Interactions
As for Tetracycline, p.348.

Antimicrobial Action
As for Tetracycline, p.348.

Demeclocycline is stated to be somewhat more active against certain strains of some organisms including *Neisseria gonorrhoeae* and *Haemophilus influenzae*, as well as to being the most active of the tetracyclines *in vitro* against *Brucella* spp.

Pharmacokinetics
For the general pharmacokinetics of the tetracyclines, see Tetracycline, p.349.

About 60 to 80% of a dose of demeclocycline is absorbed from the gastrointestinal tract. Peak plasma concentrations of about 1.5 to 1.7 micrograms/mL have been reported 3 to 4 hours after a single oral dose of 300 mg, but higher plasma concentrations may be achieved with repeated dosage. Its plasma elimination half-life is about 12 hours, although this may be prolonged in patients with renal impairment; values of 42 to 68 hours have been reported in severe impairment. The renal clearance of demeclocycline is about half that of tetracycline.

Uses and Administration
Demeclocycline is a tetracycline derivative with uses similar to those of tetracycline (p.349). It is excreted more slowly and effective blood concentrations are maintained for a longer period.

Demeclocycline is given orally as the hydrochloride; the usual adult dose is 600 mg daily in 2 or 4 divided doses, preferably 1 hour before or 2 hours after meals. For atypical pneumonia, 900 mg daily in 3 divided doses may be given. It is also sometimes given orally with other tetracycline derivatives.

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

Demeclocycline may also be given to adults in the treatment of chronic hyponatraemia associated with the syndrome of inappropriate antidiuretic hormone secretion, when water restriction has proved ineffective. Initially 900 to 1200 mg is given daily in divided doses, reducing to maintenance doses of 600 to 900 mg daily.

For dosage recommendations in patients with hepatic impairment, see below.

The calcium and magnesium salts of demeclocycline have also been used.

Administration in children. In children, the effects on teeth should be considered and tetracyclines only used when absolutely essential; demeclocycline may be used for the treatment of susceptible infections. In the UK, it is licensed for use in children aged 12 years and over; the usual adult dose (see above) may be given orally. However, in the USA, it may be given to those over 8 years old in usual doses of 7 to 13 mg/kg daily by mouth in 2 or 4 divided doses.

Administration in hepatic impairment. UK licensed product information states that the dosage of demeclocycline should not exceed 1 g daily in patients with known liver disease.

Syndrome of inappropriate ADH secretion. Demeclocycline may be given in the treatment of the syndrome of inappropriate ADH (antidiuretic hormone) secretion (SIADH—p.2182) to antagonise the effect of ADH on the renal tubules; lithium has been given as an alternative. Both lithium and demeclocycline act by interfering with the cellular action of ADH to produce nephrogenic diabetes insipidus. Demeclocycline was reported to be superior to lithium[1] and became the preferred treatment for chronic SIADH if water restriction was unsuccessful,[2] although fluid restriction is probably still the treatment of choice. However, since nephrotoxicity has been reported in patients with cardiac or hepatic disease, the usefulness of demeclocycline in the treatment of hyponatraemic states might be limited; this view was supported by studies in patients with heart failure[3] and cirrhosis.[4]

1. Forrest JN, *et al.* Superiority of demeclocycline over lithium in the treatment of chronic syndrome of inappropriate secretion of antidiuretic hormone. *N Engl J Med* 1978; **298:** 173–7.
2. Schrier RW. Treatment of hyponatremia. *N Engl J Med* 1985; **312:** 1121–2.
3. Zegers de Beyl D, *et al.* Demeclocycline treatment of water retention in congestive heart failure. *BMJ* 1978; **1:** 760.
4. Miller PD, *et al.* Plasma demeclocycline levels and nephrotoxicity: correlation in hyponatremic cirrhotic patients. *JAMA* 1980; **243:** 2513–15.

Preparations
BP 2008: Demeclocycline Capsules;
USP 31: Demeclocycline Hydrochloride Capsules; Demeclocycline Hydrochloride Tablets; Demeclocycline Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Ledermycin†; ***Canad.:*** Declomycin; ***Fr.:*** Ledermycine; ***India:*** Ledermycin; ***Neth.:*** Ledermycin; ***UK:*** Ledermycin; ***USA:*** Declomycin.

Multi-ingredient: ***Austria:*** Ledermix; ***Denm.:*** Ledermix†; ***Ger.:*** Ledermix; ***Israel:*** Ledermix; ***Ital.:*** Rubrociclina†; ***S.Afr.:*** Tritet; ***Switz.:*** Ledermix; ***UK:*** Deteclo†; Ledermix.

Dibekacin Sulfate *(rINNM)*

Dibekacin Sulphate *(BANM)*; Dibékacine, Sulfate de; Dibekacini Sulfas; 3′,4′-Dideoxykanamycin B; Sulfato de dibekacina. 6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-2-deoxy-4-*O*-(2,6-diamino-2,3,4,6-tetradeoxy-α-D-*erythro*-hexopyranosyl)-streptamine sulphate.

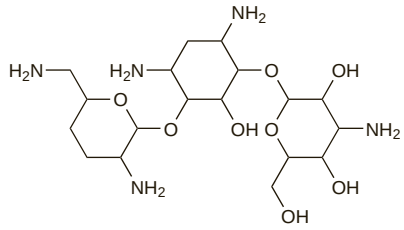
Дибекацина Сульфат

$C_{18}H_{37}N_5O_8.xH_2SO_4$.

CAS — 34493-98-6 (dibekacin); 58580-55-5 (dibekacin sulfate).

ATC — J01GB09.

ATC Vet — QJ01GB09.



(dibekacin)

Pharmacopoeias. In *Jpn.*

Profile
Dibekacin is an aminoglycoside derived from kanamycin with actions and uses similar to those of gentamicin (p.282). It has been given intramuscularly as the sulfate in doses equivalent to dibekacin 1 to 3 mg/kg daily in divided doses. It has also been given in similar doses by slow intravenous infusion. Dosage should be adjusted based on serum-dibekacin concentration monitoring. It has also been used topically for eye infections.

Preparations
Proprietary Preparations (details are given in Part 3)
Belg.: Dikacine†; ***Jpn:*** Panimycin; ***Venez.:*** Dibekan.

Dicloxacillin *(BAN, USAN, rINN)*

BRL-1702; Dicloxacilina; Dicloxacilline; Dicloxacillinum; Diklоksasilliini; Dikloxacillin; R-13423. (6*R*)-6-[3-(2,6-Dichlorophenyl)-5-methylisoxazole-4-carboxamido]penicillanic acid.

Диклоксациллин

$C_{19}H_{17}Cl_2N_3O_5S$ = 470.3.

CAS — 3116-76-5.

ATC — J01CF01.

ATC Vet — QJ01CF01; QJ51CF01.

Dicloxacillin Sodium *(BANM, USAN, rINNM)*

Dicloxacilina sódica; Dicloxacilline sodique; Dicloxacillinum natricum; Dicloxacillinum Natricum Monohydricum; Diklоksacilino natrio druska; Dikloksasilliininatrium; Dikloxacilin sodná sůl monohydrát; Dikloxacillinnatrium; Dikloxacillin-nátrium; Natrii Dicloxacillinum; P-1011. Sodium dicloxacillin monohydrate.

Натрий Диклоксациллин

$C_{19}H_{16}Cl_2N_3NaO_5S,H_2O$ = 510.3.

CAS — 343-55-5 (anhydrous dicloxacillin sodium); 13412-64-1 (dicloxacillin sodium monohydrate).

ATC — J01CF01.

ATC Vet — QJ01CF01.

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

Ph. Eur. 6.2 (Dicloxacillin Sodium). A white or almost white, hygroscopic, crystalline powder. Freely soluble in water; soluble in alcohol and in methyl alcohol. A 10% solution in water has a pH of 5.0 to 7.0. Store at a temperature not exceeding 25° in airtight containers.

USP 31 (Dicloxacillin Sodium). A white to off-white crystalline powder. Freely soluble in water. pH of a 1% solution in water is between 4.5 and 7.5. Store in airtight containers.

Adverse Effects and Precautions
As for Flucloxacillin, p.277.

Effects on the liver. References.

1. Kleinman MS, Presberg JE. Cholestatic hepatitis after dicloxacillin-sodium therapy. *J Clin Gastroenterol* 1986; **8**: 77–8.

Sodium content. Each g of dicloxacillin sodium contains about 2 mmol of sodium.

Interactions
As for Benzylpenicillin, p.214.

Antimicrobial Action
As for Flucloxacillin, p.277.

Pharmacokinetics
Dicloxacillin is better absorbed from the gastrointestinal tract than cloxacillin but absorption is reduced by the presence of food in the stomach. After an oral dose of 500 mg, peak plasma concentrations of 10 to 18 micrograms/mL in about 1 hour have been reported in fasting subjects. Doubling the dose can double the plasma concentration. About 97% of dicloxacillin in the circulation is bound to plasma proteins. Dicloxacillin has been reported to have a plasma half-life of 0.5 to 1 hour. The half-life is prolonged in neonates.

The distribution of dicloxacillin in body tissues and fluids is similar to that of cloxacillin (p.256).

Dicloxacillin is metabolised to a limited extent and the unchanged drug and metabolites are excreted in the urine by glomerular filtration and renal tubular secretion. About 60% of an oral dose is excreted in the urine. Only small amounts are excreted in the bile. Dicloxacillin is not removed by haemodialysis.

Plasma concentrations are enhanced by probenecid. Reduced concentrations have been reported in patients with cystic fibrosis.

Uses and Administration
Dicloxacillin is an isoxazolyl penicillin used similarly to flucloxacillin (p.277) in the treatment of infections due to staphylococci resistant to benzylpenicillin.

Dicloxacillin is given intravenously and orally as the sodium salt. All doses are expressed in terms of the equivalent amount of dicloxacillin; 1.09 g of dicloxacillin sodium is equivalent to about 1 g of dicloxacillin. Oral doses should be taken at least 1 hour before, or 2 hours after, meals since the presence of food in the stomach reduces absorption. The usual adult oral dose is 250 mg every 6 hours. Similar doses may be given by slow intravenous injection or, preferably, by intravenous infusion. Doses may be doubled in severe infections.

Preparations
USP 31: Dicloxacillin Sodium Capsules; Dicloxacillin Sodium for Oral Suspension.

Proprietary Preparations (details are given in Part 3)
Austral.: Diclocil; Dicloxsig; Distaph; ***Denm.:*** Dicillin; Diclocil; ***Fin.:*** Diclocil; ***Ger.:*** InfectoStaph; ***Gr.:*** Diclocil; ***Mex.:*** Amifarin; Antiben; Brispen; Butimaxil; Cilpen; Clobioxal; Dicleophen; Diclo-Tecno; Dicloxaquim; Diluxina; Dipxapen†; Ditterolina; Dixen; Doxil; Pardix; Penclox; Posipen; ***Norw.:*** Diclocil; ***NZ:*** Diclocil; ***Port.:*** Diclocil; ***Swed.:*** Diclocil; ***Thai.:*** Amcidil; Cloxydin; Diclex; Diclocil; Diclocillin; Dicloson; Diclox†; Dicloxia; Dicloxin; Dicloxman†; Dicloxno; Diloxin; Ditum†; Dixocillin; Dorox; Servidiclox†; ***Venez.:*** Diclocil; Diclolak†.

Multi-ingredient: ***Ital.:*** Ampiplus†; Diamplicil†; ***Mex.:*** Ampiclox-D; Anglotex; Brucilina; Diamprex; Doxapen; Panac; Panac K; Pentidix.

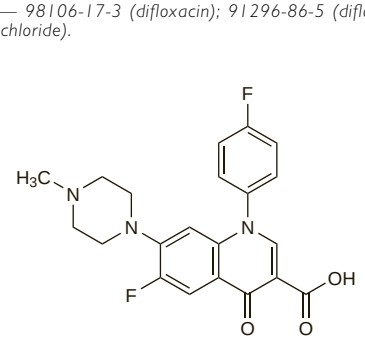
Difloxacin Hydrochloride *(USAN, rINNM)*

A-56619; Abbott-56619; Difloxacine, chlorhydrate de; Difloxacini hydrochloridum; Hidrocloruro de difloxacino. 6-Fluoro-1-(*p*-fluorophenyl)-1,4-dihydro-7-(4-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hydrochloride.

Дифлоксацина Гидрохлорид

$C_{21}H_{19}F_2N_3O_3$,HCl = 435.9.

CAS — 98106-17-3 (difloxacin); 91296-86-5 (difloxacin hydrochloride).



(difloxacin)

Profile
Difloxacin is a fluoroquinolone antibacterial used as the hydrochloride in veterinary medicine for the treatment of susceptible infections in poultry. It was formerly used in humans but was associated with an unacceptable incidence of adverse CNS effects.

Dihydrostreptomycin Sulfate *(rINNM)*

Dihidrosztreptomicin-szulfát; Dihydrostreptomycin sulfát; Dihydrostreptomycin Sulphate *(BANM)*; Dihydrostreptomycine, sulfate de; Dihydrostreptomycini sulfas; Dihydrostreptomycinsulfat; Dihydrostreptomysiinisulfaatti; Sulfato de dihidroestreptomicina. *O*-2-Deoxy-2-methylamino-α-L-glucopyranosyl-(1→2)-*O*-5-deoxy-3-*C*-hydroxymethyl-α-L-lyxofuranosyl-(1→4)-*N*^{1},*N*^{3}-diamidino-D-streptamine sulphate.

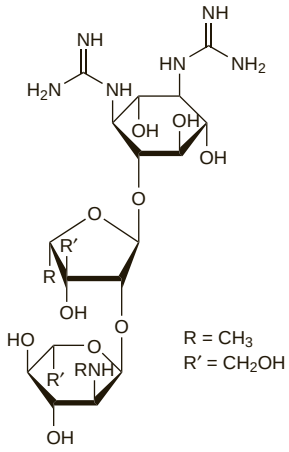
Дигидрострептомицина Сульфат

$(C_{21}H_{41}N_7O_{12})_2,3H_2SO_4$ = 1461.4.

CAS — 128-46-1 (dihydrostreptomycin); 5490-27-7 (dihydrostreptomycin sulfate).

ATC — S01AA15.

ATC Vet — QS01AA15.



(dihydrostreptomycin)

Pharmacopoeias. In *Eur.* (see p.vii) and *US*, both for veterinary use only.
Ph. Eur. 6.2 (Dihydrostreptomycin Sulphate for Veterinary Use; Dihydrostreptomycin Sulphate BP(Vet) 2008). The sulfate of a substance obtained by catalytic hydrogenation of streptomycin or by any other means. The semi-synthetic product is derived from a fermentation product. Stabilisers may be added. A white or almost white, hygroscopic powder. It contains a maximum of 2.0% streptomycin sulfate calculated with reference to the dried drug. Freely soluble in water; practically insoluble in alcohol, in acetone, and in methyl alcohol. A 25% solution in water has a pH of 5.0 to 7.0. Store in airtight containers. Protect from light.
USP 31 (Dihydrostreptomycin Sulfate). A white or almost white amorphous or crystalline powder; the amorphous form is hygroscopic. Freely soluble in water; practically insoluble in acetone, in chloroform, and in methyl alcohol. pH of a solution in water containing the equivalent of dihydrostreptomycin 20% is between 4.5 and 7.0, except that if it is labelled as being solely for oral use, the pH is between 3.0 and 7.0. Store in airtight containers.

Profile
Dihydrostreptomycin is an aminoglycoside antibacterial with actions similar to those of streptomycin (p.333). Since it is more likely than streptomycin to cause partial or complete loss of hearing it is not used parenterally in humans. It is not absorbed after oral doses, and has been given by this route for gastrointestinal infections. It is also used as the sulfate in veterinary medicine.

Preparations

Proprietary Preparations (details are given in Part 3)

Spain: Citrocil.

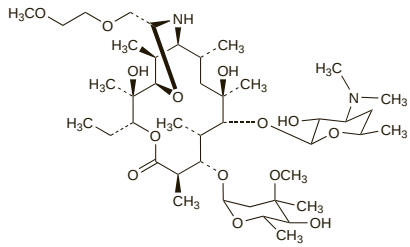
Multi-ingredient: ***Arg.:*** Gemipasmol†; Vagisan; Vagisan Compuesto; ***Mex.:*** Estrefen; ***Spain:*** Cilinafosal Dihidroestreptomicina; Estreptoenterol†; Salitanol Estreptomicina; Sulfintestin Neomicina.

Dirithromycin *(BAN, USAN, rINN)*

ASE-136BS; Dirithromycine; Dirithromycinum; Diritromicin; Diritromicina; Diritromicinas; Diritromisin; Diritromycin; Diritromysiini; LY-237216. (1*R*,2*R*,3*R*,6*R*,7*S*,8*S*,9*R*,10*R*,12*R*,13*S*,15*R*,17*S*)-7-(2,6-Dideoxy-3-*C*,3-*O*-dimethyl-α-L-*ribo*-hexopyranosyloxy)-3-ethyl-2,10-dihydroxy-15-(2-methoxyethoxymethyl)-2,6,8,10,12,17-hexamethyl-9-(3,4,6-trideoxy-3-dimethylamino-β-L-*xylo*-hexopyranosyloxy)-4,16-dioxa-14-azabicyclo[11.3.1]heptadecan-5-one; (9*S*)-9-Deoxo-11-deoxy-9,11-{imino[(1*R*)-2-(2-methoxyethoxy)-ethylidene]oxy}erythromycin.

Диритромицин

$C_{42}H_{78}N_2O_{14}$ = 835.1.
CAS — 62013-04-1.
ATC — J01FA13.
ATC Vet — QJ01FA13.



Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
Ph. Eur. 6.2 (Dirithromycin). A white or almost white powder. It exhibits polymorphism. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.
USP 31 (Dirithromycin). A white or practically white powder. Very slightly soluble in water; very soluble in dichloromethane and in methyl alcohol.

Adverse Effects and Precautions
As for Erythromycin, p.270.

The most frequent adverse effects of dirithromycin are gastrointestinal disturbances; headache has also occurred. Dirithromycin should be used with caution in patients with moderate to severe hepatic impairment since its active metabolite erythromycylamine is primarily eliminated in the bile. It should also be used with caution in those with severe renal impairment.

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

Cytochrome P450 isoenzymes. Dirithromycin is reported to have little or no effect on hepatic cytochrome P450 isoenzymes and may therefore produce fewer interactions than erythromycin with other drugs metabolised by this enzyme system (see Mechanism, under Interactions of Erythromycin, p.271). The lack of interactions between dirithromycin and theophylline, terfenadine, or warfarin would appear to support this.

Antimicrobial Action
As for Erythromycin, p.271.

Dirithromycin is reported to be generally less active than erythromycin *in vitro*, but may show greater activity *in vivo* than is indicated by *in-vitro* studies and may exert a postantibiotic effect.

Pharmacokinetics
Dirithromycin is readily absorbed after oral doses and undergoes rapid non-enzymatic hydrolysis to its active metabolite erythromycylamine. Absorption is enhanced by food. Bioavailability is about 10%. Daily doses of dirithromycin 500 mg produce peak plasma concentrations of erythromycylamine of about 400 nanograms/mL.

Erythromycylamine is widely distributed and tissue concentrations exceed those in plasma. Protein binding is 15 to 30%. Erythromycylamine is mainly excreted unchanged in the bile with only about 2% in the urine. The mean plasma half-life is about 8 hours and the mean urinary terminal elimination half-life is about 44 hours.

Distribution into milk has been found in studies in *rodents*.

◊ References.

1. Sides GD, *et al.* Pharmacokinetics of dirithromycin. *J Antimicrob Chemother* 1993; **31** (suppl C): 65–75.
2. LaBreque D, *et al.* Pharmacokinetics of dirithromycin in patients with impaired hepatic function. *J Antimicrob Chemother* 1993; **32:** 741–50.
3. Mazzei T, *et al.* Pharmacokinetics of dirithromycin in patients with mild or moderate cirrhosis. *Antimicrob Agents Chemother* 1999; **43:** 1556–9.

Uses and Administration
Dirithromycin is a prodrug of the macrolide antibacterial erythromycylamine, which has similar properties to those of erythromycin (p.269) and is used in respiratory-tract, skin, and soft-tissue infections caused by susceptible organisms.

Dirithromycin is given orally as enteric-coated tablets in a usual dose of 500 mg once daily.

◊ References.

1. Various. Dirithromycin: a new once-daily macrolide. *J Antimicrob Chemother* 1993; **31** (suppl C): 1–185.
2. Brogden RN, Peters DH. Dirithromycin: a review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **48:** 599–616.
3. Wintermeyer SM, *et al.* Dirithromycin: a new macrolide. *Ann Pharmacother* 1996; **30:** 1141–9.
4. McConnell SA, Amsden GW. Review and comparison of advanced-generation macrolides clarithromycin and dirithromycin. *Pharmacotherapy* 1999; **19:** 404–15.

Preparations

USP 31: Dirithromycin Delayed-Release Tablets.

Proprietary Preparations (details are given in Part 3)
Belg.: Unibac†; ***Chile:*** Dynabac†; ***Fr.:*** Dynabac; ***Gr.:*** Dynabac†; ***Malaysia:*** Dynabac†; ***Turk.:*** Dynabac; ***USA:*** Dynabac†.

Doripenem *(USAN, rINN)*

Doripénem; Doripenemum; S-4661. (+)-(4*R*5*S*,6*S*)-6-[(1*R*)-1-Hydroxyethyl]-4-methyl-7-oxo-3-({(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl}thio)-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid.

Дорипенем

$C_{15}H_{24}N_4O_6S_2$ = 420.5.
CAS — 148016-81-3.

Adverse Effects and Precautions
As for Imipenem, p.286.

Doripenem is more stable to renal dehydropeptidase I than imipenem and use with cilastatin, which inhibits the enzyme, is not required.

Interactions
Probenecid inhibits the renal excretion of doripenem thereby increasing its plasma concentrations and prolonging its elimination half-life.

Antiepileptics. For reports of decreased plasma-*valproate* concentrations (sometimes with loss of seizure control) attributed to carbapenem antibacterials, see p.510.

Antimicrobial Action
As for Imipenem, p.287,

Doripenem is claimed to have particular activity against *Pseudomonas aeruginosa*.

Pharmacokinetics
After intravenous infusion of doripenem 500 mg over 1 hour, a mean peak plasma concentration of 23 micrograms/mL is attained, falling to 10 micrograms/mL after 1.5 hours and 1 microgram/mL after 6 hours.

Doripenem is less than 10% bound to plasma proteins and is widely distributed into body tissues and fluids. It is metabolised via hydrolysis of its beta-lactam ring by dehydropeptidase I to an open-ringed metabolite (doripenem-M1). The plasma elimination half-life is about 1 hour in adults; the half-life may be prolonged in patients with renal impairment. Doripenem is mainly excreted in the urine by tubular secretion and glomerular filtration. About 70% and 15% of a dose is recovered as unchanged drug and metabolite, respectively, in the urine within 48 hours. Less than 1% is excreted in faeces.

Doripenem is removed by haemodialysis.

Uses and Administration
Doripenem is a carbapenem antibacterial similar to imipenem (p.286). It is more stable to renal dehydropeptidase I than imipenem and need not be given with an enzyme inhibitor such as cilastatin. It is used in the treatment of susceptible infections such as intra-abdominal infections and complicated urinary-tract infections, including pyelonephritis. For details of these infections and their treatment, see under Choice of Antibacterial, p.162.

For treatment of susceptible infections doripenem is given by intravenous infusion over 1 hour, in a usual adult dose of 500 mg every 8 hours. For details of reduced doses in renal impairment, see below.

◊ References.

1. Lister PD. Carbapenems in the USA: focus on doripenem. *Expert Rev Anti Infect Ther* 2007; **5:** 793–809.
2. Poulakou G, Giamarellou H. Doripenem: an expected arrival in the treatment of infections caused by multidrug-resistant Gram-negative pathogens. *Expert Opin Invest Drugs* 2008; **17:** 749–71.
3. Chastre J, *et al.* Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med* 2008; **36:** 1089–96.
4. Lucasti C, *et al.* Efficacy and tolerability of IV doripenem versus meropenem in adults with complicated intra-abdominal infection: a phase III, prospective, multicenter, randomized, double-blind, noninferiority study. *Clin Ther* 2008; **30:** 868–83.

Administration in renal impairment. Doses of doripenem given by intravenous infusion should be reduced in patients with renal impairment according to creatinine clearance (CC):

- CC 30 to 50 mL/minute: 250 mg every 8 hours
- CC greater than 10 to less than 30 mL/minute: 250 mg every 12 hours