

1. PRODUCT NAME

Doxy-50 tablets
Doxy-100 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Doxy-50 tablet contains doxycycline hydrochloride 57 mg (as hyclate, equivalent to doxycycline 50 mg)

Each Doxy-100 tablet contains doxycycline hydrochloride 114 mg (as hyclate, equivalent to doxycycline 100 mg)

Excipient(s) with known effect

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Doxy-50 and Doxy-100 tablets are white, film coated, circular biconvex tablet.

Doxy-50 tablets have a diameter of approximately 6.3 mm.

Doxy-100 tablets are scored on one side and have a diameter of 8 mm.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Doxycycline is indicated in the treatment of uncomplicated chest, urethral, endocervical or rectal infections in adults caused by susceptible organisms (see below) 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. 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*
- *Haemophilis 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 pertenue* (syphilis and yaws)
- *Listeria monocytogenes*
- *Clostridium* species
- *Bacillus anthracis*
- *Fusobacterium fusiforme* (Vincent's infection)
- *Actinomyces* species.

4.2. Dose and method of administration

Dose

Adults

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 have subsided. If used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

For the treatment of acne vulgaris the recommended dose is 50 mg of doxycycline taken daily with food, for up to 12 weeks.

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.

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.

Children

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.

Method of Administration

In all cases Doxy 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.

4.3. Contraindications

- Hypersensitivity to doxycycline, or any other ingredient in Doxy tablets.
- 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 (refer to section 4.6 and 5.3).
- Nursing mothers. Tetracyclines are excreted into milk and affect teeth and skeletal development (refer to section 4.6 and 5.3).

4.4. Special warnings and precautions for use

Clostridium difficile associated diarrhoea (CDAD) and antibiotic associated pseudomembranous colitis

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.

Gastrointestinal irritation

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.

Other considerations

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.

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.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone forming tissue. A decrease in fibula growth rate has been observed in pre-matures given oral tetracycline. This reaction was shown to be reversible when the medicine was discontinued.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Treatment should be discontinued at the first evidence of skin erythema.

The use of Doxy may occasionally result in overgrowth of non-susceptible organisms. If a resistant organism appears, the antibiotic should be discontinued, and appropriate therapy instituted. In long term therapy, because tetracyclines have been shown to depress plasma

prothrombin activity, patients who are on anti-coagulant therapy may require downward adjustment of their anti-coagulant dosage.

Paediatric population

Increased Intracranial Pressure

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.

4.5. Interaction with other medicines and other forms of interaction

Doxy may interfere with the bacterial effect of penicillins and vice versa.

Anticoagulants

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.

Methoxyflurane

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

Oral contraceptives

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

Antacids and Iron preparations

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.

Medicines reducing doxycycline concentrations

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.

4.6. Fertility, pregnancy and lactation

Pregnancy

The importance of this in humans is not known, however, Doxy should not be used in pregnant women unless the benefit outweighs the risk (refer to section 5.3).

Breast-feeding

Doxy has been found in the milk of lactating women it should not be used in nursing mothers.

Fertility

Refer to section 5.3.

4.7. 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.

4.8. Undesirable effects

More Common Reactions

Skin and subcutaneous tissue: Photosensitive skin reactions (see section 4.4), 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.

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 section 4.4), inflammatory lesions (with monilial overgrowth) in the anogenital region; dyspepsia and pseudomembranous colitis (see section 4.4); *C. difficile* diarrhoea.

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

Skin and subcutaneous tissue: Exfoliative dermatitis; Stevens-Johnson syndrome, Toxic Epidermal Necrolysis (TEN).

Musculoskeletal: Arthralgia; myalgia.

Renal: Acute renal failure.

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

Blood and lymphatic system: 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.

Eye: Conjunctivitis, periorbital oedema.

Ear: Tinnitus.

Psychiatric: Depression, anxiety, hallucination.

Respiratory: Bronchospasm.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. Overdose

Symptoms

No reports of overdosage have been received.

Management

If such a case occurs, treatment requires discontinuation of Doxy and use of symptomatic treatment measures.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines, ATC code: J01AA02

Mechanism of action

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.

5.2. Pharmacokinetic properties

Absorption

Doxycycline is virtually completely absorbed after oral administration of either tablets and the absorption is not notably influenced by the ingestion of food or milk.

Distribution

Peak serum levels of approximately 2.6 mcg/ml are achieved at 2 hours following a 200 mg tablet dose. Doxycycline diffuses readily into most body tissues, fluid and/or cavities and the volume of distribution has been measured as 0.7 L/kg. Plasma protein binding is variable.

Bioformation and Elimination

Doxycycline is concentrated by the liver in the bile. It is also excreted in the urine as the unchanged medicine in high concentration. The serum half-life of doxycycline ranges from 18-22 hours and this is not altered by severe renal failure, haemodialysis, age or hepatic failure.

5.3. Preclinical safety data

Carcinogenicity

Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell lines, positive responses for mutagenicity occurred at concentrations of 60 and 10 mcg/ml respectively. In humans no association between tetracyclines and these effects have been made.

Teratogenicity

Results of animal studies indicate that tetracyclines cross the placenta, are found in foetal tissues and have toxic effects on the developing foetus manifested by retardation of skeletal development.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Doxy-50 and Doxy-100 tablet contains colloidal silicon dioxide, magnesium stearate, maize starch, microcrystalline cellulose, Opadry white Y-1R-7000B.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

24 months in bottles and 36 months in blister.

6.4. Special precautions for storage

Store at or below 30°C. Protect from light.

6.5. Nature and contents of container

Doxy-50 tablets: 30 tablets in a bottle; 30 tablets or 7 tablets in blister pack

Doxy-100 tablets: 100 tablets in a bottle

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Douglas Pharmaceuticals Ltd
P O Box 45 027
Auckland 0651
New Zealand
Phone: (09) 835 0660

9. DATE OF FIRST APPROVAL

Doxy-50 tablets: 17 May 1996

10.DATE OF REVISION OF THE TEXT

22 January 2019

Summary table of changes

Section Changed	Summary of new information
All	SPC format