 45S–54S.
6. Zhanel GG, *et al.* A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 2002; **62:** 13–59.
7. Carson C, Naber KG. Role of fluoroquinolones in the treatment of serious bacterial urinary tract infections. *Drugs* 2004; **64:** 1359–73.
8. Shams WE, Evans ME. Guide to selection of fluoroquinolones in patients with lower respiratory tract infections. *Drugs* 2005; **65:** 949–91.
9. Andriole VT. The quinolones: past, present, and future. *Clin Infect Dis* 2005; **41** (suppl 2): S113–S119.
10. Davis R, *et al.* Ciprofloxacin: an updated review of its pharmacology, therapeutic efficacy and tolerability. *Drugs* 1996; **51:** 1019–74.
11. Campoli-Richards DM, *et al.* Ciprofloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1998; **35:** 373–447.
12. Gould FK, *et al.*, eds. Ten years of ciprofloxacin: the past, present and future. *J Antimicrob Chemother* 1999; **43** (suppl A): 1–134.
13. Blondeau JM. Current issues in the management of urinary tract infections: extended-release ciprofloxacin as a novel treatment option. *Drugs* 2004; **64:** 611–28.

Administration in children. Ciprofloxacin is not recommended for general use in children and adolescents (see under Precautions, above) but, if considered essential, UK licensed product information recommends oral doses of 5 to 15 mg/kg twice daily or intravenous doses of 4 to 8 mg/kg twice daily. The *BNFC* suggests that similar doses may be given to those as young as 1 month of age and that neonates may be given 7.5 mg/kg by mouth twice daily or 5 mg/kg by intravenous infusion twice daily. It is also licensed in different doses for specific indications as outlined below.

Ciprofloxacin is licensed in the UK and the USA for the treatment and postexposure prophylaxis of inhalation ***anthrax*** in children and adolescents. A 60-day course of treatment with initial intravenous doses of 10 mg/kg (to a maximum of 400 mg) twice daily followed by oral doses of 15 mg/kg (to a maximum of 500 mg) twice daily is recommended; the *BNFC* suggests that similar doses may be given to those as young as 1 month of age. Although unlicensed, the same regimen is recommended by UK and US public health agencies for the treatment of gastrointestinal anthrax. In the treatment of cutaneous anthrax (also unlicensed), a 7- to 10-day course of treatment with an oral dose of up to 15 mg/kg twice daily is similarly recommended; treatment may need to be extended to 60 days if infection is due to aerosol exposure.

It is also licensed in the UK for acute exacerbations of ***cystic fibrosis*** associated with *Pseudomonas aeruginosa* infection in those aged 5 to 17 years. An oral dose of 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 10 mg/kg (to a maximum of 400 mg) three times daily is recommended. Although not licensed for younger children, the *BNFC* suggests giving those aged 1 month to 5 years an oral dose of 5 to 15 mg/kg twice daily or an intravenous dose of 4 to 8 mg/kg twice daily.

In the USA, ciprofloxacin is also licensed for complicated ***urinary-tract infections*** or ***pyelonephritis*** caused by *Escherichia coli* in those aged 1 to 17 years. An oral dose of 10 to 20 mg/kg (to a maximum of 750 mg) twice daily or an intravenous dose of 6 to 10 mg/kg (to a maximum of 400 mg) three times daily is recommended.

Although unlicensed in the UK, the *BNFC* suggests a single oral dose of 125 mg for ***meningococcal meningitis prophylaxis*** in children aged 2 to 5 years; children aged 5 to 12 years may be given a single oral dose of 250 mg, and those aged over 12 years a single oral dose of 500 mg. Single oral doses of 500 mg have also been suggested for the treatment of gonorrhoea in those over 12 years of age.

Administration in renal impairment. The dose of ciprofloxacin should be reduced in ***adult patients*** with renal impairment by either reducing the total daily dose and/or by increasing the dosage interval in accordance with their creatinine clearance (CC); ideally plasma concentrations of ciprofloxacin should be monitored.

In the UK, halving the usual daily oral or intravenous dose in those with a CC of less than 20 mL/minute is recommended.

In the USA, the following doses are recommended:

- CC 30 to 50 mL/minute: up to 500 mg by mouth every 12 hours or the usual dose by intravenous infusion
- CC 5 to 29 mL/minute: up to 500 mg by mouth every 18 hours or up to 400 mg by intravenous infusion every 18 to 24 hours
- haemodialysis or peritoneal dialysis patients: up to 500 mg by mouth every 24 hours after dialysis

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with either venovenous haemofiltration or haemodiafiltration suggested that a dose of ciprofloxacin 400 mg every 24 hours would be suitable in such situations.[1]

There appears to be little guidance on the use of ciprofloxacin in ***paediatric patients*** with renal impairment but the *BNFC* states

that half the usual dose should be used for those with a CC of less than 20 mL/minute per 1.73 m^2.

1. Malone RS, *et al.* Pharmacokinetics of levofloxacin and ciprofloxacin during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother* 2001; **45:** 2949–54.

Inflammatory bowel disease. Ciprofloxacin has been given, sometimes with metronidazole, to treat active Crohn's disease[1,2] (see Inflammatory Bowel Disease, p.1697).

1. Prantera C, *et al.* An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996; **91:** 328–32.
2. Ishikawa T, *et al.* Metronidazole plus ciprofloxacin therapy for active Crohn's disease. *Intern Med* 2003; **42:** 318–21.

Tuberculosis. Reviews[1,2] of data obtained from controlled studies, cohorts, and case series, published up to March 2006, evaluating the clinical efficacy of fluoroquinolones for the treatment of tuberculosis (p.196) concluded that substituting or adding fluoroquinolones (in particular the older fluoroquinolones such as ciprofloxacin or ofloxacin) to established first-line treatment regimens did not confer additional benefits, although the newer fluoroquinolones are reported to have good *in-vitro* (levofloxacin, gatifloxacin, moxifloxacin) and *in-vivo* (gatifloxacin and moxifloxacin) bactericidal activity against *Mycobacterium tuberculosis*.[2]

There are very few controlled studies evaluating the use of fluoroquinolones in multi-drug resistant tuberculosis, but 2 retrospective studies support their effectiveness.[2] WHO guidelines[3,4] recommend that patients with multi-drug resistant tuberculosis and those who relapse after completing standard treatment regimens should receive second-line antituberculous drugs as part of a DOTS-plus regimen; such drugs do include ciprofloxacin and ofloxacin, as well as gatifloxacin, levofloxacin, and moxifloxacin. The usual recommended oral doses during the initial phase are as follows:

- ciprofloxacin: 1 to 1.5 g daily
- gatifloxacin: 400 mg daily
- moxifloxacin: 400 mg daily
- levofloxacin: 750 mg daily
- ofloxacin: 400 mg twice daily

1. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 07/07/08).
2. Moadebi S, *et al.* Fluoroquinolones for the treatment of pulmonary tuberculosis. *Drugs* 2007; **67:** 2077–99.
3. WHO. *Treatment of tuberculosis: guidelines for national programmes*. 3rd ed. Geneva: WHO, 2003 (and 2004 revision). Available at: http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf (accessed 24/01/07)
4. WHO. *Guidelines for the programmatic management of drug-resistant tuberculosis*. Geneva: WHO, 2006. Available at: http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf (accessed 03/03/08)

Preparations

BP 2008: Ciprofloxacin Intravenous Infusion; Ciprofloxacin Tablets; ***USP 31:*** Ciprofloxacin and Dexamethasone Otic Suspension; Ciprofloxacin Injection; Ciprofloxacin Ophthalmic Ointment; Ciprofloxacin Ophthalmic Solution; Ciprofloxacin Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Argeflox; Atibax C; Biotic; Blader†; Ciloxan; Cipro; Cipro-Otico; Ciprotenk; Cirflox-G; Ciriax; Crisacide; Exertial; Floraxina; Gino Ciriax; Golysine; Lorbifloxacina; Medaflox; Microsulf; Neflox; Novidat; Ocefax; Omaflaxina†; Plusgin†; Quisegen; Rexner; Septicide; Ultramicina; ***Austral.:*** C-Flox; Ciloquin; Ciloxan; Ciprol; Ciproxin; Profloxin; Proquin; ***Austria:*** Agyr†; Ciflox; Ciloxan; Cipromed; Ciprostad; Ciproxin; ***Belg.:*** Ciloxan; Ciprobel; Ciproxine; Docciproflo; ***Braz.:*** Bactoflox†; Biamotil; Ciflocina†; Ciflox; Cifloxan†; Cifloxtron; Ciloxan; Cinoflax; Ciprix; Cipro; Ciproant†; Ciprobiot†; Ciprocilin; Ciprocina†; Ciprodine; Ciprofar; Ciprofloxax†; Ciproflox†; Ciprofloxil; Cipromizin†; Cipronal†; Cipronom; Ciproxan†; Ciproxen; Ciproxil†; Ductocina; Floxan; Maxiflox; Nixin; Ofoxin; Procin†; Proflox; Proxacin; Quiflox; Quinoflox; Sifloxan†; ***Canad.:*** Ciloxan; Cipro; ***Chile:*** Baycip; Ciflоxin; Ciloxacin; Ciproval; Ciproxino; Grifociprox; Oflono; Oftaciprox; ***Cz.:*** Cifloxinal; Cifran; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprobid†; Ciprum; Quintor†; Quipro†; ***Denm.:*** Cifin; Ciloxan; Ciproxin; Sancipro; Sibunar; ***Fin.:*** Cipromed; Ciproxin; Siprion†; ***Fr.:*** Ciflox; Ciloxan; Uniflox; ***Ger.:*** Ciloxan; Cipro; Cipro-Lich†; Cipro-Q; Cipro-saar; Cipro-Wolff; Ciprobay; Ciprobeta; Ciprodoc; Ciprodura; Ciprofat; Ciproflox; Ciproflox-Puren; Ciprogamma; Ciprohexal; Ciprox; Gyracip; Keciflox; Panotile cipro; ***Gr.:*** Afenoxin; Aristin-C; Balepton; Biocipro; Bivorilan; Cidrops†; Ciloxan; Ciprobay†; Ciprofal; Cipromycin; Ciprospes; Ciproxin; Citrovenot; Droll; Flociprin; Forterra; Ginorectol; Glossyfin; Grenis-cipro; Infectina; Labentrol; Ladinin; Limox; Nafloxin; Ravalton; Remena; Revion; Revionorm; Topistin; Ufexil; Urodixin; ***Hong Kong:*** Ciflоxin; Ciloxan; Cipide; Ciplox; Ciprol; Ciproxin; Ciproxyl; Cyfloxin; Enoxin; Gonning; Medociprin; Proxacin; Quinocin; Uroxin; Utahzone; ***Hung.:*** Ciflоxin; Cifran; Ciloxan; Ciphin; Ciplox; Ciprinol; Ciprobay; Ciprolen; Cipropharm; Ciprum; Cydonin; ***India:*** Bactoquin†; Biocip; Cifran; Cipgen; Cipro-Cent; Ciprobid; Ciprodac; Ciprowin; Ificipro†; Neocip; Procip†; Quinobact; Strox†; Zoxan; ***Indon.:*** Bactiprox; Baquinor; Bernoflox; Bidiprox; Cetafloxo; Ciflos; Cilox; Ciproxin; Civell; Coroflex; Corsacin; Cylowam; Disfabac; Duflomex; Etacin; Floksid; Floxbio; Floxigra; Girabloc; Interflox; Isotic Renator; Jayacin; Kifarox; Lapiflox; Licoprox; Meflosin; Mensipox; Nilaflox; Poncoflox; Proxcip; Proxitor; Qinox; Quamiprox; Quidex; Quinobiotic; Renator; Scanax; Tequinol; Vidintal; Viflox; Vioquin; Volinol; Wiaflox; Ximex Cylowam; Zumaflox; ***Irl.:*** Biofloxcin; Cifloxager; Ciproxin; Profloxin; Truoxin; ***Israel:*** Ciloxan; Ciplox; Ciprodex; Ciprogis; Ciproxin; Ufexil; ***Ital.:*** Ciproxin; Flociprin; Oftacilox; ***Jpn:*** Ciproxan; ***Malaysia:*** Bactiflox; Cifloxin; Cifran; Ciloxan; Ciprobay; Enoxin; ***Mex.:*** Antimed; Apoflox; Arfloxina; Bacproin; Bioflox; Ci-Sons; Cifran; Ciloxan; Cimogal; Ciprain; Cipro; Ciprobac; Ciprobiotic; Ciproflox; Ciprofur; Ciprohexal; Ciproser; Ciprotec; Ciproxina; Ciqfadin; Dinaflox; Eni; Eufloxin; Floxager; Floxantina; Floxelena; Floxitul; Gibac; Infloxa; Italnik; Kenzoflex; Lemyflox; Lifexina; Maviflox†; Microrgan; Mitroken; Nivoflox†; Novoquin; Oftaquin†; Opthaflox; Patox; Pharcina; Profluxol; Provay; Proxitec†; Quifloxona†; Quinoflox; Rictor; Sinfexina; Sophixin; Spectroflex†; Suiflox; Trigen; Vifloxina; Zipra; ***Neth.:*** Ciloxan; Ciprinol; Ciproxin; ***Norw.:*** Cilox; Ciproxin; ***NZ:*** Cifran; Ciloxan; Cipflox; Ciproxin; DP-Cipro; Topistin; Ufexil; ***Philipp.:*** Baxolyn; Brelcip; Ciclodin; Cidroxal; Ciloxan; Ciprobay; Cipromax; Cipromet; Ciprotor; Cirok; Floroc; Iprolan; Ipromax; Kinoves; Laitun; Nexproxyn; Proxivex; Qinosyn; Quilox; Quinoryl; Quiprime; Rapiqure; Xipro; Zalvos; Zyflox; ***Pol.:*** Cifran; Ciloxan; Ciphin; Ciprinol; Ciprobay; Cipronex; Ciropol; Ciprum; Proxacin; ***Port.:*** Carmicina†; Ciflan; Ciplox; Ciproquinol†; Ciproxina; Colintil; Estecina; Floxacipront†; Giroflox; ISINO; Keefloxin†; Megaflox; Nivoflox; Nixin; Oftacilox; Quinox; Xorpic†; ***Rus.:*** Ciflоxinal (Ципрофлоксинал); Cifran (Ципран); Ciloxan (Цилоксан); Ciprex (Ципрекс); Ciprinol (Ципринол); Ciprobay (Ципробай); Ciprobid (Ципробид); Ciprolet (Ципролет); Ciprolone (Ципролон); Cipromed (Ципромед); Ciprosun (Ципросан); Ificipro (Ифиципро); Medociprin (Медоциприн); Quintor (Квинтор); Sifloks (Сифлокс); ***S.Afr.:*** Adco-Ciprin; Biocip; Cifloc; Cifran; Ciloxan; Ciploxx; Cipro-Hexal; Ciprobay; Ciprogen; Dynafloc; Orpic; Spec-Topistin; ***Singapore:*** Ciloxan; Ciprobay; Ciprolet; Cirok†; Ciroxin†; Cycin; Ginorectol; Neofloxin; Serviflox; Uroxin; ***Spain:*** Aceoto; Baycip; Belmacina; Catex; Ceprimax†; Cetraxal; Cipobacter†; Ciprenit Otico; Ciproctal; Ciproxina Simple; Cunesin; Doriman; Estecina; Felixene; Giroflox; Globuce; Huberdoxina; Numen; Oftacilox; Otociprin; Otosat; Piprol; Plenolyt; Quipro; Rigoran; Sepcen; Septocipro; Tam; Ultramicina; Velmonit†; ***Swed.:*** Ciloxan; Ciproxin; ***Switz.:*** Ciloxan; Cip eco; Ciprine; Cipro-Med; Ciproflox; Ciproxine; Principrox; ***Thai.:*** C-Floxacin; Ciflo; Ciflolan; Cifloxin; Cifran; Cilab; Ciloxan; Cinfloxine; Cipflocin; Cipon; Ciprobay; Ciprobid; Ciprocep; Ciprofin; Ciprogen; Ciproglen†; Ciprolet; Ciprom-H; Ciprosun†; Ciprovid; Ciproxan; Ciproxyl; Cobay; Cyflox; Forexin; Microflox; Poli-Cifloxin; Proflox; Serviflox†; Ultraflox; Uroxin; Vesprocin; ***Turk.:*** Ciflosin; Cifluron; Ciloxan; Ciprasid; Cipro; Ciproktan; Ciproxin; Loxasid; Proxacin; Roflazin; Roxin; Sanset; Sifloks; Siprobel; Siprogut; Siprosan; Sispres; UroCiproxin; ***UAE:*** Sarf; ***UK:*** Ciloxan; Ciproxin; ***USA:*** Ciloxan; Cipro; ***Venez.:*** Bacipro; Baflox; Ciflox; Ciloxan; Ciprivax; Ciproflox; Ciprolet†; Cipronax; Ciproquin; Ciproxina; Cirok; Cypral; Gerxidin†; Iproxin; Klicina†; Lisipin; Oxtin; Quinoftal; Quinotic; Serviflox; Sophixin; Zolina.

Multi-ingredient: ***Arg.:*** Ciloxadex; Cipro HC; Ciproflox-Otic; Ciriax Otic; Ciriax Otic L; Decadron con Ciprofloxina; Delos Otic; Otex HC; Oto Biotaer; Otobiotic; Otocipro; Otosporin C; Prootocipro; Quidex; Tacines; ***Austral.:*** Ciproxin HC; ***Austria:*** C-Bildz; ***Braz.:*** Biamotil-D; Cilodex; Cipro HC; Cylocort; Maxiflox D; Otociriax; ***Canad.:*** Cipro HC; Ciprodex; ***Chile:*** Cilodex; Ciprodex; Oflono-D; Otex HC; ***Cz.:*** Ciprobay HC Otic; ***Denm.:*** Ciflox; ***Fin.:*** Ciproxin-Hydrocortison; ***Gr.:*** Ciprofloxacin HY†; ***Hong Kong:*** Cipro HC; ***Hung.:*** Ciprobay†; ***India:*** Biocip-TZ; Cipgen TZ; Ciplox; Ciplox D; Ciplox TZ; Ciptini; Citizol; Neocip FC; Neocip M; Ocimix; Tinvista-CF; ***Israel:*** Ciproxin HC; ***Malaysia:*** Cipro HC†; ***Mex.:*** Cilodex; Ciproxina HC; Dinill-D; Oto Eni; Quinoflox Otico; UV IX†; Vodelan; ***NZ:*** Ciproxin HC; ***S.Afr.:*** Ciprobay HC; ***Singapore:*** Ciprobay HC; ***Spain:*** Aceoto Plus; Cetraxal Plus; Cexidal Otico†; Ciproxina; Synalotic; Ultramicina Plus†; ***Switz.:*** Ciproxin HC; ***USA:*** Cipro HC; Ciprodex; ***Venez.:*** Otalex; Quinocort; Quinotic HC.

Clarithromycin *(BAN, USAN, rINN)*

A-56268; Abbott-56268; Clarithromycine; Clarithromycinum; Claritromicina; Klarithromycin; Klaritromicinas; Klaritromisin; Klaritromycin; Klaritromysiini; TE-031. (2*R*,3*S*,4*S*,5*R*,6*R*,8*R*,10*R*,11*R*,12*S*,13*R*)-3-(2,6-Dideoxy-3-*C*,3*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-11,12-dihydroxy-6-methoxy-2,4,6,8,10,12-hexamethyl-9-oxo-5-(3,4,6-trideoxy-3-dimethylamino-β-D-*xylo*-hexopyranosyloxy)pentadecan-13-olide; 6-*O*-Methylerythromycin.

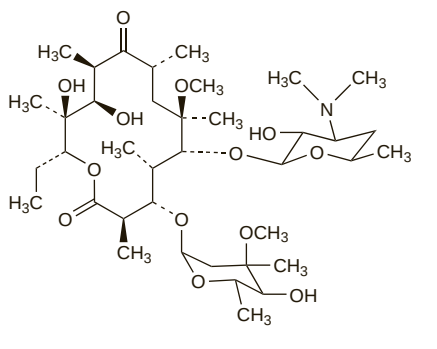
Кларитромицин

$C_{38}H_{69}NO_{13}$ = 748.0.

CAS — 81103-11-9.

ATC — J01FA09.

ATC Vet — QJ01FA09.



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

Ph. Eur. 6.2 (Clarithromycin). A white or almost white, crystalline powder. Practically insoluble in water; soluble in acetone and in dichloromethane; slightly soluble in methyl alcohol.

USP 31 (Clarithromycin). A white to off-white crystalline powder. Practically insoluble in water; slightly soluble in dehydrated alcohol, in methyl alcohol, and in acetonitrile; soluble in acetone; slightly soluble in phosphate buffer at pH values of 2 to 5. pH of a 0.2% suspension in a mixture of water and methyl alcohol (19:1) is between 8.0 and 10.0. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270. Gastrointestinal disturbances are the most frequent adverse effect but are usually mild and less frequent with clarithromycin than with erythromycin. Smell and taste disturbances, stomatitis, glossitis, tongue and tooth discoloration, and headache have occurred. There have also been reports of transient CNS effects. Other adverse effects include arthralgia, myalgia, hypoglycaemia, leucopenia, and thrombocytopenia. Interstitial nephritis and renal failure have been reported rarely.

Intravenous doses may cause phlebitis and pain at the injection site.

Caution is required in patients with hepatic or renal impairment and doses should be reduced in those with renal impairment (see under Uses and Administration below). It should not be used during pregnancy if possible as high doses have been associated with embryotoxicity in *animal* studies.

Effects on the blood. Single cases of thrombocytopenia[1] and thrombocytopenic purpura[2,3] associated with clarithromycin have been reported. Cases of agranulocytosis have also been reported.[4] A case of thrombocytopenia accompanied by interstitial nephritis, hepatitis, and elevated serum amylase levels was attributed to an allergic reaction to clarithromycin.[5] Toxic epidermal necrolysis and subsequent death due to aplastic anaemia have been reported in a patient after taking clarithromycin for 3 days.[6]

1. Price TA, Tuazon CU. Clarithromycin-induced thrombocytopenia. *Clin Infect Dis* 1992; **15:** 563–4.
2. Oteo JA, *et al.* Clarithromycin-induced thrombocytopenic purpura. *Clin Infect Dis* 1994; **19:** 1170–1.
3. Alexopoulou A, *et al.* Thrombotic thrombocytopenic purpura in a patient treated with clarithromycin. *Eur J Haematol* 2002; **69:** 191–2.
4. Jacobs P, *et al.* Immune agranulocytosis and clarithromycin. *Hematology* 2004; **9:** 291–6.
5. Baylor P, Williams K. Interstitial nephritis, thrombocytopenia, hepatitis, and elevated serum amylase levels in a patient receiving clarithromycin therapy. *Clin Infect Dis* 1999; **29:** 1350–1.
6. Baz K, *et al.* Fatal aplastic anaemia in a patient with clarithromycin-induced toxic epidermal necrolysis. *J Eur Acad Dermatol Venereol* 2004; **18:** 104–5.

Effects on the cardiovascular system. QT prolongation and torsade de pointes were associated with use of clarithromycin in 2 patients.[1] Renal impairment in 1 of the patients and hepatic impairment and organic heart disease in both could have increased their susceptibility to these effects.

For mention of an unexpected increase in cardiovascular mortality in patients with stable coronary heart disease given clarithromycin, see Ischaemic Heart Disease, in Uses and Administration of Azithromycin, above.

1. Lee KL, *et al.* QT prolongation and torsades de pointes associated with clarithromycin. *Am J Med* 1998; **104:** 395–6.

Effects on the eyes. Corneal opacities, reversible on stopping treatment, were reported in a patient receiving oral clarithromycin as part of a regimen for disseminated *Mycobacterium avium* complex infection.[1] Corneal subepithelial deposits have also been reported in a patient after prolonged use of clarithromycin eye drops for *Mycobacterium avium* complex keratitis. The deposits did not cause any ocular discomfort and resolved on stopping therapy.[2]

1. Dorrell L, *et al.* Toxicity of clarithromycin in the treatment of Mycobacterium avium complex infection in a patient with AIDS. *J Antimicrob Chemother* 1994; **34:** 605–6.
2. Tyagi AK, *et al.* An unreported side effect of topical clarithromycin when used successfully to treat Mycobacterium avium-intracellulare keratitis. *Cornea* 1999; **18:** 606–7.

Effects on the gastrointestinal tract. Pseudomembranous colitis associated with *Clostridium difficile* developed in a child receiving clarithromycin.[1]

1. Braegger CP, Nadal D. Clarithromycin and pseudomembranous enterocolitis. *Lancet* 1994; **343:** 241–2.

Effects on the liver. Progressive cholestatic jaundice, which subsequently proved fatal, developed in a 59-year-old woman after 3 days of clarithromycin therapy for acute maxillary sinusitis.[1] Fulminant hepatic failure in another patient, which developed during clarithromycin therapy, resolved once the drug was withdrawn.[2] Clarithromycin itself was considered responsible although there was the possibility that it had increased concentrations of isradipine, another known hepatotoxic drug that the patient was also receiving.

1. Fox JC, *et al.* Progressive cholestatic liver disease associated with clarithromycin treatment. *J Clin Pharmacol* 2002; **42:** 676–80.
2. Tietz A, *et al.* Fulminant liver failure associated with clarithromycin. *Ann Pharmacother* 2003; **37:** 57–60.

Effects on the lungs. On 2 occasions fever and pulmonary infiltration with eosinophilia occurred in a patient given clarithromycin.[1] Another patient developed eosinophilic pneumonia 3 days after starting clarithromycin; symptoms improved when the drug was stopped.[2]

1. Terzano C, Petroianni A. Clarithromycin and pulmonary infiltration with eosinophilia. *BMJ* 2003; **326:** 1377–8.
2. Ohnishi H, *et al.* Clarithromycin-induced eosinophilic pneumonia. *Intern Med* 2004; **43:** 231–5.

Effects on mental state. Acute psychoses occurred in 2 patients receiving clarithromycin as part of prophylactic treatment for *Helicobacter pylori* infection and were similar to 3 previous-