

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DOXYCYCLINE HYCLATE DELAYED-RELEASE TABLETS safely and effectively. See Full Prescribing Information for DOXYCYCLINE HYCLATE DELAYED-RELEASE TABLETS.

DOXYCYCLINE HYCLATE DELAYED-RELEASE TABLETS USP, for oral use.

Initial U.S. Approval: 1987

Warnings and Precautions (5.5) 05/2015

INDICATIONS AND USAGE

Doxycycline hyclate delayed-release tablets, USP are a tetracycline-class antibacterial 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 and other antibacterial drugs, doxycycline hyclate delayed-release tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1)

DOSEAGE AND ADMINISTRATION

- 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 infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. (2.1)
- For children above 8 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)

DOSEAGE FORMS AND STRENGTHS

Tablets: 75 mg, 80 mg and 100 mg (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- 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. Reevaluate therapy if superinfection occurs. (5.4)

ADVERSE REACTIONS

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 Mylan Pharmaceuticals Inc. at 1-877-446-3878 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage. (7.1)
- Avoid co-administration 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)
- Avoid co-administration 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)

USE IN SPECIFIC POPULATIONS

- 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)

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REVISED NOVEMBER 2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 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 antibiogram. 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:

- Rickettsial Infections**
Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial alx, and tick fevers caused by *Rickettsia*.
- Sexually Transmitted Infections**
Uncomplicated urethral, endocervical or rectal infections caused by *Chlamydia trachomatis*.
Nongonococcal urethritis caused by *Ureaplasma urealyticum*.
Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
Granu oa inguinale caused by *Klebsiella granulomatis*.
Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
Chancroid caused by *Haemophilus ducreyi*.
- Respiratory Tract Infections**
Respiratory tract infections caused by *Mycoplasma pneumoniae*.
Psittacosis (ornithosis) caused by *Chlamydia 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*.
- Specific Bacterial Infections**
Reapsing 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).
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*Sections or subsections omitted from the Full Prescribing Information are not listed.

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.
- 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*.
 - 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*.
 - Alternative Treatment for Selected Infections when Penicillin is Contraindicated**
When penicillin is contraindicated, doxycycline is an alternate drug in the treatment of the following infections:
Syphilis caused by *Treponema pallidum*.
Yaws caused by *Treponema pallidum* subspecies *pertense*.
Vincent's infection caused by *Fusobacterium fusiforme*.
Acinetobacter caused by *Acinetobacter israelii*.
Infections caused by *Clostridium* species.
 - 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.
 - 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 chroquine and/or pyrimethamine-sulfadoxine resistant strains. (See Dosage and Administration (2.2) and Patient Counseling Information (17)).

2 DOSEAGE AND ADMINISTRATION

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 or for more severe infections up to 4.4 mg/kg of body weight may be used. For Pediatric Patients Above 8 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 and reduce the risk of esophageal irritation and ulceration. (See Adverse Reactions (6)). 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 Urinary, Endocervical, or Rectal Infection Caused by Chlamydia Trachomatis:** 100 mg by mouth twice a day for 7 days. As an alternate dosing regimen for uncomplicated urethral or endocervical infection caused by *Chlamydia trachomatis*, administer 200 mg by mouth once 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 alternate single visit dose, administer 300 mg stat followed in one 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-a-day for 4 weeks. **Acute Epididymo-Orchitis Caused by C. Trachomatis:** 100 mg, by mouth, twice-a-day for 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 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 also may be administered by carefully breaking up the tablet and sprinkling the tablet contents (delayed-release beads) on a spoonful of applesauce. The delayed-release beads must not be crushed or damaged when breaking up the tablet. Any loss of beads in the tumbler should prevent using the dose. The applesauce/doxycycline 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 cannot be taken immediately, the mixture should be discarded and not stored for later use.

3 DOSEAGE FORMS AND STRENGTHS
Doxycycline hyclate delayed-release tablets, 75 mg are white, round, scored tablets containing yellow beads debossed with M on one side of the tablet and 8 to the left of the score and 31 to the right of the score on the other side. Each tablet contains specially coated beads of doxycycline hyclate, USP equivalent to 75 mg of doxycycline.

Doxycycline hyclate delayed-release tablets, 80 mg are white, capsule shaped, scored tablets containing yellow beads debossed with M on one side of the tablet and 8 to the left of the score and 35 to the right of the score on the other side. Each tablet contains specially coated beads of doxycycline hyclate, USP equivalent to 80 mg of doxycycline.

Doxycycline hyclate delayed-release tablets, 100 mg are white, round, scored tablets containing yellow beads debossed with M on one side of the tablet and 8 to the left of the score and 32 to the right of the score on the other side. Each tablet contains specially coated beads of doxycycline hyclate, USP equivalent to 100 mg of doxycycline.

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

5 WARNINGS AND PRECAUTIONS

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 acute colicky abdominal pain. Careful medical history is necessary since CDAD has been reported to occur over 2 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 should 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 may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline including doxycycline. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilloedema can be found on funduscopic. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Avoid concurrent use of isotretinoin and doxycycline because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

5.6 Skeletal Development
All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fetal growth rate has been observed in premature given oral tetracycline in doses of 25 mg/kg every 6 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 Antibiotic Action

The antibiologic 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* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes under 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.

6 ADVERSE REACTIONS
The following adverse reactions have been identified during post-approval use of doxycycline. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate a causal relationship to drug exposure.

Due to oral doxycycline's virtual 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 angual 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, edematous 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 Vial 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.

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycline. (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.

7 DRUG INTERACTIONS

7.1 Anticoagulant Drugs
Because tetracyclines have been shown to depress prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of the anticoagulant dosage.

7.2 Penicillin

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid a drug tetracycline 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 Penitran
The concurrent use of tetracycline and Penitran[®] (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.

8 USE IN SPECIFIC POPULATIONS

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 pregnancy are 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.¹

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 (that is, 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.²

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 one year of age.³

Nonteratogenic Effects. (See Warnings and Precautions (5.1, 5.6, 1)).

8.2 Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known.

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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 effects in breast-feeding 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).)

6.4 Pediatric Use

Because of the effects of drugs of the tetracycline class on tooth development and growth, doxycycline 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 Advice and Administration (2.1, 2.3).)

6.5 Geriatric Use

Clinical studies of doxycycline did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. Doxycycline hydrochloride delayed-release 75 mg tablets contain 2.15 mg (0.09 mg) of sodium. Doxycycline hydrochloride delayed-release 80 mg tablets contain 2.28 mg (0.09 mg) of sodium. Doxycycline hydrochloride delayed-release 100 mg tablets contain 2.86 mg (0.12 mg) of sodium.

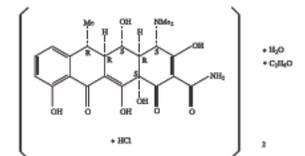
10 OVERDOSAGE

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

11 DESCRIPTION

Doxycycline hydrochloride delayed-release tablets, USP, for oral administration, contain specially coated beads of doxycycline hydrochloride, a broad-spectrum antibiogram synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.

The structural formula for doxycycline hydrochloride is:



with a molecular formula of $C_{22}H_{26}N_2O_9 \cdot HCl$ and a molecular weight of 462.89. The chemical designation for doxycycline hydrochloride is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthylcarbamoyl monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hydrochloride, USP is a yellow to light tan powder soluble in water and a solution of a half 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 epiaxanthin form. Inactive ingredients in the tablet formulation are: hydroxypropyl methylcellulose, croscarmellose sodium, hypromellose phthalate, lactose monohydrate, polydextrose, pregelatinized starch (corn), sodium chloride, sodium lauryl sulfate, stearic acid, talc, and triethyl citrate.

The 75 mg and 100 mg tablet strengths meet USP Dissolution Test 3.

For the 80 mg tablet strength, the USP Dissolution Test is pending.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is an antibacterial drug. (See Microbiology (12.2).)

12.2 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following single and multiple-dose administration of doxycycline hydrochloride delayed-release tablets, 200 mg to adult volunteers, average peak plasma doxycycline concentration (C_{max}) was 4.6 mg/mL and 6.3 mg/mL, respectively with median t_{max} of 3 hours; the corresponding mean plasma concentration values 24 hours after single and multiple doses were 1.5 mg/mL and 2.3 mg/mL, respectively. The mean C_{min} and AUC_{0-24} of doxycycline are 0.24% and 13% lower, respectively, following single dose administration of doxycycline hydrochloride delayed-release tablets, 100 mg with a high fat meal (not including milk) compared to tested control. The mean C_{min} of doxycycline is 19% lower and the AUC_{0-24} is unchanged following single dose administration of doxycycline hydrochloride delayed-release tablets, 150 mg with a high fat meal (not including milk) compared to tested control. The clinical significance of these decreases is unknown. Doxycycline bioavailability from doxycycline hydrochloride delayed-release tablets, 200 mg was not affected by food, but the incidence of nausea was higher in fed subjects. The 200 mg tablets may be administered without regard to meals. When doxycycline hydrochloride delayed-release tablets 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 kidneys is about 40%/72 hours in individuals with a creatinine clearance of about 75 mL/min. This percentage may fall as low as 1% to 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 with other tetracyclines is common. Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert.

Gram-Negative Bacteria

Acinetobacter species

Bacteroides species

Enterobacter aerogenes

Escherichia coli

Francisella tularensis

Haemophilus ducreyi

Haemophilus influenzae

Klebsiella pneumoniae

Klebsiella species

Neisseria gonorrhoeae

Shigella species

Yersinia enterocolitica

Yersinia species

Vibrio species

Gram-Positive Bacteria

Bacillus anthracis

Bacillus cereus

Bacillus pumilus

Bacillus subtilis

Clostridium species

Fusobacterium species

Propionibacterium species

Other Bacteria

Mycobacterium and other aerobic *Actinomyces* species

Streptococcus species

Chlamydia pneumoniae

Chlamydia trachomatis

Mycoplasma pneumoniae

Rickettsia species

Treponema pallidum

Typhlozoon species

Ureaplasma urealyticum

Parasites

Babesia microti

Entamoeba species

*Plasmodium falciparum**

*Doxycycline 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 this drug is not known.

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug use 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.

Diffusion 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).^{1,2,4,10,11} 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. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.^{1,2,4,7} 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. **Neutralization Techniques:** For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method.⁹ The MIC values should be interpreted according to the criteria provided in Table 1.

Table 1. Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria*	Minimal Inhibitory Concentration (mcg/mL)		Zone Diameter (mm)		Agar Diffusion (mcg/mL)	
	S	I	S	I	S	I
<i>Acinetobacter</i> spp. Doxycycline Tetracycline	≤ 4	8	≥ 18	≥ 13	10 to 12	≤ 8
<i>Anaerobes</i> Doxycycline	≤ 4	8	≥ 18	≥ 15	12 to 14	≤ 11
<i>Bacillus anthracis</i> [†] Doxycycline Tetracycline	≤ 1	-	-	-	-	-
<i>Bacillus cereus</i> [†] Doxycycline Tetracycline	≤ 1	-	-	-	-	-
<i>Bacillus pumilus</i> [†] Doxycycline Tetracycline	≤ 1	-	-	-	-	-
<i>Bacillus subtilis</i> [†] Doxycycline Tetracycline	≤ 1	-	-	-	-	-
<i>Bacteroides</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	≥ 14	11 to 13	≤ 10
<i>Chlamydia pneumoniae</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	≥ 15	12 to 14	≤ 11
<i>Chlamydia trachomatis</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	≥ 15	12 to 14	≤ 11
<i>Francisella tularensis</i> [†] Doxycycline Tetracycline	≤ 4	-	-	-	-	-
<i>Haemophilus ducreyi</i> Doxycycline Tetracycline	≤ 4	-	-	-	-	-
<i>Haemophilus influenzae</i> Doxycycline Tetracycline	≤ 2	4	≥ 8	≥ 20	20 to 26	≤ 25
<i>Mycoplasma pneumoniae</i> [†] Doxycycline Tetracycline	-	-	-	-	-	≤ 2
<i>Mycoplasma genitalium</i> [†] Doxycycline Tetracycline	-	-	-	-	-	≤ 2
<i>Mycobacterium</i> and other aerobic <i>Actinomyces</i> species Doxycycline	≤ 1	2 to 4	≥ 8	-	-	-
<i>Propionibacterium</i> species Doxycycline	≤ 0.25	0.5	≥ 1	≥ 20	25 to 27	≥ 24
<i>Rickettsia</i> Doxycycline	≤ 1	2	≥ 4	≥ 20	25 to 27	≥ 24
<i>Treponema pallidum</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	-	-	-
<i>Typhlozoon</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	-	-	-
<i>Ureaplasma urealyticum</i> Doxycycline Tetracycline	≤ 4	8	≥ 18	-	-	-
<i>Ureaplasma urealyticum</i> Doxycycline Tetracycline	-	-	-	-	-	≤ 1
<i>Vibrio</i> species Doxycycline Tetracycline	≤ 4	8	≥ 18	-	-	-

*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.

[‡]Concave or 30 mcg tetracycline disk zone diameter of < 19 mm usually indicates a plasmid-mediated tetracycline-resistant *Mycoplasma genitalium* isolate. Resistance in these strains should be confirmed by a dilution MIC (≥ 16 mcg/mL).

[§]Zone of Susceptibility (S) indicates that antimicrobials are 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 testable drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product 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 pathogen 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 quality control strains to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals

performing the test.^{1,2,4,7,9,10,11} Standard doxycycline and tetracycline powers should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria in Table 2 should be achieved.

Table 2. Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline

NC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Diffusion (mcg/mL)
<i>Enterococcus faecalis</i> ATCC 29212 Doxycycline Tetracycline	2 to 8 8 to 32	- -	- -
<i>Escherichia coli</i> ATCC 25922 Doxycycline Tetracycline	0.5 to 2 0.5 to 2	18 to 24 18 to 25	- -
<i>Escherichia coli</i> ATCC 43047 Doxycycline Tetracycline	2 to 16 4 to 32	- 14 to 22	- -
<i>Haemophilus influenzae</i> ATCC 49226 Doxycycline Tetracycline	- -	30 to 42	0.25 to 1
<i>Staphylococcus aureus</i> ATCC 15923 Doxycycline Tetracycline	- -	23 to 29 24 to 30	- -
<i>Staphylococcus aureus</i> ATCC 13533 Doxycycline Tetracycline	0.12 to 0.5 0.12 to 1	- -	- -
<i>Staphylococcus pneumoniae</i> ATCC 49619 Doxycycline Tetracycline	0.015 to 0.12 0.06 to 0.5	25 to 34 27 to 31	- -
<i>Bacteroides fragilis</i> ATCC 25285 Doxycycline Tetracycline	- -	- -	0.12 to 0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741 Doxycycline Tetracycline	2 to 6 -	- -	6 to 32
<i>Mycoplasma pneumoniae</i> ATCC 21442 Doxycycline Tetracycline	0.06 to 0.5 -	- -	0.06 to 0.5

13 NONCLINICAL TOXICOLOGY

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, a large mutagenicity study of doxycycline have not been conducted, positive results in *in vivo* mammalian cell assays have been reported for related antibiotics (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

Hypertension of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline P₆, and methacycline, in mice by doxycycline, minocycline, tetracycline P₆, and methacycline, in dogs by doxycycline and minocycline, in monkeys by minocycline. Minocycline, tetracycline P₆, methacycline, doxycycline, tetracycline base, oxytetracycline hydrochloride, and tetracycline hydrochloride, were produced in rats fed a low iodine diet. This potentiating effect was accompanied by high radioactive iodine uptake. Animal administration of doxycycline produced a large gut with high radioactive 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 mice (chlorotetracycline and minocycline); in rats and mice (oxytetracycline). Adrenal gland hyperplasia has been observed in guinea pigs treated with oxytetracycline. Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

16 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

Doxycycline Hydrochloride Delayed-release Tablets, USP are available containing delayed-release beads of doxycycline hydrochloride, USP equivalent to 75 mg, 80 mg or 100 mg of doxycycline.

The 75 mg tablets are white, round, scored tablets containing yellow beads debossed with M on one side of the tablet and D to the left of the score and 31 to the right of the score on the other side. They are available as follows:

NDC 0378-4531-91

bottles of 60 tablets

The 80 mg tablets are white, capsule shaped, scored tablets containing yellow beads debossed with M on one side of the tablet and D to the left of the score and 35 to the right of the score on the other side. They are available as follows:

NDC 0378-4534-93

bottles of 30 tablets

NDC 0378-4534-91

bottles of 60 tablets

NDC 0378-4534-77

bottles of 90 tablets

NDC 0378-4534-05

bottles of 500 tablets

The 100 mg tablets are white, round, scored tablets containing yellow beads debossed with M on one side of the tablet and D to the left of the score and 32 to the right of the score on the other side. They are available as follows:

NDC 0378-4532-01

bottles of 100 tablets

Store at 20° to 25°C (68° to 77°F). [See USP Control of Room Temperature.] Dispense in a tight, light-resistant container as defined in USP using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Patients taking doxycycline for malaria prophylaxis should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- that doxycycline prophylaxis may be ineffective by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, staying in well-screened areas, using insect repellent, covering the body with clothing, and using an effective bed mosquito net).
- that doxycycline prophylaxis:
 - should begin 1 to 2 days before travel to the malarious area,
 - should be continued daily while in the malarious area and after leaving the malarious area,
 - should be continued for