DOXYCYCLINE HYCLATE- doxycycline hyclate tablet, delayed release
Mayne Pharma International Pty Ltd

Doxycycline hyclate delayed-release tablet is a tetracycline-class antimicrobial indicated for:

Rickettsial infections (1.1)

Sexually transmitted infections (1.2)

Respiratory tract infections (1.3)

Specific bacterial infections (1.4)

Ophthalmic infections (1.5)

Anthrax, including inhalational anthrax (post-exposure) (1.6)

Alternative treatment for selected infections when penicillin is contraindicated (1.7)

Adjunctive therapy in acute intestinal amebiasis and severe acne (1.8)

Prophylaxis of malaria (1.9)

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate delayed-release tablets, USP and

other antibacterial drugs, doxycycline hyclate delayed-release tablets, USP should be used only to treat or prevent infections that are proven or

strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in

selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the

empiric selection of therapy.

Doxycycline is a tetracycline-class antimicrobial indicated in the following conditions or diseases:

Sections or subsections omitted from the full prescribing information are not listed.

1.1 Rickettsial infections

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by

Rickettsiae.

1.2 Sexually transmitted infections

Uncomplicated urethral, endocervical or rectal infections in adults caused by Chlamydia trachomatis.

Nongonococcal urethritis caused by Ureaplasma urealyticum.

Lymphogranuloma venereum caused by Chlamydia trachomatis.

Granuloma inguinale caused by Calymmatobacterium granulomatis.

Uncomplicated gonorrhea caused by Neisseria gonorrhoeae.

Chancroid caused by Haemophilus ducreyi.

1.3 Respiratory tract infections

Respiratory tract infections caused by Mycoplasma pneumoniae.

Psittacosis (ornithosis) caused by Chlamydophila psittaci.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility

testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following microorganisms, when bacteriological testing indicates appropriate

susceptibility to the drug:

Respiratory tract infections caused by Haemophilus influenzae.

Respiratory tract infections caused by Klebsiella species.

Upper respiratory infections caused by Streptococcus pneumoniae.

1.4 Specific bacterial infections

Relapsing fever due to Borrelia recurrentis.

Plague due to Yersinia pestis.

Tularemia due to Francisella tularensis.

Cholera caused by Vibrio cholerae.

Campylobacter fetus infections caused by Campylobacter fetus.

Brucellosis due to Brucella species (in conjunction with streptomycin). Bartonellosis due to Bartonella bacilliformis.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility

testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacteriological testing indicates

appropriate susceptibility to the drug:

Escherichia coli

Enterobacter aerogenes

Shigella species

Acinetobacter species

Urinary tract infections caused by Klebsiella species.

1.5 Ophthalmic infections

Trachoma caused by Chlamydia trachomatis, although the infectious agent is not always eliminated as judged by immunofluorescence.

Inclusion conjunctivitis caused by Chlamydia trachomatis.

1.6 Anthrax including inhalational anthrax (post-exposure)

Anthrax due to Bacillus anthracis, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following

exposure to aerosolized Bacillus anthracis.

1.7 Alternative treatment for selected infections when penicillin is contraindicated

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following

infections:

Syphilis caused by Treponema pallidum. Yaws caused by Treponema pertenue.

Vincent's infection caused by Fusobacterium fusiforme.

Actinomycosis caused by Actinomyces israelii.

Infections caused by Clostridium species.

1.8 Adjunctive therapy for acute intestinal amebiasis and severe acne

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides.

In severe acne, doxycycline may be useful adjunctive therapy.

1.9 Prophylaxis of malaria

Doxycycline is indicated for the prophylaxis of malaria due to Plasmodium falciparum in short-term travelers (less than 4 months) to areas with

chloroquine and/or pyrimethamine- sulfadoxine resistant strains [see Dosage and Administration (2.2) and Patient Counseling Information

(17)].

Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe nfections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. (2.1)

For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used. (2.1)

2.1 Usual Dosage and Administration

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a maintenance dose of 100 mg daily. The maintenance dose 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.

For pediatric patients above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg/kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline-class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration [see Adverse Reactions (6.1)].

If gastric irritation occurs, doxycycline may be given with food or milk [see Clinical Pharmacology (12)].

When used in streptococcal infections, therapy should be continued for 10 days.

Uncomplicated urethral, endocervical, or rectal infection in adults caused by

Chlamydia trachomatis: 100 mg by mouth twice-a-day for 7 days.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternative single visit dose, administer 300 mg stat followed in an hour by a second 300 mg dose.

Nongonococcal urethritis (NGU) caused by U. urealyticum: 100 mg by mouth twice-a-day for 7 days.

Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-a-day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice-aday for 4 weeks.

Acute epididymo-orchitis caused by C. trachomatis: 100 mg, by mouth, twice-a-day for at least 10 days.

2.2 For prophylaxis of malaria

For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.3 Inhalational anthrax (post-exposure)

ADULTS: 100 mg, of doxycycline, by mouth, twice-a-day for 60 days.

CHILDREN: weighing less than 45 kg, 2.2 mg/kg of body weight, by mouth, twice-a-day for 60 days. Children weighing 45 kg or more should receive the adult dose.

2.4 Sprinkling the tablet over applesauce

Doxycycline hyclate delayed-release tablets may also be administered by carefully breaking up the tablet and sprinkling the tablet contents (delayed-release pellets) on a spoonful of applesauce. The delayed-release pellets must not be crushed or damaged when breaking up the tablet. Any loss of pellets in the transfer would prevent using the dose. The applesauce/doxycycline hyclate delayed-release tablet mixture should be swallowed immediately without chewing and may be followed by a glass of water if desired. The applesauce should not be hot, and it should be soft enough to be swallowed without chewing. In the event that a prepared dose of applesauce/doxycycline hyclate delayed-release tablet cannot be taken immediately, the mixture should be discarded and not stored for later use.

Tablets: 75 mg and 100 mg (3)

Doxycycline hyclate delayed-release tablets, USP, 75 mg are white, oval scored tablets containing yellow pellets and debossed with "D|5" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 75 mg of doxycycline.

Doxycycline hyclate delayed-release tablets, USP, 100 mg are white, oval scored tablets containing yellow pellets and debossed with "D|0" on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 100 mg of doxycycline.

Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

The drug is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)

Clostridium difficile-associated diarrhea: Evaluate patients if diarrhea occurs. (5.2)

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)

Overgrowth of non-susceptible organisms, including fungi, may occur. Re-evaluate therapy if superinfection occurs. (5.4)

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Doxycycline should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

5.2 Clostridium difficile associated diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline hyclate delayed-release tablets, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

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 diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

5.3 Photosensitivity

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

5.4 Superinfection

As with other antibacterial preparations, use of doxycycline hyclate delayed-release tablets, USP may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

5.5 Benign Intracranial Hypertension

Bulging fontanels in infants and benign intracranial hypertension in adults have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

5.6 Skeletal Development

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

5.7 Antianabolic Action

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

5.8 Malaria

Doxycycline offers substantial but not complete suppression of the asexual blood stages of Plasmodium strains.

Doxycycline does not suppress P. falciparum's sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

5.9 Development of Drug-Resistant Bacteria

Prescribing doxycycline hyclate delayed-release tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.10 Laboratory Monitoring for Long-Term Therapy

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

Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Midlothian Laboratories at 1-800-344-8661 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

6.1 Postmarketing Experience

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline-class. Most of these patients took medications immediately before going to bed [see Dosage and Administration (2.1)].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [see Warnings and Precautions (5.3)].

Renal: Rise in BUN has been reported and is apparently dose-related [see Warnings and Precautions (5.7)].

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

Benign Intracranial Hypertension: Bulging fontanels in infants and benign intracranial hypertension in adults [see Warnings and Precautions (5.5)]

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)

Avoid coadministration of tetracyclines with penicillin (7.2)

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium,

bismuth subsalicylate and iron-containing preparations (7.3)

Concurrent use of tetracycline may render oral contraceptives less effective (7.4)

Barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline (7.5)

7.1 Anticoagulant Drugs

Because tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.

7.2 Penicillin

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

7.3 Antacids and Iron Preparations

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives

Concurrent use of tetracycline may render oral contraceptives less effective.

7.5 Barbiturates and anti-epileptics

Barbiturates, carbamazepine, and phenytoin decrease the half-life of doxycycline.

7.6 Penthrane

The concurrent use of tetracycline and Penthrane® (methoxyflurane) has been reported to result in fatal renal toxicity.

7.7 Drug/Laboratory Test Interactions

False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

Pregnancy Category D (8.1)

Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. Doxycycline use during nursing should be avoided if possible. (8.3)

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category D:

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. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax 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 56 (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 of 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 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1

year of age.

Nonteratogenic effects: [see Warnings and Precautions (5.1, 5.6)].

8.3 Nursing Mothers

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. The effects of prolonged exposure to doxycycline in breast milk are unknown. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [see Warnings and Precautions (5.1, 5.6)].

8.4 Pediatric use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, doxycycline hyclate delayed-release tablets, USP should not be used in pediatric patients to the age of 8 years, unless the potential benefits are expected to outweigh the risks such as for anthrax, or when other drugs are not likely to be effective or are contraindicated [see Warnings and Precautions (5.1, 5.6) and Dosage and Administration (2.1, 2.3)].

8.5 Geriatric use

Clinical studies of doxycycline hyclate delayed-release tablets, USP did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

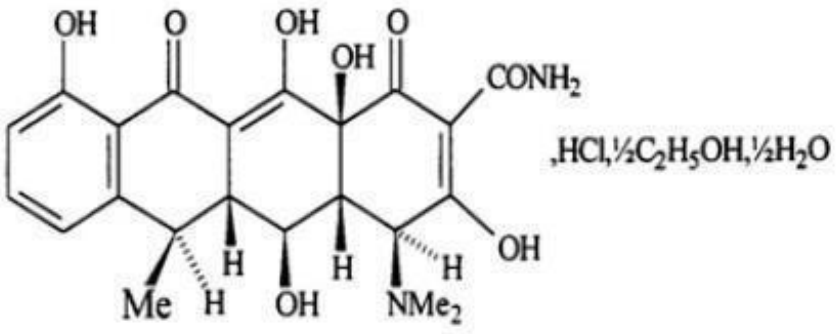
Doxycycline hyclate delayed-release tablets, USP 75 mg tablets contain 4.5 mg (0.196 mEq) of sodium.

Doxycycline hyclate delayed-release tablets, USP 100 mg tablets contain 6 mg (0.261 mEq) of sodium.

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

Doxycycline hyclate delayed-release tablets, USP, for oral administration, contain specially coated pellets of doxycycline hyclate, a broadspectrum antibacterial synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.

The structural formula for doxycycline hyclate is:



with a molecular formula of C H N O , HCl, ½ C H O, ½ H O and a molecular weight of 512.9. The chemical designation for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6- methyl-1,11-deoxonapthtacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. 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. Inactive ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl

sulfate; sodium chloride; talc; anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

12.1 Mechanism of Action

Doxycycline is an antimicrobial drug [see Microbiology (12.4)].

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following administration of a single 200 mg dose to adult volunteers, average peak serum doxycycline levels were 2.6 mcg/mL at 2 hours, decreasing to 1.45 mcg/mL at 24 hours. The mean C and AUC of doxycycline are 24% and 13% lower, respectively, following single dose administration of doxycycline hyclate delayed-release tablets, USP 100 mg with a high fat meal (including milk) compared to fasted conditions. The clinical significance of this decrease is unknown.

When doxycycline hyclate delayed-release tablets, USP are sprinkled over applesauce and taken with or without water, the extent of doxycycline absorption is unchanged, but the rate of absorption is increased slightly.

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1-5%/72 hours in individuals with a creatinine clearance below 10 mL/min.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross-resistance between tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert for doxycycline hyclate delayed-release tablets, USP.

Gram-Negative Bacteria

Acinetobacter species

Bartonella bacilliformis

Brucella species

Calymmatobacterium granulomatis

Campylobacter fetus

Enterobacter aerogenes

Escherichia coli

Francisella tularensis

Haemophilus ducreyi

Haemophilus influenzae

Klebsiella species

Neisseria gonorrhoeae

Shigella species

Vibrio cholerae

Yersinia pestis

Gram-Positive Bacteria

Bacillus anthracis

Streptococcus pneumoniae

Anerobic Bacteria

Clostridium species

Fusobacterium fusiforme Propionibacterium acnes

Other Bacteria

Actinomyces species

Borrelia recurrentis

Chlamydophila psittaci

Chlamydia trachomatis

Mycoplasma pneumoniae

Rickettsiae

Treponema pallidum

Treponema pertenue

Ureaplasma urealyticum

Parasites

Balantidium coli

Entamoeba

species

Plasmodium falciparum1

1Doxycycline has been found to be active against the asexual erythrocytic forms of Plasmodium falciparum but not against the gametocytes of P. falciparum. The precise mechanism of action of the drug is not known.

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method (broth and/or agar). The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible

estimates of the susceptibility of bacteria to antimicrobial compounds. Zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standard test method . This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacteria to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic Techniques

For anaerobic bacteria the susceptibility to doxycycline can be determined by a standardized test method . The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Bacteria[*]	Minimal Inhibitory Concentration (mcg/mL)			Zone Diameter (mm)			Agar Dilution (mcg/mL)		
	S	I	R	S	I	R	S	I	R
Acinetobacter spp,									
Doxycycline	≤4	8	≥16	≥13	10-12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
Bacillus anthracis[*†]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Brucella species[*†]									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Enterobacteriacea									
Doxycycline	≤4	8	≥16	≥14	11-13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Franciscella tularensis[*†]									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
Haemophilus influenzae									
Tetracycline	≤2	4	≥8	≥29	26-28	≤25	-	-	-
Mycoplasma pneumoniae									
Tetracycline	-	-	-	-	-	-	≤2	-	-
Nocardiae and other aerobic *Actinomyces* species[*†]									
Doxycycline	≤1	2-4	≥8						
Neisseria gonorrhoeae[‡]									
Tetracycline	-	-	-	≥38	31-37	≤30	≤0.25	0.5-1	≥2
Streptococcus pneumoniae									
Tetracycline	≤2	4	≥8	≥23	19-22	≤18	-	-	-
Vibrio cholerae									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Yersinia pestis									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
Ureaplasma urealyticum									
Tetracycline	-	-	-	-	-	-	≤1	-	≥2

[*] Organisms susceptible to tetracycline are also considered susceptible to doxycycline, However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

[†] The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[‡] Gonococci with 30 mcg tetracycline disk zone diameters of less than 19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC greater than or equal to 16 mcg/mL).

A report of Susceptible (S) indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. A report of Intermediate (I) indicates that the result should be considered equivocal, and, if the bacteria 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 that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant (R) indicates that the antimicrobial is not likely to

inhibit growth of the pathogen if the antimicrobial compound reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Dilution (mcg/mL)
Enterococcus faecalis ATCC 29212			
Doxycycline	2-8	-	-
Tetracycline	8-32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5-2	18-24	-
Tetracycline	0.5-2	18-25	-
Haemophilus influenzae ATCC 49247 Tetracycline	4-32	14-22	-
Neisseria gononhoeae ATCC 49226 Tetracycline	-	30-42	0.25-1
Staphylococcus aureus ATCC 25923			
Doxycycline	-	23-29	-
Tetracycline	-	24-30	-
Staphylococcus aureus ATCC 29213			
Doxycycline	0.12-0.5		-
Tetracycline	0.12-1		-
Staphylococcus pneumoniae ATCC 49619			
Doxycycline	0.015-0.12	25-34	-
Tetracycline	0.06-0.5	27-31	-
Bacteroides fragilis ATCC 25285 Tetracycline	-	-	0.125-0.5
Bacteroides thetaiotaomicron ATCC 29741 Tetracycline	-	-	8-32
Mycoplasma pneumoniae ATCC 29342 Tetracycline	0.06-0.5	-	0.06-0.5
Ureaplasma urealyticum ATCC 33175 Tetracycline	-	-	≥8

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in in vitro mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO , and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO , and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO , methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and

tetracycline HCl, were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

Treatment of various animal species with this class of drugs has also resulted in the induction of thyroid hyperplasia in the following: in rats and dogs (minocycline); in chickens (chlortetracycline); and in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in goats and rats treated with oxytetracycline.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

DOXYCYCLINE HYCLATE

doxycycline hyclate tablet, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:50546-710
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DOXYCYCLINE HYCLATE (DOXYCYCLINE ANHYDROUS)	DOXYCYCLINE ANHYDROUS	75 mg in 100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE	
CELLULOSE, MICROCRYSTALLINE	
SODIUM LAURYL SULFATE	
SODIUM CHLORIDE	
TALC	
ANHYDROUS LACTOSE	
STARCH, CORN	
CROSPOVIDONE	
MAGNESIUM STEARATE	

Product Characteristics

Color	white ((containing yellow pellets))	**Score**	2 pieces
Shape	OVAL	**Size**	13mm
Flavor		**Imprint Code**	D;5
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50546-710-10	100 in 1 BOTTLE		
1		100 mg in 1 CAPSULE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA authorized generic	NDA050795	07/08/2013	

Labeler - Mayne Pharma International Pty Ltd (756003745)

Establishment

Name	Address	ID/FEI	Business Operations
Mayne Pharma International Pty Ltd		756003745	manufacture(50546-710)

Revised: 7/2013 Mayne Pharma International Pty Ltd