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, 75 mg and 100 mg for Oral use.
Initial U.S. Approval: 1967

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)

RECENT MAJOR CHANGES

Additional Skin Adverse Events have been added (6.2)

INDICATIONS AND USAGE

Doxycycline hyclate delayed-release tablets are 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)

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) followed by a maintenance dose of 100 mg/day. 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 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For children over 100 lbs, the usual adult dose should be used. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 75 mg and 100 mg

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. Toll free at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

To report SUSPECTED ADVERSE REACTIONS, contact at 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 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)

USE IN SPECIFIC POPULATIONS

- 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)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2013

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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 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 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:

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*.

1.3 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*.

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 (< 4 months) to areas with chloroquine and/or pyrimethaminesulfadoxine resistant strains. *[See Dosage and Administration (2.2) and Patient Counseling Information (17).]*

2 DOSAGE 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/day. 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 Children Above 8 Years of Age
The recommended dosage schedule for children weighing 45 kg (100 lbs) or less is 4.4 mg/kg (2 mg/lb) of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb 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 (2 mg/lb) of body weight may be used. For children over 45 kg (100 lbs), 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.

Nongonococcal Urethritis (NGU) Caused by C. Trachomatis and 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 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 to 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 (100 lbs) 2.2 mg/kg (1 mg/lb) of body weight, by mouth, twice a day for 60 days. Children weighing 45 kg (100 lbs) 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 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 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 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 specially coated beads of doxycycline hyclate, USP equivalent to 75 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 **D** 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. TETRACYCLINE DRUGS, THEREFORE, 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 Pseudomembranous Colitis

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 antibiotic use. 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic 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 antibiotic preparations, use of this drug may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, the antibiotic 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 Growth and 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 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 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 Incision and Drainage

Incision and drainage or other surgical procedures should be performed in conjunction with antibiotic therapy, when indicated.

5.9 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.

5.10 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.

5.11 Syphilis Testing
In venereal disease when coexistent syphilis is suspected, dark-field examinations should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

5.12 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
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:

6.1 Gastrointestinal
Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of 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)]*.

6.2 Skin
Maculopapular and erythematous rashes, Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme have been reported. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above *[see Warnings and Precautions (5.3)]*.

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

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

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

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

6.7 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 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.

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 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.[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 (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.[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)].

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; however, 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, except for inhalational anthrax (post-exposure), unless 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. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Doxycycline hyclate delayed-release 75 mg tablets contain 2.15 mg (0.09 mEq) of sodium.

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

8.6 Renal Impairment

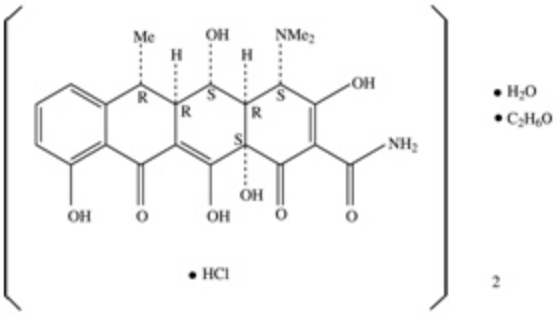
Administration of doxycycline at the usual recommended dose does not result in excessive accumulation in patients with renal impairment. Dosage adjustment is not necessary in patients with renal impairment *[see Clinical Pharmacology (12)]*.

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 antibiotic synthetically derived from oxytetracycline, in a delayed-release formulation for oral administration.
The structural formula for doxycycline hyclate is:



with a molecular formula of $C_{22}H_{24}N_2O_8$, HCl, ½ C_2H_6O, ½ H_2O and a molecular weight of 512.9. 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 crystalline powder, freely soluble in water and methanol, slightly soluble in alcohol, soluble in solutions of alkali hydroxides and carbonates, and practically insoluble in chloroform and in ether. 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. Inert ingredients in the tablet formulation are: anhydrous lactose, colloidal silicon dioxide, crospovidone, hypromellose phthalate, lactose monohydrate, povidone, pregelatinized starch, sodium chloride, sodium lauryl sulfate, stearic acid, talc, and triethyl citrate.
Meets USP Dissolution Test 3.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is an antimicrobial drug *[see Clinical Pharmacology (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_{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.
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 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% 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

The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative organisms. Cross-resistance between tetracyclines is common.
Because isolates of the following gram-negative, gram-positive, anaerobic and other microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing when possible is recommended prior to initiating therapy.

Gram-Negative Microorganisms

Acinetobacter species
Brucella species
Calymmatobacterium granulomatis
Enterobacter aerogenes
Escherichia coli
Francisella tularensis

Haemophilus ducreyi
Haemophilus influenzae
Klebsiella species
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Yersinia pestis
Gram-Positive Microorganisms
Alpha-hemolytic streptococci (viridans group)
Bacillus anthracis
Enterococcus faecalis
Enterococcus faecium
Streptococcus pyogenes
Streptococcus pneumoniae
Anaerobic Microorganisms
Bacteroides species
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes
Other Microorganisms
Actinomyces species
Bartonella bacilliformis
Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema 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 Test Methods
When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas 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 procedure based on dilution methods (broth, agar, or microdilution),[5,7] or equivalent using standardized inoculum and concentrations of doxycycline. The MIC values should be interpreted according to the criteria provided in Table 1.

Diffusion Techniques
Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The standard procedure[6,7] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of microorganisms to doxycycline. Interpretation involves the correlation of the diameter obtained in the disk test with the MIC for doxycycline. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 30 mcg doxycycline disk should be interpreted according to the criteria in Table 1:

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline

Pathogen	Susceptibility Interpretive Criteria Minimal Inhibitory	Disk Diffusion Zone Diameter (mm) - 30 mcg disk

	Concentration (mcg/mL)					
	S	I	R	S	I	R
Acinetobacter spp.	≤ 4	8	≥ 16	≤ 9	10 to 12	≥ 13
Enterobacteriaceae	≤ 4	8	≥ 16	≤ 10	11 to 13	≥ 14
Enterococcus *faecalis* and *faecium*	< 4	8	≥ 16	≤ 12	13 to 15	≥ 16
Vibrio cholerae	≤ 4	8	≥ 16	-	-	-
Yersinia pestis	≤ 4	8	≥ 16	-	-	-
Bacillus anthracis[*]	≤ 1	-	-	-	-	-
Brucella species[*]	≤ 1	-	-	-	-	-
Franciscella tularensis[*]	≤ 4	-	-	-	-	-

*****The current absence of resistance isolates precludes defining any results other than "Susceptible" Isolates yielding results other than susceptible should be subjected to additional testing.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism 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” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound reaches the concentrations usually achievable; 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.[5,6,7] Standard doxycycline

powder should provide the MIC values provided in Table 2. For the diffusion technique using the 30 mcg tigecycline disk the criteria provided in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Doxycycline to be Used for Validation of Susceptibility Test Results

	Acceptable Quality Control Ranges	
Pathogen	Minimal Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameter (mm) - 30 mcg disk
Enterococcus faecalis ATCC 29212	2 to 8	NONE
Escherichia coli ATCC 25922	0.5 to 2	18 to 24
Staphylococcus aureus ATCC 25923		
for *Enterococcus* spp.	Not Applicable	23 to 29
Staphylococcus aureus ATCC 29213		
for *Enterococcus* spp., *B. anthracis*	0.12 to 0.5	Not Applicable
and *F. tularensis*		
Streptococcus pneumoniae		

ATCC 49619 for *Brucella* spp.	0.015 to 0.12	Not Applicable

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, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* 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

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

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Doxycycline Hyclate Delayed-release Tablets, USP are available containing delayed-release beads of doxycycline hyclate, USP equivalent to 75 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
NDC 0378-4531-05
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
NDC 0378-4532-05
bottles of 500 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 for malaria prophylaxis 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, staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellant).
- 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 phototoxicity (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 (6.1)]*.
- 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 antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 antibiotic. 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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Morgantown, WV 26505 U.S.A.
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PRINCIPAL DISPLAY PANEL - 75 mg
NDC 0378-4531-91
Doxycycline
Hyclate
Delayed-release
Tablets, USP
75 mg*
Rx only 60 Tablets
*Each tablet contains delayed-release
beads of doxycycline hyclate, USP
equivalent to 75 mg of doxycycline.
Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication

out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Usual Adult Dosage: See accompanying prescribing information.
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PRINCIPAL DISPLAY PANEL - 100 mg
NDC 0378-4532-01
Doxycycline
Hyclate
Delayed-release
Tablets, USP
100 mg*
Rx only 100 Tablets
*Each tablet contains delayed-release beads of doxycycline hyclate, USP equivalent to 100 mg of doxycycline.
Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.
Keep container tightly closed.
Keep this and all medication out of the reach of children.
Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room Temperature.]
Usual Adult Dosage: See accompanying prescribing information.
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*Each tablet contains delayed-release beads of doxycycline hyclate, USP equivalent to 100 mg of doxycycline.

NDC 0378-4532-01

Doxycycline Hyclate

Delayed-release

Tablets, USP

100 mg*

Mylan®

Rx only **100 Tablets**

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication out of the reach of children.

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Usual Adult Dosage: See accompanying prescribing information.

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