

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DORYX® (doxycycline hyclate) Delayed-Release Tablets safely and effectively. See Full Prescribing Information for DORYX Tablets.

DORYX® (doxycycline hyclate) Delayed-Release Tablets, 75 mg, 100 mg and 150 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, DORYX 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

Dosage Forms and Strengths, added DORYX Tablets 150 mg (3) 06/2008
Geriatric Use, added mg (mEq) sodium for DORYX Tablets 150 mg (8.5) 06/2008
Pharmacokinetics, added food effect wording for DORYX Tablets 150 mg (12.3) 06/2008
How Supplied/Storage and Handling, added DORYX Tablets 150 mg (16) 06/2008

INDICATIONS AND USAGE

DORYX is a tetracycline-class antimicrobial indicated for:

- Rickettsial infections (1.1)
- Sexually transmitted infections (1.2)
- Respiratory tract infections (1.3)
- Specific bacterial infections (1.4)
- Ophthalmic infections (1.5)
- Anthrax, including inhalational anthrax (post-exposure) (1.6)
- Alternative treatment for selected infections when penicillin is contraindicated (1.7)
- Adjunctive therapy in acute intestinal amebiasis and severe acne (1.8)
- Prophylaxis of malaria (1.9)

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 eight 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 lb, the usual adult dose should be used. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablets: 75, 100 and 150 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. Re-evaluate 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 Warner Chilcott at 1-800-521-8813 and www.wcix.com 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 (7.7)
- Barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline

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** and FDA-approved Patient Labeling.

Revised: June 2008

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING

1 INDICATIONS AND USAGE

- 1.1 Rickettsial Infections
- 1.2 Sexually Transmitted Infections
- 1.3 Respiratory Tract Infections
- 1.4 Specific Bacterial Infections
- 1.5 Ophthalmic Infections
- 1.6 Anthrax, Including Inhalational Anthrax (Post-Exposure)
- 1.7 Alternative Treatment for Selected Infections when Penicillin is Contraindicated
- 1.8 Adjunctive Therapy for Acute Intestinal Amebiasis and Severe Acne
- 1.9 Prophylaxis of Malaria

2 DOSAGE AND ADMINISTRATION

- 2.1 Usual Dosage and Administration
- 2.2 For Prophylaxis of Malaria
- 2.3 Inhalation Anthrax (post exposure)
- 2.4 Sprinkling the tablet over applesauce

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Tooth Development
- 5.2 Pseudomembranous Colitis
- 5.3 Photosensitivity
- 5.4 Superinfection
- 5.5 Benign Intracranial Hypertension
- 5.6 Growth and Development
- 5.7 Antianabolic Action
- 5.8 Incision and Drainage
- 5.9 Malaria
- 5.10 Development of Drug-Resistant Bacteria
- 5.11 Syphilis Testing
- 5.12 Laboratory Testing for Long-Term Therapy

6 ADVERSE REACTIONS

- 6.1 Gastrointestinal
- 6.2 Skin
- 6.3 Renal
- 6.4 Hypersensitivity Reactions
- 6.5 Blood
- 6.6 Benign Intracranial Hypertension
- 6.7 Thyroid Gland Changes

7 DRUG INTERACTIONS

- 7.1 Anticoagulant Drugs
- 7.2 Penicillin
- 7.3 Antacids and Iron Preparations
- 7.4 Oral Contraceptives
- 7.5 Barbiturates and Anti-epileptics
- 7.6 Penthrane
- 7.7 Drug/Laboratory Test Interactions

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the Full Prescribing Information are not listed.

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 75 mg, 100 mg and 150 mg

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of DORYX and other antibacterial drugs, DORYX 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 pyrimethamine-sulfadoxine 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 eight years of age: The recommended dosage schedule for children weighing 45 kg (100 lb) 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 lb), 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 1-2 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 lb) 2.2 mg/kg (1 mg/lb) of body weight, by mouth, twice a day for 60 days. Children weighing 45 kg (100 lb) or more should receive the adult dose.

2.4 Sprinkling the tablet over applesauce

DORYX Tablets may also be administered by carefully breaking up the tablet and sprinkling the tablet contents (delayed-release pellets) on a spoonful of applesauce. The delayed-release pellets must not be crushed or damaged when breaking up the tablet. Any loss of pellets in the transfer would prevent using the dose. The applesauce/DORYX 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/DORYX Tablet cannot be taken immediately, the mixture should be discarded and not stored for later use.

3 DOSAGE FORMS AND STRENGTHS

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 75 mg are white oval tablets containing yellow pellets and debossed with “D75” on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 75 mg of doxycycline.

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 100 mg are white oval tablets containing yellow pellets and debossed with “D100” on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 100 mg of doxycycline.

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 150 mg are white, oval scored tablets containing yellow pellets and debossed with “D1|50” on one face and plain on the other. Each tablet contains specially coated pellets of doxycycline hyclate equivalent to 150 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 DORYX 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 two 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 fontanel 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 six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity also has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

5.7 Antianabolic Action

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

5.8 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 DORYX 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. 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 fontanel 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 1 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, DORYX 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 DORYX 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.

DORYX 75 mg tablets contain 4.5 mg (0.196 mEq) of sodium.

DORYX 100 mg tablets contain 6 mg (0.261 mEq) of sodium.

DORYX 150 mg tablets contain 9 mg (0.392 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)].

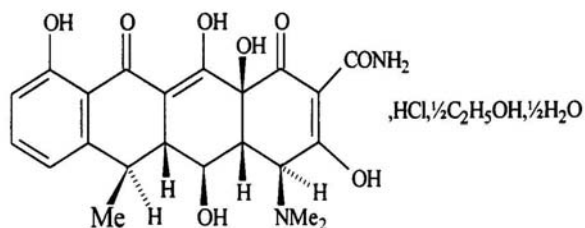
10. OVERDOSAGE

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

DORYX (doxycycline hyclate) Delayed-Release Tablets, for oral administration, contain specially coated pellets 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 C₂₂H₂₄N₂O₈, HCl, ½ C₂H₆O, ½ H₂O and a molecular weight of 512.9. The chemical designation for doxycycline hyclate is [4S(4aR,5S,5aR,6R,12aS)]-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-deoxonaphthacene-2-carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate. Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form. Inert ingredients in the tablet formulation are: lactose monohydrate; microcrystalline cellulose; sodium lauryl sulfate; sodium chloride; talc; anhydrous lactose; corn starch; crospovidone; magnesium stearate; cellulosic polymer coating.

12 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-∞} of doxycycline are 24% and 13% lower, respectively, following single dose administration of DORYX 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-∞} is unchanged following single dose administration of DORYX Tablets, 150 mg with a high fat meal (including milk) compared to fasted conditions. The clinical significance of these decreases is unknown.

When DORYX 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 1-5%/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 18-22 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

Aerobic 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 pertenu

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 Concentration (mcg/mL)			Disk Diffusion Zone Diameter (mm) - 30 mcg disk		
		<u>I</u>	<u>R</u>	<u>S</u>	<u>I</u>	<u>R</u>
<i>Acinetobacter</i> spp.	≤4	8	≥16	≤9	10-12	≥13
<i>Enterobacteriaceae</i>	≤4	8	≥16	≤10	11-13	≥14
<i>Enterococcus faecalis</i> and <i>faecium</i>	<4	8	≥16	≤12	13-15	≥16
<i>Vibrio cholerae</i>	≤4	8	≥16	-	-	-
<i>Yersinia pestis</i>	≤4	8	≥16	-	-	-
<i>Bacillus anthracis</i> ^a	≤1	-	-	-	-	-
<i>Brucella</i> species ^a	≤1	-	-	-	-	-
<i>Francisella tularensis</i> ^a	≤4	-	-	-	-	-

^aThe 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 tige cycline 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

Pathogen	Acceptable Quality Control Ranges Minimal Inhibitory Concentration (mcg/mL)	Disk Diffusion Zone Diameter (mm) - 30 mcg disk
<i>Enterococcus faecalis</i> ATCC 29212	2 - 8	NONE
<i>Escherichia coli</i> ATCC 25922	0.5 - 2	18 - 24
<i>Staphylococcus aureus</i> ATCC 25923		
for <i>Enterococcus</i> spp.	Not Applicable	23 - 29
<i>Staphylococcus aureus</i> ATCC 29213		
for <i>Enterococcus</i> spp., <i>B. anthracis</i> and <i>F. tularensis</i>	0.12 - 0.5	Not Applicable
<i>Streptococcus pneumoniae</i> ATCC 49619 for <i>Brucella</i> spp.	0.015 - 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 PO₄, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO₄, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO₄, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl, were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

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

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

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 Kundsinn 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). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically – 7th ed.* Approved Standard, CLSI document M7-A7, Vol. 26. CLSI, Wayne, PA. January 2006.
6. CLSI. *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests – 9th ed.* Approved Standard, CLSI document M2-A9, Vol. 26. CLSI, Wayne, PA. January 2006.
7. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing – 18th Informational Supplement.* Approved Standard, CLSI document M100-S18, Vol. 28. CLSI, Wayne, PA. January 2008.

16 HOW SUPPLIED/STORAGE AND HANDLING

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 75 mg: Bottles of 60 tablets
N 0430-0111-20

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 100 mg: Bottles of 100 tablets
N 0430-0112-24

DORYX[®] (doxycycline hyclate) Delayed-Release Tablets, 150 mg: Bottles of 60 tablets
N 0430-0113-20

Store at 25° C (77° F); excursions permitted to 15° - 30° C (59° - 86° F) [see USP Controlled Room Temperature]; dispense in a tight, light-resistant container (USP).

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 (e.g., staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
 - should begin 1-2 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 (e.g., skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered [See **WARNINGS AND PRECAUTIONS** (5.6)].
- 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** (7.4)].
- 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 two 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 DORYX should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When DORYX is 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 DORYX or other antibacterial drugs in the future.

Rx only

U.S. Patent No: 6,958,161

Manufactured by:

Mayne Pharma International Pty Ltd
1538 Main North Road
Salisbury South, South Australia 5106

Marketed by:

Warner Chilcott (US), LLC
Rockaway, NJ 07866
1-800-521-8813

0112G035

Revised June 2008

