Preparations

USP 31: Kanamycin Injection: Kanamycin Sulfate Capsules.

Proprietary Preparations (details are given in Part 3)

Arg.: Cristalomicina; Ger.: Kan-Ophtal; Kana-Stulln; Kanamytrex; India: Kancin; Kaycin; Indon.: Kanabiotic; Kanarco; Kanoxin; Ital.: Keimicina; Maysic: Kancin; Mex.: Cancina; Kanacil†; Kanadrex‡; Kanapat; Kartrex; Randikan†; Solkan; Sulmyn; Singapore: Kancin-L; Kancin†; Spain: Kantrex†
Thai.: Anbikan; Kan-Mycin†; Kancin; Kangen; KMIH; USA: Kantrex; Venez.: Kanacv†; Kantrex

Multi-ingredient: Arg.: Cristalomicina; Fr.: Sterimycine†; Ital.: Derma-flogil; S.Afr.: Kantrexil; Spain: Kanafosal; Kanafosal Predni; Kanapomada; Naso Pekamin; Thal.: KA-Cilone; Venez.: Kanasone†; Monosulpa; Rinomax.

Kitasamycin (BAN, USAN, rINN)

Kitasamicina; Kitasamycine; Kitasamycinum; Leucomycin.

Китазамицин

CAS — 1392-21-8 (kitasamycin); 37280-56-1 (kitasamycin tartrate); 178234-32-7 (acetylkitasamycin). ATC Vet — QJ01FA93.

OH
HC
OR

Kitasamycin A: R=H
Kitasamycin A: R=COCH

Pharmacopoeias. In Chin. and Jpn.

Jpn also includes Acetylkitasamycin and Kitasamycin Tartrate.

Profile

Kitasamycin is a macrolide antibacterial produced by *Streptomyces kitasatoensis*, consisting mainly of kitasamycins A_4 and A_5 . It has actions and uses similar to those of erythromycin (p.269) and has been given orally as the base or intravenously as the tartrate in the treatment of susceptible infections. Acetylkitasamycin has also been given orally.

Kitasamycin has been added to animal feeding stuffs as growth promotors for pigs.

Latamoxef Disodium (BANM, rINNM)

Latamoksefidinatrium; Latamoxef disódico; Latamoxef Disodique; Latamoxefdinatrium; Latamoxefum Dinatricum; LY-127935; Moxalactam Disodium (USAN); 6059-S. (7R)-7-[2-Carboxy-2-(4-hydroxyphenyl)acetamido]-7-methoxy-3-(1-methyl-1H-tetrazol-5-ylthiomethyl)-1-oxa-3-cephem-4-carboxylic acid, disodium salt.

Динатрий Латамоксеф

 $C_{20}H_{18}N_6Na_2O_9S = 564.4.$

CAS — 64952-97-2 (latamoxef); 64953-12-4 (latamoxef disodium).

ATC — JOIDDO6.

ATC Vet — QJ01DD06.

Pharmacopoeias. In Jpn.

Profile

Latamoxef is an oxacephalosporin antibacterial that has been given intramuscularly or intravenously as the disodium salt in the treatment of susceptible infections. It differs from the cephalosporins in that the sulfur atom of the 7-aminocephalosporanic acid nucleus is replaced by oxygen. Like cefamandole (p.220) it has an N-methylthiotetrazole side-chain and may cause hypoprothrombinaemia. Serious bleeding episodes have been reported with latamoxef and prophylaxis with vitamin K and monitoring of bleeding time have been recommended during treatment. In addition to hypoprothrombinaemia, inhibition of platelet function and more rarely immune-mediated thrombocytopenia may be responsible for interference with haemostasis. As with the methylthiotetrazole-containing cephalosporins, a disulfiram-like reaction with alcohol may occur.

Latamoxef has antimicrobial activity similar to that of the thirdgeneration cephalosporin cefotaxime (p.228), although it is generally less active against Gram-positive bacteria and more active against Bacteroides fragilis.

Breast feeding. The authors of a pharmacokinetic study¹ in 8 lactating women given latamoxef cautioned that there was a possibility of colonisation of the infant's bowel with Gram-positive bacteria and in consequence a risk of enterocolitis. They therefore advised against breast feeding during maternal use of the drug. However, no adverse effects have been seen in breast-fed

infants whose mothers were receiving latamoxef, and the American Academy of Pediatrics considers² that it is therefore usually compatible with breast feeding.

- Miller RD, et al. Human breast milk concentration of moxalactam. Am J Obstet Gynecol 1984; 148: 348–9.
- 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 27/05/04)

Preparations

Proprietary Preparations (details are given in Part 3)

Levofloxacin (BAN, USAN, rINN)

DR-3355; HR-355; Levofloksasiini; Levofloksasin; Lévofloxacine; Levofloxacino; Levofloxacinum; S-(-)-Ofloxacin; RWJ-25213. (-)-(S)-9-Fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7*H*-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

Левофлоксацин

 $C_{18}H_{20}FN_3O_4 = 361.4.$

CAS — 100986-85-4 (levofloxacin); 138199-71-0 (levofloxacin hemihydrate).

ATC — JOIMA12; SOIAX19.

ATC Vet — QJ01MA12; QS01AX19.

Adverse Effects and Precautions

As for Ciprofloxacin, p.244.

Symptomatic hyperglycaemia and/or hypoglycaemia have been reported, usually in diabetics who are also taking hypoglycaemics or insulin. Such patients should have their blood-glucose concentrations closely monitored and if signs or symptoms of glucose disturbances develop, levofloxacin should be stopped.

Effects on glucose metabolism. See also under Gati-floxacin, p.281.

Interactions

As for Ciprofloxacin, p.246.

Use of levofloxacin with drugs that alter blood-glucose concentrations increases the risk of blood-glucose disturbances.

Levofloxacin does not appear to interact significantly with theophylline or ciclosporin.

Antimicrobial Action

As for Ciprofloxacin, p.246.

Levofloxacin is generally considered to be about twice as active as ofloxacin (p.310), the racemic substance. Levofloxacin has a broad spectrum of activity which includes Gram-positive bacteria.

♦ References.

 Brown DFJ, et al., eds. Levofloxacin: an extended spectrum 4quinolone agent. J Antimicrob Chemother 1999; 43 (suppl C): 1–90.

Pharmacokinetics

Levofloxacin is rapidly and almost completely absorbed after oral doses with peak plasma concentrations occurring within 1 to 2 hours. It is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor. Levofloxacin is about 30 to 40% bound to plasma proteins. Only small amounts are metabolised, to inactive metabolites. The elimination half-life of levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted

largely unchanged, primarily in the urine with less than 5% as metabolites. It is not removed by haemodialysis or peritoneal dialysis.

♦ References.

- Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. Clin Pharmacokinet 1997; 32: 101–19.
- Piscitelli SC, et al. Pharmacokinetics and safety of high-dose and extended-interval regimens of levofloxacin in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 1999; 43: 2323–7.

Uses and Administration

Levofloxacin is the S-(-)-isomer of the fluoroquinolone antibacterial ofloxacin (p.310). It is given orally, or by intravenous infusion as a 5 mg/mL solution over 30 to 90 minutes, to treat susceptible infections including tuberculosis (but see under Uses and Administration of Ciprofloxacin, p.248). Levofloxacin is given as the hemihydrate but doses are expressed in terms of the base; levofloxacin hemihydrate 256 mg is equivalent to about 250 mg of levofloxacin. Usual doses range from 250 to 500 mg once or twice daily for 7 to 14 days depending on the severity and nature of the infection. A dose of 250 mg once daily for 3 days may be given for uncomplicated urinary-tract infections. A 28-day course of treatment with a dose of 500 mg once daily should be given for chronic bacterial prostatitis. In the USA, doses of 750 mg once daily for 7 to 14 days may be used for complicated skin infections and for hospital-acquired pneumonia; a shorter course of 750 mg once daily for 5 days may be given for community-acquired pneumonia, acute bacterial sinusitis, complicated urinary-tract infections, and acute pyelonephritis. A 60-day course of treatment with a dose of 500 mg once daily is also licensed in the USA for treatment and postexposure prophylaxis of inhalation anthrax.

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

Levofloxacin is also used topically as the hemihydrate in eye drops. A solution containing the equivalent of 0.5% of levofloxacin is used for the treatment of bacterial conjunctivitis and 1.5% for corneal ulcers caused by susceptible strains of bacteria.

♦ Reviews.

- Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; 4: 677–700.
- Martin SJ, et al. Levofloxacin and sparfloxacin: new quinolone antibiotics. Ann Pharmacother 1998; 32: 320–36.
- Martin SJ, et al. A risk-benefit assessment of levofloxacin in respiratory, skin and skin structure, and urinary tract infections. *Drugs* 2001; 24: 199–222.
- Croom KF, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 2003: 63: 2769–2802.
- Anderson VR, Perry CM. Levofloxacin: a review of its use as a high-dose, short-course treatment for bacterial infection. *Drugs* 2008; 68: 535–65.

Administration in children. Since fluoroquinolones can cause degenerative changes in weight-bearing joints of young animals they should only be used in children and adolescent where their use may be justified if the benefits outweigh the risks. Although levofloxacin is not licensed for use in this age group in either the UK or USA, a pharmacokinetic study¹ has suggested that the following doses would be needed:

- · children 5 years of age and older, 10 mg/kg daily
- infants and children from 6 months to less than 5 years of age, 10 mg/kg every 12 hours
- 1. Chien S, et al. Levofloxacin pharmacokinetics in children. J Clin Pharmacol 2005; **45:** 153–60.

Administration in renal impairment. Although initial doses (see above) remain unchanged in patients with renal impairment, subsequent doses of levofloxacin should be adjusted according to creatinine clearance (CC).

In the UK, the following doses are recommended:

- CC 20 to 50 mL/minute: subsequent doses are halved
- CC 10 to 19 mL/minute: subsequent doses are reduced to onequarter of the usual dose; a regimen of 250 mg daily should be reduced to 125 mg every 48 hours
- CC less than 10 mL/minute (including haemodialysis and continuous peritoneal dialysis patients): usual doses of 250 mg or 500 mg daily are reduced to 125 mg every 48 or 24 hours respectively; a regimen of 500 mg twice daily is reduced to 125 mg every 24 hours

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.
- Gisbert JP, et al. First-line triple therapy with levofloxacin for Helicobacter pylori eradication. Aliment Pharmacol Ther 2007; 26: 495–500.
- Rispo A, et al. Levofloxacin in first-line treatment of Helico-bacter 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; C.: Oftaquix; Tavanic; Denm.: Oftaquix; Fin.: Oftaquix; Tavanic; Fr.: Tavanic; Ger.: Ger.: Tavanic; Ger.: Ge Tavanic; Indon.: Armolev, Cravit; Cravox, Difloxin; Farlev, Lefos, Levocin; Levores; Levovid; Levoxal; Lexa; Lovequin; Mosardal; Nislev; Nufalev, Prolecin; Prolevox; Reskuin; Rinvox; Tevox; Volequin; Voxin; Inl.: Tavanic; Israel: Levo; Tavanic; Israel: Levo; Tavanic; Israel: Levo; Tavanic; Israel: Levosci, Mex.: Eleguine; Ran-Levo; Tavanic; Neth.: Oftaquix; Prixar; Tavanic; Philipp.: Floxel; Levox; Oftaquix; Pol.: Oftaquix, Port.: Oftaquix; Rus.: Lefoxin (Λeφοκιμν+ί); Tavanic; Tasanic; Singapore: Cravit; Spain: Tavanic; Swed.: Oftaquix; Tavanic; Switz.: Tavanic; Thal.: Cravit; Lefoxin; Turk.: Cravit; Tavanic; UAE: Jenoquine; UK: Oftaquix; Tavanic; USA: Iquix; Levaquin; Quixin; Venez.: Levaquin; Proxime: Tavanic; Vaixin; vaguin: 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-[(2S,4R)-1-methyl-4-propylprolyl]- I-thio-α-D-erythro-D-galacto-octopyranoside.

Линкомишин

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

CAS — 154-21-2. ATC - 101 FF02. 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

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

CAS — 859-18-7 (anhydrous lincomyciii liyalocii. 7179-49-9 (lincomycin hydrochloride, monohydrate). 859-18-7 (anhydrous lincomycin hydrochloride); ATC — JOIÈFO2.

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 crossresistance 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

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

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†; Lincociax†; 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; Pritaline; Tamcocin; Tismamisin; Zumalin; Ral.: Lincocin; Malaysia: Linco; Lincos; Medoglycin; Mex.: Libiocid; Limidras; Linbac; Lincocin; Lincopar; Lincover; Lisonin; Princol; Rimsalin; Yectolin; Philipp.: Adlyns; Lincocin; Pol.: Lincocin; Neloren; Port.: Lincocina; Rus.: Neloren (Нелорен); S.Afr.: Lincocin; Singapore: Lincocin; Spain; Cillimicina; Lincocin; Thai.: Linco; Lincocilin; Lincocin; Lincogin†; Lincolan; Lincomax; Lincomay†; Lincono; Lingo; Linmycin; Utolincomycin; Turk.: Lincocin; Lincomed; Linkoles; Linkosol; Linosin; USA: Lincocin; Lincorex†; Venez.: Bekalen†; Formicina;

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 - 101XX08.

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.