

PRODUCT INFORMATION

Doxylin

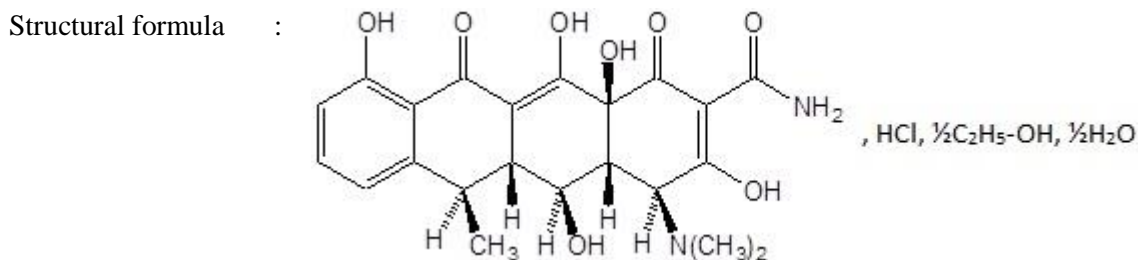
Doxycycline (hydrochloride)



NAME OF THE MEDICINE

Active ingredient : doxycycline (as doxycycline hydrochloride)

Chemical name : hydrochloride hemiethanol hemihydrate of (4*S*,4*aR*,5*S*,5*aR*,6*R*,12*aS*)-4-(dimethylamino)-3,5,10,12,12*a*-pentahydroxy-6-methyl-1,11-dioxo-1,4,4*a*,5,5*a*,6,11,12*a*-octahydrotetracene-2-carboxamide



Molecular formula : C₂₂H₂₄N₂O₈·HCl, $\frac{1}{2}$ C₂H₆O, $\frac{1}{2}$ H₂O Molecular weight : 512.9

CAS Registry no. : 24390-14-5

DESCRIPTION

Doxycycline is a yellow, crystalline powder, hygroscopic. It is freely soluble in water and in methanol, sparingly soluble in ethanol (96%). It dissolves in solutions of alkali hydroxides and carbonates.

Doxycycline is a broad spectrum antibiotic synthetically derived from oxytetracycline. It has a high lipid solubility and a low affinity for calcium binding, is highly stable in normal human serum, and will not degrade into an epianhydro form.

Each tablet contains doxycycline hydrochloride equivalent to 50 mg or 100 mg of doxycycline. The tablets also contain the following inactive excipients: microcrystalline cellulose, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate, lactose, hypromellose, macrogol 4000, titanium dioxide, quinoline yellow CI 47005, sunset yellow FCF CI 15985 and indigo carmine CI 73015.

PHARMACOLOGY

Microbiology

Doxycycline is primarily bacteriostatic and is active against a wide range of Gram-positive and Gram-negative organisms. It is thought to exert its antimicrobial effect by the inhibition of protein synthesis.

Susceptibility testing

Dilution or Diffusion Techniques. Either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. CLSI, formerly NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable.

A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small-uncontrolled technical factors from causing major discrepancies in interpretation.

A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Tetracyclines are readily absorbed, but to a varying extent. They are concentrated by the liver in the bile, and excreted in the urine and faeces at high concentrations and in a biologically active form.

Doxycycline is almost completely absorbed following oral administration. Its absorption is not significantly affected by the presence of food or milk.

Following a 200 mg dose to normal adult volunteers, average peak plasma levels of 4.5 microgram/mL of doxycycline occur at approximately 2 hours, decreasing to 1.2 microgram/mL at 24 hours. Excretion of doxycycline by the kidney is about 40% in 72 hours in individuals with normal renal function (creatinine clearance above 75 mL/min). Excretion may fall to as low as 1 to 5% in 72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min).

The plasma half-life of doxycycline ranges from 10 to 24 hours. No significant difference in serum half-life has been seen in individuals with normal and severely impaired renal function. Haemodialysis does not alter serum half-life.

More than 90% of an oral dose of doxycycline is eliminated from the body within 72 hours of drug administration. The fraction of drug that is not eliminated with urine is mainly excreted in the faeces.

The metabolism of doxycycline in humans has not been investigated. *In vitro* serum protein binding of doxycycline varies from 23 to 93%.

INDICATIONS

Note: The 50 mg tablet is not a paediatric formulation.

Doxycycline is indicated in the treatment of infections caused by the following microorganisms:

Mycoplasma pneumoniae: primary atypical pneumonia

Rickettsiae: Queensland tick typhus, epidemic typhus fever, Q fever, murine endemic typhus fever, Australo-Pacific endemic scrub typhus

Chlamydia psittaci: psittacosis

Calymmatobacterium (Donovania) granulomatis: granuloma inguinale

Chlamydia trachomatis: lymphogranuloma venereum, trachoma, inclusion conjunctivitis.

(Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence. Inclusion conjunctivitis may be treated with oral doxycycline alone, or in combination with topical agents.)

Doxycycline is indicated in the treatment of infections caused by the following Gram-negative microorganisms:

Vibrio species: cholera

Brucella species: Brucellosis (in conjunction with streptomycin)

Yersinia pestis: plague

Francisella tularensis: tularaemia

Bartonella bacilliformis: Bartonellosis

Bacteroides species.

Doxycycline is indicated, in adults and children older than 10 years, as chemoprophylaxis for malaria caused by *Plasmodium falciparum* and, in combination with other antimalarial agents, against malaria caused by *Plasmodium vivax*. Doxycycline is only able to suppress malaria caused by *P. vivax*. As there are relatively few locations where *P. vivax* does not co-exist to some extent with *P. falciparum*, it is recommended that doxycycline should be used routinely with other agents, e.g. chloroquine.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to:

Treponema pallidum: syphilis

Treponema pertenue: yaws

Neisseria gonorrhoeae: gonorrhoea (see Dosage and Administration)

Doxycycline may be a useful adjunct to amoebicides in the treatment of acute intestinal amoebiasis.

In the treatment of severe acne, doxycycline may be a useful adjunctive therapy.

Doxycycline is not the drug of choice in the following:

Any type of staphylococcal infection or infections caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, *Enterococcus faecalis*, or any type of enteric bacteria because many strains of these organisms have been shown to be resistant to doxycycline. Doxylin should not be used for these infections unless the organism has been shown to be sensitive. For upper respiratory infections due to group A β -haemolytic streptococci, (including prophylaxis of rheumatic fever), penicillin is the usual drug of choice.

CONTRAINDICATIONS

Hypersensitivity to doxycycline, any of the excipients in Doxylin, or to any of the tetracyclines.

Rare cases of benign intracranial hypertension have been reported after tetracyclines and oral retinoids, such as isotretinoin or etretinate, and vitamin A. Concomitant treatment is therefore contraindicated.

PRECAUTIONS

Tooth Discolouration

The use of tetracyclines, including doxycycline, during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This occurs more commonly during long term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Tetracycline drugs, therefore, should not be used in this age group unless other drugs are unlikely to be effective or are contraindicated.

Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients taking tetracycline drugs should be advised against exposure to direct sunlight or ultra-violet light, and treatment should be discontinued at the first sign of skin erythema.

Increased Serum Urea

The antianabolic action of the tetracyclines may cause an increase in serum urea. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Intracranial Hypertension

Intracranial hypertension (IH) has been associated with the use of tetracyclines including doxycycline (see **CONTRAINDICATIONS** and **ADVERSE EFFECTS**). The use of tetracyclines in infants, even in the usual therapeutic doses, may cause increased intracranial pressure and bulging of the fontanelles. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Clinical manifestations include headache, blurred vision, diplopia and vision loss. Although intracranial hypertension typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Discontinuation of therapy typically results in prompt return of the pressure to normal. However, since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilise.

Clostridium Difficile Associated Diarrhoea

Clostridium difficile associated diarrhoea (CDAD) and antibiotic associated pseudomembranous colitis have been reported with nearly all antibacterial agents including doxycycline, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile* and *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

Superinfection

The use of antibiotics may occasionally result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

Treatment of Venereal Disease with Coexistent Syphilis

In venereal disease when coexistent syphilis is suspected, proper diagnostic measures including a dark field examination should be performed before treatment is started and the blood serology repeated monthly for at least four months.

Long Term Therapy

In long term therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies should be performed.

Oesophagitis/Oesophageal Ulceration

Rarely, oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline tablets. Most of these patients took medication immediately before going to bed. Administration of adequate amounts

of fluid with the tablets is recommended to reduce the risk of oesophageal irritation and ulceration, and late evening ingestion of the dose should be avoided.

Gastric Irritation

To reduce the possibility of gastric irritation, it is recommended that Doxylin be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

Treatment of Group A β -haemolytic Streptococci Infections

All infections due to group A β -haemolytic streptococci should be treated for at least 10 days.

Hepatic Effects

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in Pregnancy (Category D)

(See **PRECAUTIONS, Tooth Discolouration**)

During the period of mineralisation of a child's teeth (the last half of pregnancy, the neonatal period and the first 8 years of life) tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton. These products should be avoided during the latter half of pregnancy.

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS (the Teratogen Information System) concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk. A case control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and fifty-six (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period organogenesis (i.e. in the second and third months of gestation) with the exception of a marginal relationship with neural tube defect based on only two exposed cases.

A small prospective study of 81 pregnancies describes 43 pregnant women treated for ten days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.

Results in animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and can have toxic effects on the developing foetus (often related to retardation of skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy.

Large doses of tetracyclines have caused acute fatty necrosis of the liver in pregnant women, especially those with pyelonephritis.

Use in Lactation

(See **PRECAUTIONS, Paediatric Use**)

Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown. Because of the potential for serious adverse reactions in breastfeeding infants from doxycycline, a decision

should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account how important the drug is to the mother.

Paediatric Use

(See **PRECAUTIONS, Tooth Discolouration** and **Intracranial Hypertension**)

Like other tetracyclines, doxycycline forms a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in premature infants given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Effects on Laboratory Tests

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence tests.

INTERACTIONS WITH OTHER MEDICINES

Anticoagulants

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage, as tetracyclines have been shown to depress plasma prothrombin activity.

Antacids

Antacids containing aluminium, calcium or magnesium, or other drugs containing these cations, bismuth salts and preparations containing iron impair absorption and should not be given to patients taking Doxylin.

Penicillin

It is advisable to avoid giving tetracyclines concomitantly with penicillin as bacteriostatic drugs may interfere with the bactericidal action of penicillin.

Drugs that Reduce Plasma Levels of Doxycycline

Plasma levels of doxycycline are reduced by the ingestion of alcohol or the administration of barbiturates, anticonvulsants (phenytoin, carbamazepine), disodium hydrogen edetate, sodium bicarbonate, sodium lactate, acetazolamide and ethoxzolamide.

Oral Contraceptives

There have been anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective. A barrier method of contraception should be used while taking Doxylin and for seven days following completion of the course of Doxylin.

Methoxyflurane

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity.

ADVERSE EFFECTS

Doxycycline is generally well tolerated. Due to doxycycline's virtually complete absorption, side effects of the lower bowel, particularly diarrhoea, have been infrequent. The following adverse reactions have been observed in patients receiving doxycycline.

More common reactions**Dermatological.**

Photosensitive skin reactions (see Precautions), erythematous rash, maculopapular rash, morbilliform rash, pustular rash, urticaria, photo-onycholysis and discolouration of the nails.

Gastrointestinal.

Nausea, anorexia, vomiting, dysphagia, diarrhoea, oesophagitis, oesophageal ulceration, abdominal pain, glossitis, black hairy tongue.

Hypersensitivity reactions.

Urticaria, exacerbation of systemic lupus erythematosus.

Hepatic.

Cholestatic hepatitis, fatty liver degeneration.

Renal.

Dose related increase in serum urea (see Precautions).

Musculoskeletal.

Tooth discolouration, enamel hypoplasia.

Others.

Bulging fontanelles have been reported in young infants following full therapeutic dosage. The sign disappeared rapidly when the drug was discontinued.

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discolouration of thyroid glands. No abnormalities of thyroid function studies are known to occur.

Less common reactions**Gastrointestinal.**

Enterocolitis (see Precautions), inflammatory lesions (with monilial overgrowth) in the anogenital region; dyspepsia and pseudomembranous colitis (see Precautions); *C. difficile* diarrhoea; hepatotoxicity, hepatitis. Abnormal hepatic function has been reported rarely (<1 in 1000).

Hepatic.

hepatotoxicity.

Skin.

Exfoliative dermatitis; Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN).

Musculoskeletal.

Arthralgia; myalgia.

Genitourinary.

Acute renal failure.

Hypersensitivity reactions.

Angioneurotic oedema, anaphylaxis, anaphylactic shock, anaphylactic reaction, anaphylactoid purpura, serum sickness, pericarditis; hypotension, dyspnoea, peripheral oedema, tachycardia, erythema multiforme.

Haematological and Reticuloendothelial.

Phlebitis associated with intravenous administration, leucopenia, thrombocytopenic purpura, increase in prothrombin time, haemolytic anaemia, eosinophilia.

Nervous system.

Flushing, malaise, headache, confusion, taste loss, stupor, hypoaesthesia, paraesthesia, somnolence, benign intracranial hypertension in adults, increased intracranial pressure in infants.

Ocular.

Conjunctivitis, periorbital oedema.

Hearing/Vestibular.

Tinnitus.

Psychiatric.

Depression, anxiety, hallucination.

Respiratory.

Bronchospasm.

DOSAGE AND ADMINISTRATION**Note:**

1. The 50 mg tablet is not a paediatric formulation.
2. Administration of adequate amounts of fluid with the tablets is recommended to reduce the risk of oesophageal irritation and ulceration. Morning, rather than late night dosing may be preferable. As the recumbent posture may delay oesophageal transit of the tablets, the patient should not lie down for some time after taking the tablets. To reduce the possibility of gastric irritation, it is recommended that Doxylin be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. Antacids containing aluminium, calcium or magnesium, bismuth salts and preparations containing iron impair absorption and should not be given to patients taking Doxylin.
3. The usual dosage and frequency of administration of Doxylin differs from that of other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided.
4. Tetracyclines are not the drugs of choice for the treatment of streptococcal infections (see **INDICATIONS**). However, when used, therapy should be continued for 10 days.

Adults and children over 8 years (and above 50 kg in weight):

The usual dose is 200 mg on the first day of treatment (100 mg every 12 hours) followed by a maintenance dose of 100 mg/day, which may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

Acute uncomplicated gonococcal infections:

100 mg twice daily for 5 to 7 days.

Resistance to tetracyclines is not uncommon amongst gonococci. The use of tetracycline in the treatment of gonorrhoea should therefore be accompanied by monitoring of efficacy.

Primary and secondary syphilis:

300 mg a day in divided doses for at least 10 days.

Louse-borne typhus:

This has been successfully treated with a single oral dose of 100 mg or 200 mg according to severity.

For the prevention of scrub typhus: 200 mg as a single dose.

Severe acne:

Some efficacy has been demonstrated in some individuals at a dose of 50 mg/day over a period of 12 weeks. No data showing efficacy beyond 12 weeks have been submitted.

Malaria chemoprophylaxis:

100 mg once daily; commencing two days prior to entering malarious areas, while in the malarious area and for four weeks after leaving the malarious area. A maximum of 100 mg daily for 8 weeks is recommended, as safety after 8 weeks has not been clearly established (see Indications about combination with other antimalarial agents for prophylaxis against *P. vivax*).

Children over 8 years of age (and below 50 kg in weight, without skeletal growth retardation):

The adult dose of 100 mg should be recalculated on a weight basis of 2 mg/kg (see Precautions – Paediatric Use).

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibiotic in patients with renal impairment.

OVERDOSAGE

Signs and Symptoms

Tetracyclines, including doxycycline, generally have low toxicity. Severe toxicity following acute overdose is unlikely, with nausea and vomiting being the most common effects after ingestion of therapeutic and overdose amounts.

Treatment of Overdosage

Treatment may include immediate discontinuation of medication, dilution with water or milk and general supportive care. Antacids may be useful in managing gastric irritation. In most cases, gastrointestinal decontamination is not required. Plasma levels are not clinically useful and specific laboratory monitoring is not needed unless otherwise indicated.

Contact the Poisons Information Centre on 131126 for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Doxylin 50 Doxycycline 50 mg tablet: round, yellow film coated, marked “DE” over “50” on one side, “G” on the reverse; Available in bottle (HDPE)* and blister (PVC/PVDC/Al) packs of 25 tablets

Note that the 50 mg tablet is not a paediatric formulation.

Doxylin 100 Doxycycline 100 mg tablet: round, yellow film coated, marked “DE” over “100” on one side “G” on the reverse; Available in bottles (HDPE) of 7 tablets and blister (PVC/PVDC/Al) packs* of 7 and 21 tablets.

Store below 30°C.

*Marketed presentation

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

22 May 1998

DATE OF MOST RECENT AMENDMENT

29 January 2016

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