Preparations

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

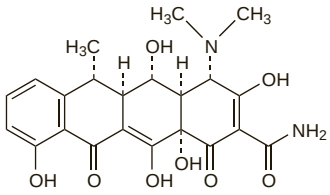
Doxycycline *(BAN, USAN, rINN)*

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