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.

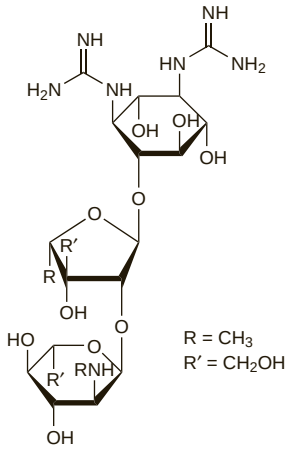
Дигидрострептомицина Сульфат

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

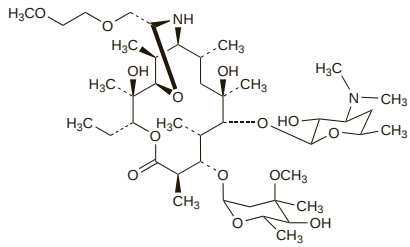
Multi-ingredient: ***Arg.:*** Gemipasmol†; Vagisan; Vagisan Compuesto; ***Mex.:*** Estrefen; ***Spain:*** Cilinafosal Dihidroestreptomicina; Estreptoenterol†; Salitanol Estreptomicina; Sulfintestin Neomicina.

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

Preparations

Proprietary Preparations (details are given in Part 3)
Jpn: Finibax; ***USA:*** Doribax.

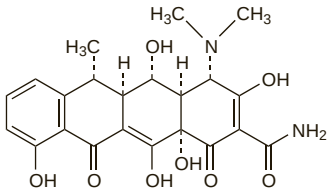
Doxycycline *(BAN, USAN, rINN)*

Doksiciklinas monohidratas; Doksisiklin; Doksisykliini; Doksisykliinimonohydraatti; Doksycyklina; Doxiciclina; Doxiciklin; Doxycyclin; Doxycycline Monohydrate; Doxycycline monohydratée; Doxycyclinum; Doxycyclinum monohydricum; Doxycyklin monohydrát; Doxycyklinmonohydrat; GS-3065. (4*S*,4a*R*,5*S*,5a*R*,6*S*,12a*S*)-4-Dimethylamino-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxonaphthacene-2-carboxamide monohydrate; 6-Deoxy-5β-hydroxytetracycline monohydrate.

Доксициклин

$C_{22}H_{24}N_2O_8,H_2O$ = 462.4.

CAS — 564-25-0 (anhydrous doxycycline); 17086-28-1 (doxycycline monohydrate).
ATC — A01AB22; J01AA02.
ATC Vet — QA01AB22; QJ01AA02.



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

Ph. Eur. 6.2 (Doxycycline Monohydrate). A yellow crystalline powder. Very slightly soluble in water and in alcohol. It dissolves in dilute solutions of mineral acids and in solutions of alkali hydroxides and carbonates. A 1% suspension in water has a pH of 5.0 to 6.5. Store in airtight containers. Protect from light.

USP 31 (Doxycycline). A yellow crystalline powder. Very slightly soluble in water; sparingly soluble in alcohol; practically insoluble in chloroform and in ether; freely soluble in dilute acid and in alkali hydroxide solutions. pH of a 1% suspension in water is between 5.0 and 6.5. Store in airtight containers. Protect from light.

Doxycycline Calcium *(BANM, rINNM)*

Calcii Doxycyclinum; Doxiciclina cálcica; Doxycycline Calcique.

Кальций Доксициклин

ATC — A01AB22; J01AA02.
ATC Vet — QA01AB22; QJ01AA02.

Doxycycline Fosfatex *(BAN, USAN)*

AB-08; DMSC; Doxiciclina fosfatex. 6-Deoxy-5β-hydroxytetracycline—metaphosphoric acid—sodium metaphosphate in the ratio 3:3:1.

$(C_{22}H_{24}N_2O_8)_3(HPO_3)_3NaPO_3$ = 1675.2.

CAS — 83038-87-3.
ATC — A01AB22; J01AA02.
ATC Vet — QA01AB22; QJ01AA02.

Doxycycline Hyclate *(BANM, rINNM)*

Doksiciklino hiklatas; Doksisykliinihyklaatti; Doksycykliny hyklan; Dossiciclina Iclato; Doxiciklin-hiklát; Doxycycline, hyclate de; Doxycycline Hydrochloride; Doxycyclini hyclas; Doxycyklinhyklat; Doxycyklin-hyklát; Hiclato de doxiciclina. Doxycycline hydrochloride hemiethanolate hemihydrate.

Доксициклина Гиклат

$C_{22}H_{24}N_2O_8,HCl,½C_2H_5OH,½H_2O$ = 512.9.

CAS — 10592-13-9 (doxycycline hydrochloride); 24390-14-5 (doxycycline hyclate).
ATC — A01AB22; J01AA02.
ATC Vet — QA01AB22; QJ01AA02.

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

Ph. Eur. 6.2 (Doxycycline Hyclate). A yellow hygroscopic crystalline powder. Freely soluble in water and in methyl alcohol; sparingly soluble in alcohol. It dissolves in solutions of alkali hydroxides and of carbonates. A 1% solution in water has a pH of 2.0 to 3.0. Store in airtight containers. Protect from light.

USP 31 (Doxycycline Hyclate). A yellow crystalline powder. Soluble in water; slightly soluble in alcohol; practically insoluble in chloroform and in ether; soluble in solutions of alkali hydroxides and carbonates. pH of a solution in water containing the equivalent of doxycycline 1% is between 2.0 and 3.0. Store in airtight containers. Protect from light.

Incompatibility. Preparations of doxycycline hyclate have an acid pH and incompatibility may reasonably be expected with alkaline preparations or with drugs unstable at low pH.

Adverse Effects and Precautions

As for Tetracycline, p.347.

Gastrointestinal disturbances with doxycycline are reported to be less frequent than with tetracycline and doxycycline may also cause less tooth discoloration.

Oesophageal ulceration may be a particular problem if capsules or tablets are taken with insufficient fluid or in a recumbent posture: doxycycline should be taken with at least half a glass of water, in an upright position, and well before going to bed. Dispersible tablets or liquid formulations should be used in elderly patients, who may be at greater risk of oesophageal injury.

Unlike many tetracyclines, doxycycline does not appear to accumulate in patients with impaired renal function, and aggravation of impairment may be less likely.

Incidence of adverse effects. For the suggestion that doxycycline may cause fewer adverse effects than minocycline, see p.301.

Anosmia. Anosmia or dysosmia (absent or impaired sense of smell) have occasionally been reported in patients receiving doxycycline, although the association has not been definitely established.[1]

1. Bleasel AF, *et al.* Anosmia after doxycycline use. *Med J Aust* 1990; **152:** 440.

Effects on intracranial pressure. Doxycycline has been associated with benign intracranial hypertension; for further details, see under Tetracycline, p.348.

Porphyria. Doxycycline has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Interactions

As for Tetracycline, p.348.

Doxycycline has a lower affinity for binding with calcium than many tetracyclines. Consequently its absorption is less likely to be affected by milk or food, although it is still affected by calcium-containing antacids and other divalent and trivalent cations such as aluminium, bismuth, iron, magnesium, and zinc; even intravenous doxycycline may be affected, although less so than when given orally.

The metabolism of doxycycline may be accelerated by drugs that induce hepatic enzymes such as alcohol (chronic use), rifampicin, and antiepileptics including carbamazepine, phenobarbital, phenytoin, and primidone.

It has been suggested that doxycycline could increase ciclosporin concentrations, but evidence for this seems to be scant.

Antimicrobial Action

As for Tetracycline, p.348.

Doxycycline is more active than tetracycline against many bacterial species including *Streptococcus pyogenes*, enterococci, *Nocardia* spp., and various anaerobes. Cross-resistance is common although some tetracycline-resistant *Staphylococcus aureus* respond to doxycycline. Doxycycline is also more active against protozoa, particularly *Plasmodium* spp.

Pharmacokinetics

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

Doxycycline is readily and almost completely absorbed from the gastrointestinal tract and absorption is not significantly affected by the presence of milk or food in the stomach or duodenum. Mean peak plasma concentrations of 2.6 micrograms/mL have been reported 2 hours after a 200-mg oral dose, falling to 1.45 micrograms/mL at 24 hours. After intravenous infusion of the same dose peak plasma concentrations are briefly somewhat higher, but become very similar to those after oral dosage on equilibration into the tissues.

About 80 to 95% of doxycycline in the circulation is reported to be bound to plasma proteins. Its biological half-life varies from about 12 to 24 hours. Doxycycline is more lipid-soluble than tetracycline. It is widely distributed in body tissues and fluids.

In patients with normal renal function about 40% of a dose is slowly excreted in the urine, although more is excreted by this route if the urine is made alkaline. However, the majority of a dose of doxycycline is excreted in the faeces after chelation in the intestines. Although doxycycline has been reported to undergo partial inactivation in the liver, some sources consider this doubtful; however, the kinetics of doxycycline have been reportedly altered in patients receiving drugs that induce hepatic metabolism.

Doxycycline is stated not to accumulate significantly in patients with renal impairment, although excretion in the urine is reduced; increased amounts of doxycycline are excreted in the faeces in these patients. Nevertheless, there have been reports of some accumulation in renal failure. Removal of doxycycline by haemodialysis is insignificant.

◊ Reviews.

1. Saivin S, Houin G. Clinical pharmacokinetics of doxycycline and minocycline. *Clin Pharmacokinet* 1988; **15:** 355–66.

Uses and Administration

Doxycycline is a tetracycline derivative with uses similar to those of tetracycline (p.349). It may sometimes be preferred to other tetracyclines in the treatment of susceptible infections because of its fairly reliable absorption and its long half-life that permits less frequent (often once daily) dosing. It also has the advantage that it can be given (with care) to patients with renal impairment. However, relatively high doses may need to be given for urinary-tract infections because of its low renal excretion.

Doxycycline has antiprotozoal actions and may be given in conjunction with quinine in the management of falciparum malaria resistant to chloroquine (p.594).

Solutions of doxycycline are also used for malignant effusions (p.659).

Doxycycline is usually given orally as the base or its various salts, usually the hyclate. Doses are expressed in terms of doxycycline; doxycycline hyclate 115 mg is equivalent to about 100 mg of anhydrous doxycycline. Doxycycline capsules and tablets should be given with plenty of fluid, with the patient in an upright position, and well before going to bed. Doxycycline may be given with food or milk if gastric irritation occurs. Dispersible tablets or liquid formulations are advisable in elderly patients.

In patients in whom oral therapy is not feasible, doxycycline hyclate may be given by slow intravenous infusion of a solution containing 0.1 to 1 mg/mL, in equivalent doses. Infusions should be given over 1 to 4 hours.

The usual adult dose, either orally or intravenously, is 200 mg of doxycycline on the first day (as a single dose or in divided doses), followed by 100 mg daily. In severe infections the initial dosage is maintained throughout the course of treatment.

In patients with uncomplicated gonococcal infections, doxycycline 100 mg twice daily for 7 days is given orally, although it has occasionally been given in a single dose of 300 mg followed by a second similar dose 1 hour later. For syphilis in penicillin-allergic patients, doxycycline 100 to 200 mg twice daily is given orally for at least 14 days; some authorities suggest giving the same dose for 28 to 30 days to patients with late latent disease and those with syphilis for more than a year should be given 100 mg twice daily for 28 days.

For relapsing fever and louse-borne typhus, doxycycline 100 or 200 mg may be given as a single oral dose. For prophylaxis of scrub typhus, 200 mg may be taken as a single oral dose. For the prophylaxis of leptospirosis, 200 mg may be given orally once a week throughout exposure for up to 21 days and 200 mg is also given when leaving the area of infection risk.

Doxycycline is used in non-endemic areas for the treatment of chloroquine-resistant falciparum malaria in an oral dose of 200 mg daily for at least 7 days after treatment with quinine. Doxycycline 100 mg daily may be