Josamycin *(BAN, USAN, rINN)*

EN-141; Josamicina; Josamicinas; Josamycine; Josamycinum; Josamysiini; Jozamicin; Leucomycin A_3. A stereoisomer of 7-(formylmethyl)-4,10-dihydroxy-5-methoxy-9,16-dimethyl-2-oxo-oxacyclohexadeca-11,13-dien-6-yl 3,6-dideoxy-4-*O*-(2,6-dideoxy-3-*C*-methyl-α-L-*ribo*-hexopyranosyl)-3-(dimethylamino)-β-D-glucopyranoside 4′-acetate 4″-isovalerate.

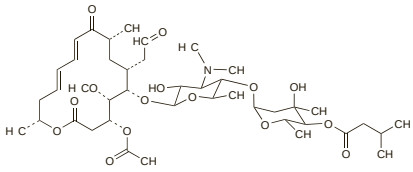
Джозамицин

$C_{42}H_{69}NO_{15}$ = 828.0.

CAS — 16846-24-5; 56689-45-3.

ATC — J01FA07.

ATC Vet — QJ01FA07.



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

Ph. Eur. 6.2 (Josamycin). A macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic powder. It contains a minimum of 900 units/mg calculated with reference to the dried substance. Very slightly soluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Josamycin Propionate *(BANM, rINNM)*

Josamicino propionatas; Josamycine, propionate de; Josamycini propionas; Josamycinpropionat; Josamycin-propionát; Josamysiinipropionaatti; Jozamicin-propionát; Propionato de josamicina; YS-20P. Josamycin 10-propionate.

Джозамицина Пропионат

$C_{45}H_{73}NO_{16}$ = 884.1.

CAS — 56111-35-4; 40922-77-8.

ATC — J01FA07.

ATC Vet — QJ01FA07.

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

Ph. Eur. 6.2 (Josamycin Propionate). It is derived from a macrolide antibiotic produced by certain strains of *Streptomyces narbonensis* var. *josamyceticus* var. *nova*, or obtained by any other means. A white or slightly yellowish, slightly hygroscopic, crystalline powder. It contains a minimum of 843 units/mg, calculated with reference to the dried substance. Practically insoluble in water; soluble in acetone; freely soluble in dichloromethane and in methyl alcohol. Store in airtight containers.

Adverse Effects and Precautions

As for Erythromycin, p.270. Josamycin is reported to produce less gastrointestinal disturbance than erythromycin.

Oedema. A report of josamycin-induced oedema of the foot.[1]

1. Bosch X, *et al.* Josamycin-induced pedal oedema. *BMJ* 1993; **307:** 26.

Interactions

For a discussion of drug interactions of macrolide antibacterials, see Erythromycin, p.271.

Cytochrome P450 isoenzymes. Josamycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore interact less than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The general absence of an interaction between josamycin and theophylline would appear to support this.

Antimicrobial Action

As for Erythromycin, p.271. Some reports suggest that josamycin may be more active against some strains of anaerobic species such as *Bacteroides fragilis*.

Uses and Administration

Josamycin is a macrolide antibacterial with actions and uses similar to those of erythromycin (p.272). It is given orally as the base or the propionate but doses are expressed in terms of the base; 1.07 g of josamycin propionate is equivalent to about 1 g of josamycin. Usual doses in the treatment of susceptible infections are the equivalent of 1 to 2 g of josamycin daily in 2 or more divided doses.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Josalid; ***Fr.:*** Josacine; ***Ger.:*** Wilprafen†; ***Hung.:*** Wilprafen†; ***Ital.:*** Iosalide; Josaxin†; ***Jpn:*** Josamy; ***Rus.:*** Wilprafen (Вильпрафен); ***Spain:*** Josamina.

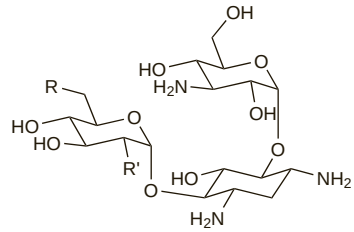
Multi-ingredient: ***Ital.:*** Corti-Fluoral.

Kanamycin Acid Sulfate

Kanamicina, sulfato ácido de; Kanamicino rūgštusis sulfatas; Kanamycin Acid Sulphate *(BANM)*; Kanamycin sulfát kyselý; Kanamycine, sulfate acide de; Kanamycini sulfas acidus; Kanamycinsyrasulfat; Kanamysiinihapposulfaatti; Savanyú kanamicin-szulfát.

ATC — A07AA08; J01GB04; S01AA24.

ATC Vet — QA07AA08; QJ01GB04; QS01AA24.



	R	R'
Kanamycin A	NH_2	OH
Kanamycin B	NH_2	NH_2
Kanamycin C	OH	NH_2

(kanamycin)

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

Ph. Eur. 6.2 (Kanamycin Acid Sulphate). A form of kanamycin sulfate prepared by adding sulfuric acid to a solution of kanamycin sulfate and drying by a suitable method. A white or almost white, hygroscopic powder containing not less than 670 units/mg and 23 to 26% of sulfate, calculated with reference to the dried material. Soluble 1 in about 1 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 5.5 to 7.5.

Kanamycin Sulfate *(rINNM)*

Kanamicin-monoszulfát; Kanamicino monosulfatas; Kanamycin A Sulphate; Kanamycin monosulfát monohydrát; Kanamycin Monosulphate; Kanamycin Sulphate *(BANM)*; Kanamycine, monosulfate de; Kanamycine, Sulfate de; Kanamycini monosulfas; Kanamycini Monosulfas Monohydricus; Kanamycini Sulfas; Kanamycinmonosulfat; Kanamycyny siarczan; Kanamysiinimonosulfaatti; Sulfato de kanamicina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine sulphate monohydrate.

Канамицина Сульфат

$C_{18}H_{36}N_4O_{11},H_2SO_4,H_2O$ = 600.6.

CAS — 59-01-8 (kanamycin); 25389-94-0 (anhydrous kanamycin sulfate).

ATC — A07AA08; J01GB04; S01AA24.

ATC Vet — QA07AA08; QJ01GB04; QS01AA24.

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

Jpn includes the anhydrous substance.

Ph. Eur. 6.2 (Kanamycin Monosulphate; Kanamycin Sulphate BP 2008). The sulfate of an antimicrobial substance produced by the growth of certain strains of *Streptomyces kanamyceticus*. A white or almost white, crystalline powder containing not less than 750 units/mg and 15.0 to 17.0% of sulfate, calculated with reference to the dried material. Soluble 1 in about 8 of water; practically insoluble in alcohol and in acetone. A 1% solution in water has a pH of 6.5 to 8.5.

USP 31 (Kanamycin Sulfate). A white, odourless crystalline powder. It has a potency equivalent to not less than 750 micrograms of kanamycin per mg, calculated on the dried basis. Freely soluble in water; insoluble in acetone, in ethyl acetate, and in benzene. pH of a 1% solution in water is between 6.5 and 8.5. Store in airtight containers.

Incompatibility. For discussion of the incompatibility of aminoglycosides such as kanamycin with beta lactams, see under Gentamicin Sulfate, p.282. Kanamycin is also reported to be incompatible with various other drugs including some other antimicrobials as well as with some electrolytes.

Adverse Effects, Treatment, and Precautions

As for Gentamicin Sulfate, p.282.

For patients given standard regimens, peak plasma concentrations of kanamycin greater than 30 micrograms/mL, and trough concentrations greater than 10 micrograms/mL, should be avoided. Auditory (cochlear) toxicity is more frequent than vestibular toxicity.

Local pain and inflammation, as well as bruising and haematoma, have been reported at the site of intramuscular injections.

Gastrointestinal disturbances and a malabsorption syndrome, similar to that seen with oral neomycin (p.305), have occurred after oral kanamycin. Oral kanamycin should be avoided in patients with gastrointestinal ulceration.

Breast feeding. Although kanamycin is distributed into breast milk[1] the American Academy of Pediatrics states that no adverse effects have been seen in breast-fed infants whose mothers were receiving kanamycin, and therefore considers[2] that its use is usually compatible with breast feeding.

1. Chyo N, *et al.* Clinical studies of kanamycin applied in the field of obstetrics and gynecology. *Asian Med J* 1962; **5:** 265–75.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Interactions

As for Gentamicin Sulfate, p.283.

Antimicrobial Action

As for Gentamicin Sulfate, p.283. It is active against a similar range of organisms although it is not active against *Pseudomonas* spp. Some strains of *Mycobacterium tuberculosis* are sensitive.

Resistance has been reported in strains of many of the organisms normally sensitive to kanamycin, and at one time was widespread, but a decline in the use of kanamycin has meant that resistance has become somewhat less prevalent. Cross-resistance occurs between kanamycin and neomycin, framycetin, and paromomycin, and partial cross-resistance has been reported between kanamycin and streptomycin.

◊ References.

1. Ho YII, *et al.* In-vitro activities of aminoglycoside-aminocyclitols against mycobacteria. *J Antimicrob Chemother* 1997; **40:** 27–32.

Pharmacokinetics

As for Gentamicin Sulfate, p.284.

Less than 1% of an oral dose is absorbed, although this may be significantly increased if the gastrointestinal mucosa is inflamed or ulcerated.

After intramuscular injection peak plasma concentrations of kanamycin of about 20 and 30 micrograms/mL are attained in about 1 hour following doses of 0.5 and 1 g respectively. A plasma half-life of about 3 hours has been reported. Absorption after intraperitoneal instillation is similar to that from intramuscular doses.

Kanamycin is rapidly excreted by glomerular filtration and most of a parenteral dose appears unchanged in the urine within 24 hours. It has been detected in cord blood and in breast milk.

Uses and Administration

Kanamycin is an aminoglycoside antibacterial with actions similar to those of gentamicin (p.284). It has been used in the treatment of susceptible Gram-negative and staphylococcal infections, including gonorrhoea (p.191) and neonatal gonococcal eye infections (p.180), although its use has declined in many centres because of the development of resistance. As with gentamicin it may be used with penicillins and with cephalosporins; the injections should be given at separate sites. Kanamycin has also been used as a second-line drug in tuberculosis (p.196), but other, safer drugs are usually preferred.

The sulfate or acid sulfate salts are often used: in the USA, preparations containing the bisulfate ($C_{18}H_{36}N_4O_{11},2H_2SO_4$), but referred to as the sulfate, are available. Doses are expressed in terms of kanamycin base; 1.2 g of kanamycin sulfate, and 1.34 g of kanamycin acid sulfate, are each equivalent to about 1 g of kanamycin. It is usually given by intramuscular injection, and in acute infections adults may be given 15 mg/kg daily, to a maximum of 1.5 g daily, in 2 to 4 divided doses. The same doses may be given by intravenous infusion of a 0.25 to 0.5% solution over 30 to 60 minutes; in the UK, up to 30 mg/kg daily has been given in 2 or 3 divided doses by this route. Similar doses are used in children. Treatment of acute infections should preferably not continue for longer than 7 to 10 days or exceed a cumulative dose of 10 g kanamycin. A dose of 3 to 4 g weekly, given as 1 g on alternate days or as 1 g twice daily on 2 days each week, has been suggested in the UK for chronic bacterial infections, up to a maximum cumulative dose of 50 g, but prolonged use increases the risk of nephrotoxicity and is not generally recommended.

A single intramuscular dose of 2 g of kanamycin has been used in the treatment of penicillin-resistant gonorrhoea. In the treatment and prophylaxis of neonatal gonococcal infections in infants born to mothers with gonorrhoea, 25 mg/kg, up to a maximum of 75 mg, may be given as a single intramuscular dose.

Peak plasma concentrations greater than 30 micrograms/mL and trough concentrations greater than 10 micrograms/mL should be avoided. It is recommended that dosage should be adjusted in all patients according to plasma-kanamycin concentrations, and this is particularly important where factors such as age, renal impairment, or prolonged therapy may predispose to toxicity, or where there is a risk of subtherapeutic concentrations. For discussion of the methods of calculating aminoglycoside dosage requirements, see Administration and Dosage, under Gentamicin, p.284.

Kanamycin has been used orally similarly to neomycin (p.305), for the suppression of intestinal flora. For pre-operative use, 1 g may be given every hour for 4 hours, then 1 g every 6 hours for 36 to 72 hours. In the management of hepatic encephalopathy, 8 to 12 g daily in divided doses may be given.

Kanamycin has also been given in doses of 250 mg as a nebulised inhalation, 2 to 4 times daily. Solutions of kanamycin 0.25% have been used for the irrigation of body cavities.

Kanamycin tannate has also been used.

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; ***Malaysia:*** Kancin; ***Mex.:*** Cancina; Kanacil†; Kanadrex†; Kanapat; Kantrex; Randikan†; Solkan; Sulmyn; ***Singapore:*** Kancin-L; Kancin†; ***Spain:*** Kantrex†; ***Thai.:*** Anbikan; Kan-Mycin†; Kancin; Kangen; KMH; ***USA:*** Kantrex; ***Venez.:*** Kanacyl†; Kantrex.

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

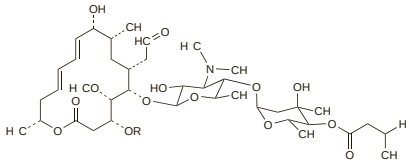
Kitasamycin *(BAN, USAN, rINN)*

Kitasamicina; Kitasamycine; Kitasamycinum; Leucomycin.

Китазамицин

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

ATC Vet — QJ01FA93.



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. (7*R*)-7-[2-Carboxy-2-(4-hydroxyphenyl)acetamido]-7-methoxy-3-(1-methyl-1*H*-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 — J01DD06.

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 third-generation 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 study[1] 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 considers[2] that it is therefore usually compatible with breast feeding.

1. Miller RD, *et al.* Human breast milk concentration of moxalactam. *Am J Obstet Gynecol* 1984; **148:** 348–9.
2. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 27/05/04)

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Shiomarin.

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.

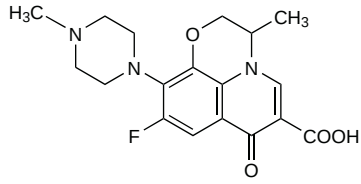
Левофлоксацин

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

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

ATC — J01MA12; S01AX19.

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 Gatifloxacin, 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.

1. Brown DFJ, *et al.*, eds. Levofloxacin: an extended spectrum 4-quinolone 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.

1. Fish DN, Chow AT. The clinical pharmacokinetics of levofloxacin. *Clin Pharmacokinet* 1997; **32:** 101–19.
2. 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.

1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. *Drugs* 1994; **4:** 677–700.
2. Martin SJ, *et al.* Levofloxacin and sparfloxacin: new quinolone antibiotics. *Ann Pharmacother* 1998; **32:** 320–36.
3. 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.
4. 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.
5. 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 adolescents 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 study[1] 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 one-quarter 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