HIGHLIGHTS OF PRESCRIBING INFORMATION

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

DOXYCYCLINE HYCLATE delayed-release tablets USP, for oral use.
Initial U S. Approval: 1967

---------- RECENT MAJOR CHANGES ----------
Warnings and Precaut ons (5.5) 05/2015

---------- INDICATIONS AND USAGE ----------
Doxycycline hyclate delayed-release tablets, USP are a tetracycline-class antibacterial indicated for:
- Rickettsial infect ons (1.1)
- Sexually transmitted nfections (1.2)
- Respiratory tract infections (1.3)
- Specific bacterial infections (1.4)
- Ophthalmic nfections (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)
- Prophy axis of malaria (1.9)

To reduce the development of drug-resistant bacter a and ma ntain the effectiveness of doxycycline hyclate and other antibacter al drugs, doxycycline hyclate delayed-release tablets should be used only to treat or prevent nfections that are proven or strongly suspected to be caused by bacteria. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) fo lowed by a maintenance dose of 100 mg daily. In the management of more severe infections (particu arly 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 nto two doses on the first day of treatment, fo lowed 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)

---------- DOSAGE FORMS AND STRENGTHS ----------
Tablets: 75 mg, 80 mg and 100 mg (3)

---------- CONTRAINDICATIONS ----------
Doxycyc ine 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, nfancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)
- *Clostridium diffic le*-associated diarrhea: Evaluate patients if d arrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn react on 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, photosensit vity, urticaria, and hemolytic anem a. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------
- Patients who are on anticoagu ant therapy may require downward adjustment of their anticoagu ant dosage (7.1)
- Avoid co-administration of tetracyclines with penici lin (7.2)
- Absorption of tetracyclines is mpaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracycline may render oral contracept ves less effective (7.4)
- Barb turates, carbamazepine and phenytoin decrease the half-life of doxycyl ne (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 avo ded if possible. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Label ng.

REVISED NOVEMBER 2015
DXYDR:R14

DXYDR:R14

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections om tted from the Fu l Prescribing Information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyc ate delayed-release tablets, USP and other ant bacterial drugs, doxycycline hyclate delayed-release tablets should be used only to treat or prevent infect ons that are proven or strong y suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered n selecting or mod fying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric select on of therapy.

Doxycycline is a tetracycline-class antibacterial ndicated in the fo lowing conditions or diseases:

1.1 Rickettsial Infections

Rocky Mounta n 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 caused by *Chlamydia trachomatis.*

Nongonococcal urethritis caused by *Ureaplasma urealyticum.*

Lymphogranuloma venereum caused by *Chlamydia trachomatis.*

Granu oma nguinale caused by *Klebsiella 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 test ng are recommended.

Doxycycline is indicated for treatment of infections caused by the following microorganisms, when bacteriological testing indicates appropriate susceptibil ty to the drug:

Respiratory tract infections caused by *Haemophilus influenzae.*

Respiratory tract infections caused by *Klebsie la* species.

Upper respiratory infections caused by *Streptococcus pneumoniae.*

1.4 Specific Bacterial Infections

Re apsing fever due to *Borrel a 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 *Brucel a* species (in conjunction w th streptomycin).

Bartonellosis due to *Bartonel a bacilliformis.*

Because many stra ns of the fo lowing groups of microorganisms have been shown to be resistant to doxycycline, culture and suscept bility testing are recommended.

Doxycyc ine is indicated for treatment of infections caused by the fo lowing gram-negative microorganisms, when bacterio ogical test ng indicates appropr ate susceptibility to the drug:

Escherichia coli

Enterobacter aerogenes

Shige la species

Acinetobacter species

Urinary tract infections caused by *Klebsiella* species.

1.5 Ophthalmic Infections

Trachoma caused by *Chlamyd a 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 Penici lin is Contraindicated

When penicillin is contraindicated, doxycycl ne is an alternat ve drug in the treatment of the fol owing infections:

Syphilis caused by *Treponema pallidum.*

Yaws caused by *Treponema pallidum* subspecies *pertenue.*

Vincent's infect on caused by *Fusobacterium fusiforme.*

Actinomycosis caused by *Actinomyces israelii.*

Infections caused by *Clostridium* species.

1.8 Adjunctive Therapy for Acute Intest nal Amebiasis and Severe Acne

In acute ntestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.

1.9 Prophylaxis of Malaria

Doxycyc ine is indicated for the prophy axis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with ch oroquine and/or pyr methamine-sulfadoxine resistant strains *[see Dosage and Administration (2 2) and Patient Counseling Information (17)].*

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage and Adm nistration

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 infect ons of the urinary tract), 100 mg every 12 hours is recommended.

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 f rst 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)].* If gastric irritation occurs, doxycyc ine may be given with food or mi k *[see Clinical Pharmacology (12)].*

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

Uncomplicated Urethral, 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,* adm nister 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 fo lowed 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 penicil in 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 at least 10 days.

2.2 For Prophylaxis of Malaria

For adults, the recommended dose is 100 mg daily. For chi dren 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 doxycyc ine, 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. Chi dren 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 spr nkling 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 transfer would prevent using the dose. The applesauce/doxycycline m xture should be swallowed mmediately 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 DOSAGE 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 **D** to the left of the score and **31** to the right of the score on the other side. Each tablet contains special y coated beads of doxycycline hyclate, USP equivalent to 75 mg of doxycyc ine.

Doxycycline hyclate delayed-release tablets, 80 mg are wh te, 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. Each tablet contains specially coated beads of doxycycline hyclate, USP equ valent to 80 mg of doxycyc ine.

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 **D** to the left of the score and **32** to the right of the score on the other side. Each tablet contains special y coated beads of doxycycline hyclate, USP equivalent to 100 mg of doxycycline.

4 CONTRAINDICATIONS

The drug is contraindicated n 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 deve opment (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent disco oration of the teeth (yel ow-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, inc uding 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, includ ng 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. d fficile.*

C. d fficile produces toxins A and B which contr bute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortal ty, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered n all patients who present with d arrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administrat on of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not d rected against *C. diffic le* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. diffic le,* and surgical evaluation should be instituted as clinica ly 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 ev dence of skin erythema.

5.4 Superinfection

As with other antibacterial preparations, use of doxycycline may resu t n overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibacterial should be discont nued and appropriate therapy instituted.

5.5 Intracranial Hypertension

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

Although IH typically resolves after discontinuation of treatment, the poss bility for permanent visual loss exists. f 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 n any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracyc ine in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discont nued.

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 w th 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 b ood stage gametocytes. Subjects completing this prophylactic reg men 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 ncreases the risk of the deve opment 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.

6 ADVERSE REACTIONS

6.2 Post-Market ng Experience

The following adverse reactions have been dentified 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 y complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The fo lowing adverse reactions have been observed n patients receiving tetracyclines:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphag a, enterocolitis, and inflammatory lesions (w th moni ial 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)].*

Sk n: Macu opapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfo iative dermatitis, and erythema multiforme have been reported. Photosensit vity is discussed above *[see Warn ngs and Precautions (5 3)].*

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

Hypersensit vity Reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus.

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

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracycl ne *[see Warnings and Precautions (5.5)].*

Thyroid Gland Changes: When given over prolonged periods, tetracyclines have been reported to produce brown-b ack 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 p asma prothrombin activity, patients who are on anticoagu ant therapy may require downward adjustment of the r anticoagulant dosage.

7.2 Penici lin

Since bacteriostatic drugs may interfere with the bactericidal action of penici lin, it is advisable to avoid g ving tetracycl nes in conjunction with penicill n.

7.3 Antacids and Iron Preparat ons

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

7.4 Oral Contraceptives

Concurrent use of tetracycline may render oral contracept ves 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category D: There are no adequate and well-contro led studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycl ne during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of ong-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 doxycycl ne use during pregnancy by TERIS - the Teratogen Information System - conc uded 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 nfants with congenital anomalies and 32,804 mothers of infants w th no congen tal anomalies) shows a weak but marginally statistica ly significant association with total malformations and use of doxycyc ine 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 conf ned 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 f rst 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).]*

8.3 Nursing Mothers

Tetracycl nes 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.[4] 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 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 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 75 mg tablets contain 2.15 mg (0.09 mEq) of sodium.

Doxycycline hyclate delayed-release 80 mg tablets contain 2.288 mg (0.096 mEq) of sodium.

Doxycycline hyclate delayed-release 100 mg tablets contain 2.86 mg (0.12 mEq) of sodium.

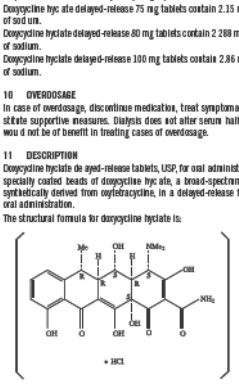
10 OVERDOSAGE

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.

11 DESCRIPTION

Doxycycline hyclate delayed-release tablets, USP, for oral administration, contain specially coated beads of doxycycline hyclate, a broad-spectrum 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 $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and a molecular weight of 1025.89. The chemical designation for doxycycline hyclate is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate, USP is a yellow to light yellow 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: anhydrous lactose, colloidal silicon dioxide, crospovidone, hypromellose phthalate, lactose monohydrate, povidone, 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 (12.4)]*.

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following single and multiple-dose administration of doxycycline hyclate delayed-release tablets, 200 mg to adult volunteers, average peak plasma doxycycline concentration (C_{max}) was 4.6 mcg/mL and 6.3 mcg/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 mcg/mL and 2.3 mcg/mL, respectively. The mean C_{max} and $AUC_{0-\infty}$ of doxycycline are 24% and 13% lower, respectively, following single dose administration of doxycycline hyclate delayed-release tablets, 100 mg with a high fat meal (including milk) compared to fasted conditions. The mean C_{max} of doxycycline is 19% lower and the $AUC_{0-\infty}$ is unchanged following single dose administration of doxycycline hyclate delayed-release tablets, 150 mg with a high fat meal (including milk) compared to fasted conditions. The clinical significance of these decreases is unknown. Doxycycline bioavailability from doxycycline hyclate delayed-release tablets, 200 mg was not affected by food, but the incidence of nausea was higher in fasted subjects. The 200 mg tablets may be administered without regard to meals.

When doxycycline hyclate 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
Actinobacter species
Bartonella bacilliformis
Brucella species
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella granulomatis
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Vibrio fetus
Yersinia pestis

Gram-Positive Bacteria
Bacillus anthracis
Streptococcus pneumoniae

Anaerobes
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria
Noocardiae and other aerobic *Actinomyces* species
Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Parasites
Balantidium coli
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 the 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 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).[5,6,8,9,10,11] 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.[5,7,8] 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.[9] The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria[A]	Minimal Inhibitory Concentration (mcg/mL)			Zone Diameter (mm)			Agar Dilution (mcg/mL)		
	S	I	R	S	I	R	S	I	R
Actinobacter spp.									
Doxycycline	≤ 4	8	≥ 16	≥ 13	10 to 12	≤ 9	-	-	-
Tetracycline	≤ 4	8	≥ 16	≥ 15	12 to 14	≤ 11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤ 4	8	≥ 16
Bacillus anthracis[B]									
Doxycycline	≤ 1	-	-	-	-	-	-	-	-
Tetracycline	≤ 1	-	-	-	-	-	-	-	-
Brucella species[B]									
Doxycycline	≤ 1	-	-	-	-	-	-	-	-
Tetracycline	≤ 1	-	-	-	-	-	-	-	-
Enterobacteriaceae									
Doxycycline	≤ 4	8	≥ 16	≥ 14	11 to 13	≤ 10	-	-	-
Tetracycline	≤ 4	8	≥ 16	≥ 15	12 to 14	≤ 11	-	-	-
Francisella tularensis[B]									
Doxycycline	≤ 4	-	-	-	-	-	-	-	-
Tetracycline	≤ 4	-	-	-	-	-	-	-	-
Haemophilus influenzae									
Tetracycline	≤ 2	4	≥ 8	≥ 29	26 to 28	≤ 25	-	-	-
Mycoplasma pneumoniae[B]									
Tetracycline	-	-	-	-	-	-	≤ 2	-	-
Neisseria gonorrhoeae[C]									
Tetracycline	-	-	-	≥ 38	31 to 37	≤ 30	≤ 0.25	0.5 to 1	≥ 2
Noocardiae and other aerobic *Actinomyces* species									
Doxycycline	≤ 1	2 to 4	≥ 8	-	-	-	-	-	-
Staphylococcus pneumoniae									
Doxycycline	≤ 0.25	0.5	> 1	> 28	25 to 27	< 24	-	-	-
Tetracycline	≤ 1	2	> 4	> 28	25 to 27	< 24	-	-	-
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

[A] 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.

[B] 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.

[C] Gonococci with 30 mcg tetracycline disk zone diameters of < 19 mm usually indicate a plasmid mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥ 16 mcg/mL).

A report of *Susceptible* (S) indicates that 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 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 laboratory controls 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.[5,6,7,8,9,10,11] 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 in Table 2 should be achieved.

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

QC Strain	Minimal Inhibitory Concentration (mcg/mL)	Zone Diameter (mm)	Agar Dilution (mcg/mL)
Enterococcus faecalis ATCC 29212			
Doxycycline	2 to 8	-	-
Tetracycline	8 to 32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5 to 2	18 to 24	-
Tetracycline	0.5 to 2	18 to 25	-
Eggerthella lenta ATCC 43055			
Doxycycline	2 to 16	-	-
Haemophilus influenzae ATCC 49247			
Tetracycline	4 to 32	14 to 22	-
Neisseria gonorrhoeae ATCC 49226			
Tetracycline	-	30 to 42	0.25 to 1
Staphylococcus aureus ATCC 25923			
Doxycycline	-	23 to 29	-
Tetracycline	-	24 to 30	-
Staphylococcus aureus ATCC 29213			
Doxycycline	0.12 to 0.5	-	-
Tetracycline	0.12 to 1	-	-
Streptococcus pneumoniae ATCC 49619			
Doxycycline	0.015 to 0.12	25 to 34	-
Tetracycline	0.06 to 0.5	27 to 31	-
Bacteroides fragilis ATCC 25285			
Tetracycline	-	-	0.12 to 0.5
Bacteroides thetaiotaomicron ATCC 29741			
Doxycycline	2 to 8	-	-
Tetracycline	-	-	8 to 32
Mycoplasma pneumoniae ATCC 29342			
Tetracycline	0.06 to 0.5	-	0.06 to 0.5
Ureaplasma urealyticum ATCC 33175			
Tetracycline	-	-	≥ 8

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 antibacterials, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, a thorough mutagenicity studies of doxycycline have not been conducted, positive results in *in vivo* 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_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline hydrochloride, and tetracycline hydrochloride, 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.

15 REFERENCES

1. Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.
3. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317.
4. Hale T. *Medications and Mothers' Milk*. 9th edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.
5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing*. Twenty-Fifth Informational Supplement, CLSI document M100-S25. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
6. Clinical and Laboratory Standards Institute. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – 10th ed.* CLSI document M07-A10. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
7. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Disk Susceptibility Tests; Approved Standard – 11th ed.* CLSI document M02-A12. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2015.
8. Clinical and Laboratory Standards Institute. *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition*. CLSI document M45-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2010.
9. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, PA 19087, USA, 2012.
10. Clinical and Laboratory Standards Institute. *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition*. CLSI document M24-A2. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA. 2011.
11. Clinical and Laboratory Standards Institute. *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA. 2011.

16 HOW SUPPLIED/STORAGE AND HANDLING

Doxycycline Hyclate Delayed-release Tablets, USP are available containing delayed-release beads of doxycycline hyclate, 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 Controlled Room Temperature.] Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

17 PATIENT COUNSELING INFORMATION

Patients taking doxycycline should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (for example, stay in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- 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 4 further weeks to avoid development of malaria after returning from an endemic area,
  - should not exceed 4 months.

All patients taking doxycycline should be advised:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if photosensitivity (for example, skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered *[see Warnings and Precautions (5.3)]*.
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration *[see Adverse Reactions (6)]*.
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk *[see Drug Interactions (7.3)]*.
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations *[see Drug Interactions (7.3)]*.
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

Diarrhea is a common problem caused by antibacterials which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterials, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as 2 or more months after having taken the last dose of antibacterial. If this occurs, patients should contact their physician as soon as possible.

Patients should be counseled that antibacterial drugs including doxycycline hyclate delayed-release tablets should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When doxycycline hyclate delayed-release tablets are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doxycycline hyclate delayed-release tablets or other antibacterial drugs in the future.

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