In the USA, the following dose modifications are recommended:

After an initial dose of 750 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 750 mg every 48 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 500 mg every 48 hours

After an initial dose of 500 mg daily,

- CC 20 to 49 mL/minute: subsequent doses are 250 mg every 24 hours
- CC up to 19 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): subsequent doses are 250 mg every 48 hours

After an initial dose of 250 mg daily,

- CC 10 to 19 mL/minute: subsequent doses are 250 mg every 48 hours

A pharmacokinetic study in 10 critically ill patients undergoing continuous renal replacement therapy with either venovenous haemofiltration or haemodiafiltration suggested that a dose of either levofloxacin 250 mg every 24 hours or 500 mg every 48 hours would be suitable in such situations.[1]

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.

Peptic ulcer disease. For mention of the potential use of levofloxacin in eradication regimens for *Helicobacter pylori*, see p.1702.

References.

1. Gisbert JP, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006; **23:** 35–44.
2. Gisbert JP, *et al.* First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26:** 495–500.
3. Rispo A, *et al.* Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12:** 364–5.
4. Perna F, *et al.* Levofloxacin-based triple therapy for Helicobacter pylori re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007; **39:** 1001–5.
5. Zullo A, *et al.* Helicobacter pylori eradication with either quadruple regimen with lactoferrin or levofloxacin-based triple therapy: a multicentre study. *Dig Liver Dis* 2007; **39:** 806–10.
6. Yee YK, *et al.* Clinical trial: levofloxacin-based quadruple therapy was inferior to traditional quadruple therapy in the treatment of resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2007; **26:** 1063–7.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Floxlevo; Grepiflox; Leflumax; Levaquin; Septibiotic; Tavanic; Teraquin; Ultraquin; Uniflox; Valiflox; ***Austria:*** Tavanic; ***Belg.:*** Tavanic; ***Braz.:*** Levaquin; Levotac; Levoxin; Tamiram; Tavanic; ***Canad.:*** Levaquin; ***Chile:*** Auxxil; Medibiox; Novacilina; Quinobiot; Recamicina; Tavanic; ***Cz.:*** Oftaquix; Tavanic; ***Denm.:*** Oftaquix; ***Fin.:*** Oftaquix; Tavanic; ***Fr.:*** Tavanic; ***Ger.:*** Oftaquix; Tavanic; ***Gr.:*** Tavanic; ***Hong Kong:*** Cravit; ***Hung.:*** Leflokin; Oftaquix; Tavanic; ***India:*** Glevo†; Leeflox; Levocide; Levoff; Levoflox; Lufi; Tavanic; ***Indon.:*** Armolev; Cravit; Cravox; Difloxin; Farlev; Lefos; Levocin; Levores; Levovid; Levoxal; Lexa; Lovequin; Mosardal; Nislev; Nufalev; Prolecin; Prolevox; Reskuin; Rinvox; Tevox; Volequin; Voxin; ***Irl.:*** Tavanic; ***Israel:*** Levo; Tavanic; ***Ital.:*** Levoxacin; Oftaquix; Prixar; Tavanic; ***Jpn:*** Cravit; ***Malaysia:*** Cravit; Glevo; Loxof; ***Mex.:*** Elequine; Ran-Levo; Tavanic; ***Neth.:*** Oftaquix; Prixar; Tavanic; ***Philipp.:*** Floxel; Levox; Oftaquix; ***Pol.:*** Oftaquix; ***Port.:*** Oftaquix; Tavanic; ***Rus.:*** Lefoxin (Лефоксин); Tavanic (Таваник); ***S.Afr.:*** Tavanic; ***Singapore:*** Cravit; ***Spain:*** Tavanic; ***Swed.:*** Oftaquix; Tavanic; ***Switz.:*** Tavanic; ***Thai.:*** Cravit; Lefloxin; ***Turk.:*** Cravit; Tavanic; ***UAE:*** Jenoquine; ***UK:*** Oftaquix; Tavanic; ***USA:*** Iquix; Levaquin; Quixin; ***Venez.:*** Levaquin; Proxime; Tavanic.

Multi-ingredient: ***India:*** Levoflox Oz Kit.

Lincomycin *(BAN, USAN, rINN)*

Lincomicina; Lincomycine; Lincomycinum; Linkomycin; Linkomysiini; U-10149. Methyl 6-amino-6,8-dideoxy-*N*-[(2*S*,4*R*)-1-methyl-4-propylprolyl]-1-thio-α-D-*erythro*-D-*galacto*-octopyranoside.

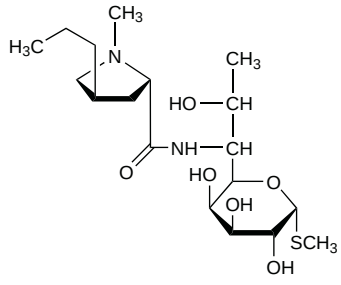
Линкомицин

$C_{18}H_{34}N_2O_6S$ = 406.5.

CAS — 154-21-2.

ATC — J01FF02.

ATC Vet — QJ01FF02.



Lincomycin Hydrochloride *(BANM, rINNM)*

Hidrocloruro de lincomicina; Lincomycine, chlorhydrate de; Lincomycini hydrochloridum; Lincomycini Hydrochloridum Monohydricum; Linkomicin-hidroklorid; Linkomicino hidrochloridas; Linkomisin Hidroklorür; Linkomycin hydrochlorid monohydrát; Linkomycinhydroklorid; Linkomycyny chlorowodorek; Linkomysiinihydrokloridi; Lyncomycini Hydrochloridum; NSC-70731. Lincomycin hydrochloride monohydrate.

Линкомицина Гидрохлорид

$C_{18}H_{34}N_2O_6S,HCl,H_2O$ = 461.0.

CAS — 859-18-7 (anhydrous lincomycin hydrochloride); 7179-49-9 (lincomycin hydrochloride, monohydrate).

ATC — J01FF02.

ATC Vet — QJ01FF02.

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

Ph. Eur. 6.2 (Lincomycin Hydrochloride). An antimicrobial substance produced by *Streptomyces lincolnensis* var. *lincolnensis* or by any other means. A white or almost white crystalline powder. It contains not more than 5% of lincomycin B. Very soluble in water; slightly soluble in alcohol; very slightly soluble in acetone. A 10% solution in water has a pH of 3.5 to 5.5. Store at a temperature not exceeding 30° in airtight containers.

USP 31 (Lincomycin Hydrochloride). A white or practically white crystalline powder, odourless or with a faint odour. Freely soluble in water; very slightly soluble in acetone; soluble in dimethylformamide. pH of a 10% solution in water is between 3.0 and 5.5. Store in airtight containers.

Incompatibility. Solutions of lincomycin hydrochloride have an acid pH and incompatibility may be expected with alkaline preparations, or with drugs unstable at low pH.

Adverse Effects, Treatment, and Precautions

As for Clindamycin, p.251.

Hypersensitivity reactions such as skin rashes, urticaria, and angioedema may be less frequent with lincomycin than with clindamycin. Other adverse effects reported rarely with lincomycin include aplastic anaemia, pancytopenia, tinnitus, and vertigo.

Lincomycin should be used with caution in patients with hepatic or renal impairment; consideration should be given to decreasing the dosage frequency and serum concentrations should be monitored during high-dose therapy. Reduced doses may be necessary in those with severe renal impairment (see below).

Interactions

As for Clindamycin, p.251.

Absorption of lincomycin is reduced by adsorbent antidiarrhoeals and cyclamate sweeteners.

Antimicrobial Action

As for Clindamycin, p.252, but it is less potent. There is complete cross-resistance between clindamycin and lincomycin. Some cross-resistance with erythromycin, including a phenomenon known as dissociated cross-resistance or macrolide effect, has been reported.

Pharmacokinetics

About 20 to 30% of an oral dose of lincomycin is rapidly absorbed from the gastrointestinal tract; after a 500-mg dose, peak plasma concentrations of about 2 to 3 micrograms/mL are reached within 2 to 4 hours. Food markedly reduces the rate and extent of absorption. An intramuscular injection of 600 mg produces average peak plasma concentrations of between 11 and 12 micrograms/mL at 60 minutes and a 2-hour intravenous infusion of 600 mg produces an average of about 16 micrograms/mL.

The biological half-life of lincomycin is about 5 hours and may be prolonged in hepatic or renal impairment. Serum half-life may be doubled in patients with hepatic impairment and up to 3 times longer in those with severe renal impairment. Lincomycin is widely distributed in the tissues including bone and body fluids but diffusion into the CSF is poor, although it may be slightly better when the meninges are inflamed. It diffuses across the placenta and is distributed into breast milk.

Lincomycin is partially inactivated in the liver; unchanged drug and metabolites are excreted in the urine, bile, and faeces. Lincomycin is not effectively removed from the blood by haemodialysis or peritoneal dialysis.

Uses and Administration

Lincomycin is a lincosamide antibacterial with actions and uses similar to those of its chlorinated derivative, clindamycin (p.252). Clindamycin is usually preferred to lincomycin because of its greater activity and better absorption, although the usefulness of both drugs is limited by the risk of pseudomembranous colitis.

Lincomycin is given orally or parenterally as the hydrochloride but doses are expressed in terms of the base; 1.13 g of lincomycin hydrochloride is equivalent to about 1 g of lincomycin. The usual adult oral dose is 500 mg 3 or 4 times daily, taken at least 1 or 2 hours before or after food. It is given parenterally by intramuscular injection in a dose of 600 mg once or twice daily, or by slow intravenous infusion in a dose of 0.6 to 1 g two or three times daily. Higher intravenous doses have been given in very severe infections, up to a total daily dose of about 8 g. For intravenous use, lincomycin 1 g should be diluted in not less than 100 mL of diluent and infused over at least 1 hour.

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

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

Lincomycin hydrochloride may be given by subconjunctival injection in a dose equivalent to 75 mg of lincomycin.

Administration in children. The usual oral dose of lincomycin for infants and children aged 1 month and over is 30 to 60 mg/kg daily in divided doses. It is given parenterally to those over 1 month old in a dose of 10 to 20 mg/kg daily in divided doses by intramuscular injection or intravenous infusion.

For suggested doses in children with renal impairment see below.

Administration in renal impairment. Doses of lincomycin may need to be reduced in patients with severe renal impairment; a reduction down to 25 to 30% of the usual dose (see above) may be appropriate.

Preparations

BP 2008: Lincomycin Capsules; Lincomycin Injection;
USP 31: Lincomycin Hydrochloride Capsules; Lincomycin Hydrochloride Syrup; Lincomycin Injection.

Proprietary Preparations (details are given in Part 3)
Arg.: Frademicina; ***Austral.:*** Lincocin; ***Belg.:*** Lincocin; ***Braz.:*** Frademicina; Framicin†; Linatron; Lincoflan; Lincomiral; Lincomyn†; Lincoplax†; Lincotax†; Lincovax; Lindemicina; Neo Linco; ***Canad.:*** Lincocin; ***Chile:*** Lincocin; ***Cz.:*** Lincocin†; Neloren; ***Fr.:*** Lincocine; ***Ger.:*** Albiotic†; ***Gr.:*** Lincocin; Pecasolin; ***Hong Kong:*** Lincocin; Medoglycin†; ***India:*** Lynx; ***Indon.:*** Biolincom; Ethilin; Linco; Lincocin; Lincophar; Lincyn; Lintropsin; Nichomycin; Percocyn; Pritalinc; Tamcocin; Tismamisin; Zumalin; ***Ital.:*** Lincocin; ***Malaysia:*** Linco; Lincosa; Medoglycin†; ***Mex.:*** Libiocid; Limidrax; Linbac; Lincocin; Lincopat; Lincover; Lisonin; Princol; Rimsalin; Yectolin; ***Philipp.:*** Adlynx; Lincocin; ***Pol.:*** Lincocin; Neloren; ***Port.:*** Lincocina; ***Rus.:*** Neloren (Нелорен); ***S.Afr.:*** Lincocin; ***Singapore:*** Lincocin; ***Spain:*** Cillimicina; Lincocin; ***Thai.:*** Linco; Lincocilin; Lincocin; Lincogin†; Lincolan; Lincomax; Lincomy†; Lincono; Lingo; Linmycin; Utolincomycin; ***Turk.:*** Lincocin; Lincomed; Linkoles; Linkosol; Linosin; ***USA:*** Lincocin; Lincorex†; ***Venez.:*** Bekalen†; Formicina; Lincocin.

Multi-ingredient: ***Arg.:*** Nicozinc.

Linezolid *(BAN, USAN, rINN)*

Linetsolidi; Linézolide; Linezolidum; PNU-100766; U-100766. *N*-{[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl}acetamide.

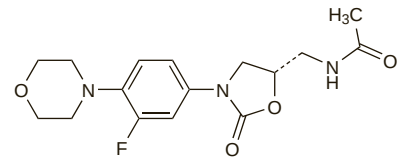
Линезолид

$C_{16}H_{20}FN_3O_4$ = 337.3.

CAS — 165800-03-3.

ATC — J01XX08.

ATC Vet — QJ01XX08.



Incompatibility and stability. References.

1. Zhang Y, *et al.* Compatibility and stability of linezolid injection admixed with three quinolone antibiotics. *Ann Pharmacother* 2000; **34:** 996–1001.

Adverse Effects and Precautions

The adverse effects most frequently reported in patients given linezolid include diarrhoea, nausea and vomiting, metallic taste, headache, insomnia, constipation, rashes, dizziness, fever, oral and vaginal candidiasis, and abnormal liver function tests. Lactic acidosis has been reported. Convulsions have also been reported in patients treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. There have been rare reports of bullous skin eruptions including Stevens-Johnson syndrome. Peripheral and optic neuropathy, sometimes progressing to loss of vision, have occurred rarely, mainly in patients given linezolid for more than 28 days. Visual blurring has been reported in some patients given less than 28 days of treatment.

Reversible myelosuppression including anaemia, leucopenia, pancytopenia and, in particular, thrombocytopenia has been reported and blood counts should be monitored weekly in patients receiving linezolid. Patients particularly at risk are those who have received linezolid for more than 10 to 14 days, who are receiving other bone marrow suppressant drugs, or who have pre-existing myelosuppression or severe renal impairment.

Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when linezolid is given as monotherapy (see Increased Mortality, below); linezolid must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients.

◊ References.

1. Rubinstein E, *et al.* Worldwide assessment of linezolid's clinical safety and tolerability: comparator-controlled phase III studies. *Antimicrob Agents Chemother* 2003; **47:** 1824–31.
2. Bishop E, *et al.* Good clinical outcomes but high rates of adverse reactions during linezolid therapy for serious infections: a proposed protocol for monitoring therapy in complex patients. *Antimicrob Agents Chemother* 2006; **50:** 1599–1602.

Effects on the blood. Reversible myelosuppression with red cell hypoplasia occurred in 3 patients treated with linezolid.[1] Features of the myelosuppression were considered by some[1,2] to be similar to those associated with chloramphenicol, although this was disputed by the manufacturers.[3]

There have been reports of thrombocytopenia occurring at a higher incidence than that reported by the manufacturers; in one study,[4] 6 of 19 patients who had been treated with linezolid developed thrombocytopenia, while another[5] found that it occurred in 23 of 48 patients given the drug for more than 5 days.

During the initial 8 months of licensed use in the UK 12 reports of haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) were received by the UK CSM.[6]

Studies have shown that the risk of thrombocytopenia and anaemia is increased in patients on prolonged linezolid therapy with pre-existing myelosuppression[7,8] or severe renal impairment.[9]

1. Green SL, *et al.* Linezolid and reversible myelosuppression. *JAMA* 2001; **285:** 1291.
2. Lawyer MC, Lawyer EZ. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1974.
3. Arellano FM. Linezolid and reversible myelosuppression. *JAMA* 2001; **286:** 1973–4.
4. Attassi K, *et al.* Thrombocytopenia associated with linezolid therapy. *Clin Infect Dis* 2002; **34:** 695–8.
5. Orrick JJ, *et al.* Thrombocytopenia secondary to linezolid administration: what is the risk? *Clin Infect Dis* 2002; **35:** 348–9.
6. Committee on Safety of Medicines/Medicines Control Agency. Reminder: linezolid (Zyvox) and myelosuppression. *Current Problems* 2001; **27:** 14. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007456&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)
7. Senneville E, *et al.* Risk factors for anaemia in patients on prolonged linezolid therapy for chronic osteomyelitis: a case-control study. *J Antimicrob Chemother* 2004; **54:** 798–802.
8. Grau S, *et al.* Linezolid: low pre-treatment platelet values could increase the risk of thrombocytopenia. *J Antimicrob Chemother* 2005; **56:** 440–1.
9. Wu V-C, *et al.* High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. *Clin Infect Dis* 2006; **42:** 66–72.

Effects on the eyes. See under Effects on the Nervous System, below.

Effects on mitochondria. Linezolid appears to inhibit mitochondrial protein synthesis when given for prolonged courses. This decreases cellular energy production in tissues that are highly dependent on oxidative phosphorylation, such as the optic nerve, skeletal muscles, liver, and kidneys, leading to adverse effects such as lactic acidosis[1] or hyperlactataemia,[1,2] and optic[3] and/or peripheral neuropathy[1] (see also below). Encephalopathy, lactic acidosis, optic neuropathy, skeletal myopathy, and renal failure were reported[1] in a 63-year-old woman after a 4-month course of linezolid. The symptoms resolved when linezolid was stopped; however, the patient remained blind and disorientated. In contrast, bilateral mitochondrial optic neuropathy seen[3] in a 6-year-old boy after a 1-year course of oral linezolid resolved 3 months after linezolid treatment was stopped. In another study[2] reversible hyperlactataemia was reported in 5 patients given linezolid for 1 to 3 months. Mitochondrial activity and lactic acid levels returned to normal when linezolid therapy was stopped.

1. De Vriese AS, *et al.* Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis* 2006; **42:** 1111–1117.
2. Garrabou G, *et al.* Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother* 2007; **51:** 962–7.
3. Javaheri M, *et al.* Linezolid-induced optic neuropathy: a mitochondrial disorder? *Br J Ophthalmol* 2007; **91:** 111–15. Correction. *ibid.*; 403.

Effects on the nervous system. The Australian Adverse Drug Reactions Advisory Committee[1] stated in February 2003 that it had received 4 reports of peripheral neuropathy in patients who had taken linezolid for 6 to 9 months; none of these cases had resolved at the time of the report. They suggested that the risk of peripheral neuropathy should be considered when treatment was extended beyond 28 days. There have been several published reports of peripheral and optic neuropathy associated with linezolid,[2-9] with some attributing these effects to the inhibition of mitochondrial protein synthesis by linezolid. For further discussion see Effects on Mitochondria, above. The regulatory authority in the UK has warned that patients should be advised to report any symptoms of visual impairment immediately, including changes in visual acuity or colour vision, blurred vision, or visual field defects.[10] Any linezolid-treated patient with new visual symptoms should be evaluated promptly and referred to an ophthalmologist if necessary; regular monitoring is advised in all patients who may require treatment for more than 28 days.

1. Adverse Drug Reactions Advisory Committee (ADRAC). Linezolid and peripheral neuropathy. *Aust Adverse Drug React Bull* 2003; **22:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0302.htm (accessed 11/01/08)
2. Corallo CE, Paull AE. Linezolid-induced neuropathy. *Med J Aust* 2002; **177:** 332.
3. Rho JP, *et al.* Linezolid-associated peripheral neuropathy. *Mayo Clin Proc* 2004; **79:** 927–30.
4. Lee E, *et al.* Linezolid-associated toxic optic neuropathy: a report of 2 cases. *Clin Infect Dis* 2003; **37:** 1389–91.
5. Bressler AM, *et al.* Peripheral neuropathy associated with prolonged use of linezolid. *Lancet Infect Dis* 2004; **4:** 528–31.
6. Willcox D. Linezolid (Zyvoxam) and neuropathy *Can Adverse React News* 2005; **15:** 2.
7. Zivkovic SA, Lacomis D. Severe sensory neuropathy associated with long-term linezolid use. *Neurology* 2005; **64:** 926–7.
8. Legout L, *et al.* Linezolid-induced neuropathy. *Clin Infect Dis* 2004; **38:** 767–8.
9. Rucker JC, *et al.* Linezolid-associated toxic optic neuropathy. *Neurology* 2006; **66:** 595–8.
10. Commission on Human Medicines/Medicines and Healthcare products Regulatory Agency. Linezolid (Zyvox): severe optic neuropathy. *Current Problems* 2006; **31:** 2–3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 11/01/08)

Increased mortality. In March 2007, the FDA[1] issued an alert advising that an open-label, randomised study comparing linezolid to vancomycin, oxacillin, or dicloxacillin in the treatment of seriously ill patients with intravascular catheter-related bloodstream infections, including catheter-site infections, had found that death rates were significantly higher in patients treated with linezolid (78 of 363) than in the comparator arm (58 of 363), particularly in those with Gram-negative or mixed infections. Mortality did not differ for patients with purely Gram-positive infections.

The FDA[1] and the UK manufacturer[2] therefore advised that linezolid should not be used in infections caused by Gram-negative bacteria and should only be used in mixed Gram-positive and Gram-negative infections when appropriate cover for Gram-negative organisms is given at the same time. Licensed product information now reflects these warnings.

1. FDA. Information for healthcare professionals: linezolid (marketed as Zyvox) (issued 16th March 2007). Available at: http://www.fda.gov/cder/drug/InfoSheets/HCP/linezolidHCP.pdf (accessed 11/01/08)
2. Pfizer, UK. Important safety information (issued 28th February, 2007). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=con2030646&RevisionSelectionMethod=Latest (accessed 11/01/08)

Interactions

Linezolid is a reversible, nonselective MAOI and therefore has the potential to interact with adrenergic and serotonergic drugs. Enhanced pressor activity has been reported in patients receiving linezolid with phenylpropanolamine or pseudoephedrine and initial doses of dopamine or adrenaline should be reduced. There have also been cases of serotonin syndrome when linezolid was taken with serotonin reuptake inhibitors, and similar symptoms when it was taken with dextromethorphan. The interactions of conventional MAOIs, both with other drugs and with foods, are described under Phenelzine, p.417.

Antidepressants. Serotonin syndrome has been reported in patients taking linezolid with serotonergic antidepressants such as venlafaxine (see p.429) and SSRIs (though concomitant use may be possible, see p.396).

Opioid analgesics. For a report of an interaction between linezolid and *pethidine*, attributed to linezolid's inhibitory actions on monoamine oxidase, see p.114.

Antimicrobial Action

Linezolid is an oxazolidinone antibacterial with activity against a range of aerobic Gram-positive bacteria including vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*. It is less active against Gram-negative bacteria, but has some *in-vitro* activity against *Haemophilus influenzae*, *Legionella* spp., *Moraxella catarrhalis* (*Branhamella catarrhalis*), *Neisseria gonorrhoeae*, and *Pasteurella* spp. It is not active against *Acinetobacter* spp., Enterobacteriaceae, or *Pseudomonas* spp.

Oxazolidinone antibacterials are bacteriostatic and act by inhibition of ribosomal protein synthesis. Cross-resistance between oxazolidinones and other classes of antibacterial is considered unlikely.

Resistant strains of enterococci and meticillin-resistant *Staph. aureus* have been reported.

◊ References.

1. Noskin GA, *et al.* In vitro activities of linezolid against important Gram-positive bacterial pathogens including vancomycin-resistant enterococci. *Antimicrob Agents Chemother* 1999; **43:** 2059–62.
2. Cercenado E, *et al.* In vitro activity of linezolid against multiply resistant Gram-positive clinical isolates. *J Antimicrob Chemother* 2001; **47:** 77–81.
3. Gemmell CG. Susceptibility of a variety of clinical isolates to linezolid: a European inter-country comparison. *J Antimicrob Chemother* 2001; **48:** 47–52.
4. Livermore DM. Linezolid in vitro: mechanism and antibacterial spectrum. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii9–ii16.
5. Jones RN, *et al.* Activity of linezolid against 3,251 strains of uncommonly isolated Gram-positive organisms: report from the SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother* 2007; **51:** 1491–3.

Resistance. There have been reports of linezolid resistance in enterococci, involving both *Enterococcus faecium*[1-4] and *E. faecalis*.[2] There is also concern over the emergence of linezolid resistance in staphylococci, such as meticillin-resistant *Staphylococcus aureus*,[5,6] *Staph. auricularis*,[7] and *Staph. epidermidis*.[7,8] A survey[9] of reported resistance to linezolid in the USA found that it was still rare but was no longer limited to enterococci having also occurred in *Staph. epidermidis* and *Streptococcus oralis*.

1. Gonzales RD, *et al.* Infections due to vancomycin-resistant Enterococcus faecium resistant to linezolid. *Lancet* 2001; **357:** 1179.
2. Auckland C, *et al.* Linezolid-resistant enterococci: report of the first isolates in the United Kingdom. *J Antimicrob Chemother* 2002; **50:** 743–6.
3. Herrero IA, *et al.* Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. *N Engl J Med* 2002; **346:** 867–9.
4. Seedat J, *et al.* Rapid emergence of resistance to linezolid during linezolid therapy of an Enterococcus faecium infection. *Antimicrob Agents Chemother* 2006; **50:** 4217–19.
5. Tsiodras S, *et al.* Linezolid resistance in a clinical isolate of Staphylococcus aureus. *Lancet* 2001; **358:** 207–8.
6. Wilson P, *et al.* Linezolid resistance in clinical isolates of Staphylococcus aureus. *J Antimicrob Chemother* 2003; **51:** 186–8.
7. Cieloszyk K, *et al.* Linezolid resistance in three isolates of coagulase-negative staphylococci. *Ann Pharmacother* 2007; **41:** 526–7.
8. Kelly S, *et al.* Linezolid resistance in coagulase-negative staphylococci. *J Antimicrob Chemother* 2006; **58:** 898–9.
9. Mutnick AH, *et al.* Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. *Ann Pharmacother* 2003; **37:** 769–74.

Pharmacokinetics

Linezolid is rapidly and extensively absorbed after oral doses and maximum plasma concentrations are achieved after 1 to 2 hours. It is about 31% bound to plasma proteins. Linezolid is reported to be distributed into bone, fat, lungs, muscle, skin blister fluids, and into the CSF. It is metabolised mainly by oxidation to 2 main inactive metabolites, the hydroxyethyl glycine metabolite (PNU-142586) and the aminoethoxyacetic acid metabolite (PNU-142300); other minor inactive metabolites have also been identified. About 40% of a dose is excreted in the urine as PNU-142586, 30% as linezolid, and 10% as PNU-142300. Small amounts of metabolites are excreted in the faeces. The elimination half-life of linezolid is about 5 to 7 hours.

Children exhibit more rapid clearance of linezolid than adults; half-life is reported to range from about 2 to 4 hours, increasing with age.

◊ References.

1. MacGowan AP. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii17–ii25.
2. Stalker DJ, Jungbluth GL. Clinical pharmacokinetics of linezolid, a novel oxazolidinone antibacterial. *Clin Pharmacokinet* 2003; **42:** 1129–40.
3. Whitehouse T, *et al*. Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother* 2005; **55:** 333–40.

Uses and Administration

Linezolid is an oxazolidinone antibacterial used for the treatment of Gram-positive infections of the skin and respiratory tract, including those due to vancomycin-resistant enterococci and meticillin-resistant *Staphylococcus aureus*.

It is given, orally or by intravenous infusion (over 30 to 120 minutes), in a usual adult dose of 600 mg every 12 hours for 10 to 14 days; treatment for up to 28 days may be necessary if there is vancomycin resistance. In uncomplicated skin and skin structure infections an oral dose of 400 mg every 12 hours for 10 to 14 days is usually sufficient.

For doses in neonates and children, see below.

◊ Reviews.

1. Plouffe JF. Emerging therapies for serious gram-positive bacterial infections: a focus on linezolid. *Clin Infect Dis* 2000; **31**(suppl 4): S144–S149.
2. Perry CM, Jarvis B. Linezolid: a review of its use in the management of serious gram-positive infections. *Drugs* 2001; **61:** 525–51.
3. Bain KT, Wittbrodt ET. Linezolid for the treatment of resistant gram-positive cocci. *Ann Pharmacother* 2001; **35:** 566–75.
4. Paladino JA. Linezolid: an oxazolidinone antimicrobial agent. *Am J Health-Syst Pharm* 2002; **59:** 2413–25.
5. Birmingham MC, *et al*. Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate-use program. *Clin Infect Dis* 2003; **36:** 159–68.
6. Wilcox MH. Efficacy of linezolid versus comparator therapies in Gram-positive infections. *J Antimicrob Chemother* 2003; **51** (suppl S2): ii27–ii35.
7. Falagas ME, *et al*. Linezolid for the treatment of patients with endocarditis: a systematic review of the published evidence. *J Antimicrob Chemother* 2006; **58:** 273–80.
8. Ntziora F, Falagas ME. Linezolid for the treatment of patients with central nervous system infection. *Ann Pharmacother* 2007; **41:** 296–308.
9. Falagas ME, *et al*. Linezolid for the treatment of adults with bone and joint infections. *Int J Antimicrob Agents* 2007; **29:** 233–9.
10. Manfredi R. Le prospettive terapeutiche di linezolid nelle infezioni da patogeni Gram-positivi multiresistenti. *Recenti Prog Med* 2007; **98:** 143–54.
11. Falagas ME, *et al*. Linezolid versus glycopeptide or beta-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials. *Lancet Infect Dis* 2008; **8:** 53–66.

Administration in children. UK licensed product information does not recommend the use of linezolid in children and adolescents below 18 years of age. However, the *BNFC* suggests the following doses of linezolid in the treatment of pneumonia or *complicated* skin and soft-tissue infections, given orally or by intravenous infusion over 30 to 120 minutes:

- neonates up to 7 days old: 10 mg/kg every 12 hours, increasing to every 8 hours if response is poor
- 7 days to 12 years of age: 10 mg/kg (to a maximum of 600 mg) every 8 hours
- 12 to 18 years: usual adult doses (see above).

Similar doses are licensed in the USA. US licensed product information also suggests that in the treatment of *uncomplicated skin* and *skin structure* infections, oral doses given every 12 hours are sufficient in those aged 5 to 11 years.

Further references.

1. Cuzzolin L, Fanos V. Linezolid: a new antibiotic for newborns and children? *J Chemother* 2006; **18:** 573–81.
2. Velissariou IM. Use of linezolid in children: an overview of recent advances. *Expert Rev Anti Infect Ther* 2006; **4:** 947–52.

Administration in renal impairment. Linezolid should be used with caution in patients with renal impairment (creatinine clearance less than 30 mL/minute). Although no dosage adjustment is required, licensed product information states that peak plasma concentrations of linezolid's two major metabolites were about tenfold higher in such patients after several days of treatment. As about 30% of a dose is removed during 3 hours of haemodialysis it is recommended that linezolid should be given after dialysis.

Mycobacterial infections. A systematic review[1] noted that linezolid has been used with some success as an adjunct in the treatment of multidrug-resistant tuberculosis (p.196); it has also been tried in nontuberculous mycobacterial infections (p.181). However, serious adverse effects such as peripheral or optic neuropathy (in 11 of 24 patients), and anaemia (10 of 24) were observed. The review concluded that although there was limited evidence suggesting linezolid may be effective as second-line adjunct therapy for patients with mycobacterial infections, its usefulness is limited by the frequent potentially severe complications of prolonged linezolid use.

1. Ntziora F, Falagas ME. Linezolid for the treatment of patients with mycobacterial infections: a systematic review. *Int J Tuberc Lung Dis* 2007; **11:** 606–11. Correction. *ibid.*; 936. (title change)

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Zyvox; ***Austral.:*** Zyvox; ***Austria:*** Zyvoxid; ***Belg.:*** Zyvoxid; ***Braz.:*** Zyvox; ***Canad.:*** Zyvoxam; ***Chile:*** Zyvox; ***Cz.:*** Zyvoxid; ***Denm.:*** Zyvoxid; ***Fin.:*** Zyvoxid; ***Fr.:*** Zyvoxid; ***Ger.:*** Zyvoxid; ***Gr.:*** Zyvoxid; ***Hong Kong:*** Zyvox; ***Hung.:*** Zyvox†; Zyvoxid†; ***India:*** Linospan; Linox; Lizolid; ***Indon.:*** Zyvox; ***Irl.:*** Zyvox; ***Israel:*** Zyvoxid; ***Ital.:*** Zyvoxid; ***Malaysia:*** Zyvox; ***Mex.:*** Zyvoxam; ***Neth.:*** Zyvoxid; ***Norw.:*** Zyvoxid; ***NZ:*** Zyvox; ***Philipp.:*** Zyvox; ***Pol.:*** Zyvoxid; ***Port.:*** Zyvoxid; ***Rus.:*** Zyvox (Зивокс); ***S.Afr.:*** Zyvoxid; ***Singapore:*** Zyvox; ***Spain:*** Zyvoxid; ***Swed.:*** Zyvoxid; ***Switz.:*** Zyvoxid; ***Thai.:*** Zyvox; ***UK:*** Zyvox; ***USA:*** Zyvox; ***Venez.:*** Zyvox.

Lomefloxacin Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de lomefloxacino; Lomefloksasiinihydrokloridi; Lomefloksasin Hidroklorür; Loméfloxacine, Chlorhydrate de; Lomefloxacinhydroklorid; Lomefloxacini Hydrochloridum; NY-198; SC-47111; SC-47111A (lomefloxacin). (*RS*)-1-Ethyl-6,8-difluoro-1,4-dihydro-7-(3-methylpiperazin-1-yl)-4-oxoquinoline-3-carboxylic acid hydrochloride.

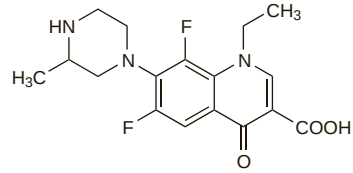
Ломефлоксацина Гидрохлорид

$C_{17}H_{19}F_2N_3O_3,HCl$ = 387.8.

CAS — 98079-51-7 (lomefloxacin); 98079-52-8 (lomefloxacin hydrochloride).

ATC — J01MA07; S01AX17.

ATC Vet — QJ01MA07; QS01AX17.



(lomefloxacin)

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

A relatively high incidence of phototoxic reactions has been seen in patients taking lomefloxacin. Patients should be advised to avoid exposure to sunlight during, and for a few days after, lomefloxacin therapy, and to stop the drug immediately if phototoxicity occurs. Risk of phototoxicity may be reduced by taking lomefloxacin in the evening.

Effects on the skin. Lomefloxacin has been associated with a higher incidence of phototoxic reactions, particularly in patients over 60 years of age and/or with a history of fluoroquinolone treatment; the incidence was also high when used for 30 days or longer.[1] Experimental results[2] suggest that use of sunscreens to protect against lomefloxacin-induced phototoxicity may be feasible.

1. Arata J, *et al*. Photosensitivity reactions caused by lomefloxacin hydrochloride: a multicenter survey. *Antimicrob Agents Chemother* 1998; **42:** 3141–5.
2. Reinhardt P, *et al*. Broad-spectrum sunscreens prevent the secretion of proinflammatory cytokines in human keratinocytes exposed to ultraviolet A and phototoxic lomefloxacin. *Can J Physiol Pharmacol* 2006; **84:** 221–6.

Interactions

As for Ciprofloxacin, p.246.

Lomefloxacin does not appear to interact significantly with theophylline or caffeine.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Most streptococci, including *Streptococcus pneumoniae*, are relatively resistant to lomefloxacin.

Pharmacokinetics

Lomefloxacin is rapidly and almost completely absorbed after oral doses with peak plasma concentrations of about 3 micrograms/mL occurring about 1.5 hours after a 400-mg dose. Lomefloxacin is about 10% bound to plasma proteins. It is widely distributed into body tissues including the lungs and prostate.

The elimination half-life of lomefloxacin is about 7 to 8 hours, and is prolonged in patients with renal impairment. Lomefloxacin is excreted in the urine, about 65% as unchanged drug, 9% as the glucuronide, and less than 0.5% as other metabolites. Small amounts (about 10%) are also eliminated unchanged in the faeces. Negligible amounts of lomefloxacin are removed by haemodialysis or peritoneal dialysis.

◊ References.

1. Freeman CD, *et al*. Lomefloxacin clinical pharmacokinetics. *Clin Pharmacokinet* 1993; **25:** 6–19.

Uses and Administration

Lomefloxacin is a fluoroquinolone antibacterial with actions and uses similar to those of ciprofloxacin (p.247).

It is given orally for the treatment of susceptible infections, including bronchitis due to *Haemophilus influenzae* or *Moraxella catarrhalis* (*Branhamella catarrhalis*), and urinary-tract infections. It is also used for surgical infection prophylaxis. Lomefloxacin is given as the hydrochloride but doses are expressed in terms of the base; lomefloxacin hydrochloride 441.5 mg is equivalent to about 400 mg of lomefloxacin. The usual dose is 400 mg once daily for 10 to 14 days. A dose of 400 mg once daily for 3 days is suitable in women with acute uncomplicated cystitis. Dosage in the evening may minimise the risk of phototoxic reactions.

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

A single dose of 400 mg is used for surgical infection prophylaxis, given 1 to 6 hours before the procedure.

Lomefloxacin is also used topically as the hydrochloride in eye drops and ear drops containing the equivalent of 0.3% of lomefloxacin for the treatment of bacterial conjunctivitis and for the treatment of otitis externa and otitis media, respectively.

◊ General references.

1. Wadworth AN, Goa KL. Lomefloxacin: a review of its antibacterial activity, pharmacokinetic properties and therapeutic use. *Drugs* 1991; **42:** 1018–60.
2. Neu HC, ed. Lomefloxacin: development of a once-a-day quinolone. *Am J Med* 1992; **92** (suppl 4A): 1S–137S.

Administration in renal impairment. Dosage of lomefloxacin should be reduced in patients with renal impairment; the initial dose of 400 mg should be followed by maintenance doses of 200 mg daily in those with a creatinine clearance of 10 to 40 mL/minute per 1.73m^2 and in those on haemodialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Okacin; ***Austria:*** Okacin; Uniquin; ***Belg.:*** Okacin; ***Braz.:*** Maxaquin; Meflox†; Okacin†; ***Chile:*** Okacin†; ***Cz.:*** Maxaquin†; Okacin; ***Denm.:*** Okacin; ***Fin.:*** Okacin; ***Fr.:*** Decalogiflox; Logiflox; ***Ger.:*** Okacin; ***Gr.:*** Okacin; ***Hong Kong:*** Lomeflox; Maxaquin; Okacin; ***Hung.:*** Okacin; ***India:*** Lomef; Lomflox; Ontop; ***Israel:*** Okacin; ***Ital.:*** Chimono; Lomebact; Maxaquin; Okacin; Uniquin; ***Jpn:*** Lomeflon; ***Malaysia:*** Lomaday†; Okacin†; ***Mex.:*** Lomacin; Maxaquin; ***Philipp.:*** Okacin; ***Pol.:*** Okacin; ***Port.:*** Basab†; Floxaquil†; Loransil; Loxina†; Maxaquin; Monoquin†; Okacin; Uniquin; ***Rus.:*** Ksenakvin (Ксенаквин); Lomflox (Ломфлокс); Maxaquin (Максаквин)†; Okacin (Окацин); ***S.Afr.:*** Maxaquin; Okacyn; Uniquin; ***Singapore:*** Lomflox; Okacin; ***Spain:*** Ocacin; ***Switz.:*** Maxaquin; Okacin; ***Thai.:*** Maxaquin†; Okacin; ***Turk.:*** Okacin; ***UAE:*** Lomax; ***USA:*** Maxaquin; ***Venez.:*** Liexina†; Loflox; Lomaday†; Lomex; Maxaquin; Okacin.

Multi-ingredient: ***Rus.:*** Lomecomb (Ломекомб); Protiocomb (Протиокомб).

Loracarbef *(BAN, USAN, rINN)*

KT-3777; Loracarbefum; Lorakarbef; Lorakarbefi; LY-163892. (6*R*,7*S*)-3-Chloro-8-oxo-7-D-phenylglycylamino-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid monohydrate.

Лоракарбеф

$C_{16}H_{16}ClN_3O_4,H_2O$ = 367.8.

CAS — 76470-66-1 (anhydrous loracarbef); 121961-22-6 (loracarbef monohydrate).

ATC — J01DC08.

ATC Vet — QJ01DC08.

Pharmacopoeias. In *US*.

USP 31 (Loracarbef). pH of a 10% suspension in water is between 3.0 and 5.5. Store in airtight containers.

Adverse Effects and Precautions

Adverse effects of loracarbef are generally similar to those of other beta lactams (see Benzylpenicillin, p.213, and Cefalotin, p.219). They include gastrointestinal disturbances, particularly diarrhoea, and hypersensitivity reactions such as skin rashes. In-