

NEW ZEALAND DATA SHEET

DOXINE

Doxycycline 100 mg Tablets



Presentation

Yellow film coated, biconvex tablets, 8.7 mm diameter, blank on both sides. Each tablet contains doxycycline hyclate equivalent to 100 mg doxycycline.

Description

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. The chemical designation of this light-yellow crystalline powder is 6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Uses

Actions

Doxycycline is a broad spectrum antibiotic that is primarily bacteriostatic. It is thought to exert its antimicrobial effect by inhibition of protein synthesis. It prevents the binding of amino-acyl-tRNA to the messenger RNA-30S ribosomal subunit. The binding of fMet-tRNA is especially sensitive. As a result, initiation and therefore polyribosome formation are blocked. Doxycycline inhibits only rapidly multiplying organisms.

Doxycycline is active against the following organisms:

- Rickettsiae: rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox, and tick fevers
- *Mycoplasma pneumoniae*
- Agents of lymphogranuloma venereum and granuloma inguinale
- The spirochetal agent of relapsing fever (*Borrelia recurrentis*)
- *Chlamydia trachomatis*
- *Haemophilus ducreyi* (chancroid)
- *Pasteurella pestis*, and *Pasteurella tularensis*, *Bartonella bacilliformis*, Bacteroids species, *Vibriocomma* and *Vibrio fetus* and *Brucella* species (in conjunction with an aminoglycoside).

Doxycycline may be active against the following organisms although this should be confirmed by culture and sensitivity testing since many strains are resistant.

- *Neisseria gonorrhoeae*
- *Escherichia coli*
- *Enterobacter aerogenes*
- *Shigella* species
- *Mima* species and *Herellea* species
- *Haemophilis influenzae*
- *Klebsiella* species
- *Streptococcus* species
- *Streptococcus pneumoniae*
- *Staphylococcus aureus* in respiratory, skin or soft tissue infection.

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

- *Treponema pallidum* and *Treponema pertenu* (syphilis and yaws)
- *Listeria monocytogenes*
- *Clostridium* species
- *Bacillus anthracis*
- *Fusobacterium fusiforme* (Vincent's infection)
- *Actinomyces* species.

Pharmacokinetics

Tetracyclines are readily absorbed, but to varying extents. 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 virtually completely absorbed after oral administration. Its absorption is not significantly affected by the presence of food or milk.

Normal adult volunteers averaged peak serum levels of approximately 2.6 µg/mL of doxycycline at 2 hours, decreasing to 1.45 µg/mL at 24 hours, following a 200 mg dose. Excretion of doxycycline by the kidney is about 40% in 72 hours in individuals with normal renal function (creatinine clearance above 75 mL/min). This percentage excretion may fall as low as 1 to 5% in 72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). The serum half-life of doxycycline ranges from 18-22 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.

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

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

Microbiology

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

Susceptibility Testing

The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common. Micro-organisms may be considered susceptible if the M.I.C. (minimum inhibitory concentration) is less than 1.0 µg/mL and intermediate if the M.I.C. is 1.0 to 5.0 µg/mL.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 µg tetracycline disc should give a zone of at least 19 mm when tested against a tetracycline-susceptible bacterial strain.

Indications

Doxycycline is indicated in the treatment of uncomplicated chest, urethral, endocervical or rectal infections in adults caused by susceptible organisms (see **Actions**) as shown by culture and sensitivity testing. It may also be a useful adjunct to amoebicides in acute intestinal amoebiasis and has a place as adjunctive therapy in severe acne.

Dosage and Administration

The usual dose in adults is 200 mg on the first day of treatment followed by a maintenance dose of 100 mg/day. This may be given as either a single dose or divided doses administered every 12 hours.

In the management of more severe infections, 200 mg daily should be given throughout the treatment period. Therapy should be continued at least 24-48 hours after symptoms and fever has subsided. If used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

For children over 12 years of age, the recommended dosage schedule for those under 50 kg is 4 mg/kg on the first day and 2 mg/kg daily subsequently. For children over 50 kg the usual adult dose is used.

In the treatment of acute gonococcal anterior urethritis in males, administer either: 200 mg stat and 100 mg at bedtime on the first day followed by 100 mg twice daily for 3-7 days, or 300 mg stat followed by 300 mg one hour later. For acute gonococcal infections in females use 200 mg twice daily until cure is effected. When treating uncomplicated urethral, endocervical or rectal infection in adults caused by chlamydia trachomatis, give 100 mg twice daily for at least 7 days. The treatment of primary or secondary syphilis requires 300 mg daily in divided doses for at least 10 days.

In all cases doxycycline should be administered with adequate amounts of fluid or food and the patient should remain sitting or standing for up to 2 hours afterwards to prevent the possible development of oesophageal irritation.

Contraindications

- Hypersensitivity to doxycycline, any of the excipients in DOXINE, or to any of the tetracyclines.
- Rare cases of benign intracranial hypertension have been reported after taking tetracyclines and oral retinoids, such as isotretinoin or etretinate, and vitamin A. Concomitant treatment is therefore contraindicated.
- Children under 12 years of age. The use of drugs of the tetracycline class, including doxycycline, during tooth development may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long term use of the medication but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported.
- Pregnancy. Tetracyclines given during pregnancy affect teeth and skeletal development.
- Nursing mothers. Tetracyclines are excreted into milk and affect teeth and skeletal development.

Warnings and Precautions

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients likely to be exposed to direct sunlight or ultra-violet light should be advised that this reaction can occur with tetracycline medicines and treatment should be discontinued at the first evidence of skin erythema.

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.

The use of tetracyclines in infants, even in the usual therapeutic doses, may cause increased intracranial pressure and bulging of the fontanelles. Discontinuation of therapy results in prompt return of the pressure to normal.

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.

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

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

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

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.

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

If doxycycline is used to treat infections due to group A beta-haemolytic streptococci, treatment should continue for at least 10 days.

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

Use in Pregnancy

Category D (See **Contraindications**).

During the period of mineralisation of a child's teeth (the last half of pregnancy, the neonatal period and the first 12 years of life) tetracyclines may induce hypoplasia of the enamel and discolouration of the teeth. Tetracyclines also accumulate in the growing skeleton.

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 of 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 **Contraindications** and **Use in Newborns, Infants and Children**)

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Because of the potential for serious adverse reactions in breastfeeding infants, doxycycline is contraindicated in nursing mothers.

Use in Newborns, Infants and Children

(See **Contraindications**)

As with 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 medicine was discontinued. Doxycycline is contraindicated in children under 12 years of age.

Effects on Ability to Drive and Use Machines

The effect of doxycycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that doxycycline may affect these abilities.

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 **Warnings and 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 **Warnings and 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 **Warnings and Precautions**), inflammatory lesions (with monilial overgrowth) in the anogenital region; dyspepsia and pseudomembranous colitis (see **Warnings and Precautions**); *C. difficile* diarrhoea.

Hepatic: Abnormal hepatic function has been reported rarely (< 1 in 1000), 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: Leucopenia, thrombocytopenia 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.

Interactions

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

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving tetracycline in conjunction with penicillin.

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

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

There have been anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective.

Effects of Laboratory Tests

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

Overdosage

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

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 National Poisons Information Centre (0800 POISON or 0800 764 766) for advice on the management of an overdose.

Pharmaceutical Precautions

Store below 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Bottles of 250 tablets.

Further Information

Ingredients

The active ingredient in DOXINE tablets is doxycycline (as doxycycline hyclate). Each tablet contains 115 mg of doxycycline hyclate, which is equivalent to 100 mg of doxycycline.

DOXINE tablets also contain the following inactive ingredients: microcrystalline cellulose, pregelatinised maize starch, colloidal silicon dioxide, and magnesium stearate. The tablet coating contains hypromellose, diethyl phthalate, hydroxypropyl cellulose, titanium dioxide (E171), quinoline yellow lake (E104) and iron oxide yellow (E172); and carnauba wax is used to polish the tablets.

DOXINE tablets are lactose and gluten free.

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