

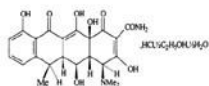
DORYX® (doxycycline hyclate) Delayed-Release Capsules, 75 mg and 100 mg

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 bacteria.

## DESCRIPTION

DORYX Capsules contain specially coated pellets 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  $C_{22}H_{24}N_2O_8$ , HCl,  $\frac{1}{2} C_2H_6O$ ,  $\frac{1}{2} H_2O$  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-2carboxamide monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.

Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inactive ingredients in the capsule formulation are: lactose; microcrystalline cellulose; povidone, starch wheat, magnesium stearate; cellulosic polymer coating. The capsule shell and/or band contains FD and C blue No. 1; FD and C yellow No. 6; D and C yellow No. 10; gelatin, silicon dioxide; sodium lauryl sulfate; titanium dioxide.

## CLINICAL PHARMACOLOGY

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 mcg/mL of doxycycline at 2 hours decreasing to 1.45 mcg/mL at 24 hours. Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

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

### 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.

#### Resistance

Cross-resistance of these organisms to tetracycline is common.

#### Antimicrobial Activity

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections (see **INDICATIONS AND USAGE**)

#### **Gram-Negative Bacteria**

*Acinetobacter* species  
*Bartonella bacilliformis*  
*Brucella* species  
*Campylobacter fetus*  
*Enterobacter aerogenes*  
*Escherichia coli*  
*Francisella tularensis*  
*Haemophilus ducreyi*  
*Haemophilus influenzae*  
*Klebsiella granulomatis*  
*Klebsiella* species  
*Neisseria gonorrhoeae*  
*Shigella* species  
*Vibrio cholerae*  
*Yersinia pestis*

#### **Gram-Positive Bacteria**

*Bacillus anthracis*  
*Listeria monocytogenes*  
*Streptococcus pneumoniae*

#### **Anaerobic Bacteria**

*Clostridium* species  
*Fusobacterium fusiforme*  
*Propionibacterium acnes*

#### **Other Bacteria**

*Nocardiae* 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 cumulative reports of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antimicrobial drug for treatment.

#### *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 dilution method<sup>1,2,4,6,7</sup> (broth and/or agar) The MIC values obtained should be interpreted according to the following criteria 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 should be determined using a standardized test method<sup>1,3,4</sup>. This procedure uses paper disks impregnated with 30 mcg doxycycline disk to test susceptibility of microorganisms 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<sup>1,5</sup>. The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Bacteria <sup>a</sup>	Minimal Inhibitory Concentration (mcg/mL)			Zone Diameter (mm)			Agar Dilution (mcg/mL)		
	S	I	R	S	I	R	S	I	R
<i>Acinetobacter spp.</i>									
Doxycycline	≤4	8	≥16	≥13	10-12	≤9	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
Anaerobes									
Tetracycline	-	-	-	-	-	-	≤4	8	≥16
<i>Bacillus anthracis</i> <sup>b</sup>									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Brucella species</i> <sup>b</sup>									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
<i>Enterobacteriaceae</i>									
Doxycycline	≤4	8	≥16	≥14	11-13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12-14	≤11	-	-	-
<i>Francisella tularensis</i> <sup>b</sup>									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-
<i>Haemophilus influenza</i>									
Tetracycline	≤2	4	≥8	≥29	26-28	≤25	-	-	-
<i>Mycoplasma pneumoniae</i> <sup>b</sup>									
Tetracycline	-	-	-	-	-	-	≤2	-	-
<i>Nocardiae</i> and other aerobic <i>Actinomyces species</i> <sup>ab</sup>									
Doxycycline	≤1	2-4	≥8	-	-	-	-	-	-
<i>Neisseria gonorrhoeae</i> <sup>c</sup>									
Tetracycline	-	-	-	≥38	31-37	≤30	≤0.25	0.5-1	≥2
<i>Streptococcus pneumoniae</i>									
Doxycycline	≤0.25	0.5	≥1	≥28	25-27	≤24	-	-	-
Tetracycline	≤1	2	≥4	≥28	25-27	≤24	-	-	-
<i>Vibrio cholera</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Yersinia pestis</i>									
Doxycycline	≤4	8	≥16	-	-	-	-	-	-
Tetracycline	≤4	8	≥16	-	-	-	-	-	-
<i>Ureaplasma urealyticum</i>									
Tetracycline	-	-	-	-	-	-	≤1	-	≥2

<sup>a</sup> 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.

<sup>b</sup> 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.

<sup>c</sup> Gonococci with 30 mcg 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 the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentrations usually achievable at the site of infection. A report of "Intermediate" (I) indicates that the result should be considered unequivocal, 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" (R) indicates that the antimicrobial drug is not likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

#### Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test<sup>1,2,3,4,5,6,7</sup>. 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 or 30 mcg tetracycline disk, the criteria noted in Table 2 should be achieved.

<b>Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline</b>			
<b>QC Strain</b>	<b>Minimal Inhibitory Concentration (mcg/mL)</b>	<b>Zone Diameter (mm)</b>	<b>Agar Dilution (mcg/mL)</b>
<i>Enterococcus faecalis</i> ATCC <sup>a</sup> 29212			
Doxycycline	2 – 8	-	-
Tetracycline	8 - 32	-	-
<i>Escherichia coli</i> ATCC 25922			
Doxycycline	0.5 – 2	18 – 24	-
Tetracycline	0.5 - 2	18 - 25	-
<i>Eggerthella lenta</i> ATCC 43055			
Doxycycline	2 - 16	-	-
<i>Haemophilus influenzae</i> ATCC 49247			
Tetracycline	4 - 32	14 - 22	-
<i>Neisseria gonorrhoeae</i> ATCC 49226			
Tetracycline	-	30 - 42	0.25 - 1
<i>Staphylococcus aureus</i> ATCC 25923			
Doxycycline	-	23 – 29	-
Tetracycline	-	24 - 30	-
<i>Staphylococcus aureus</i> ATCC 29213			
Doxycycline	0.12 – 0.5	-	-
Tetracycline	0.12 - 1	-	-
<i>Streptococcus pneumoniae</i> ATCC 49619			
Doxycycline	0.015 – 0.12	25 – 34	-
Tetracycline	0.06 – 0.5	27 - 31	-
<i>Bacteroides fragilis</i> ATCC 25285			
Tetracycline	-	-	0.125 – 0.5
<i>Bacteroides thetaiotaomicron</i> ATCC 29741			
Doxycycline	2 – 8	-	-
Tetracycline	-	-	8 - 32
<i>Mycoplasma pneumoniae</i> ATCC 29342			
Tetracycline	0.06 – 0.5	-	0.06 – 0.5
<i>Ureaplasma urealyticum</i> ATCC 33173			
Tetracycline	-	-	≥8

<sup>a</sup>ATCC is the American Type-Culture Collection

#### **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 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 empirical selection of therapy.

**Treatment:**

Doxycycline is indicated for the treatment of the following infections:

- Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsia*.
- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
- Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.
- Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
- Inclusion conjunctivitis caused by *Chlamydia trachomatis*.
- Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.
- Nongonococcal urethritis caused by *Ureaplasma urealyticum*. Relapsing fever due to *Borrelia recurrentis*.

Doxycycline also is indicated for the treatment of infections caused by the following gram-negative microorganisms:

- Chancroid caused by *Haemophilus ducreyi*.
- 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*
- Granuloma inguinale caused by *Klebsiella granulomatis*.

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
- Respiratory tract infections caused by *Haemophilus influenzae*.
- Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:

- Upper respiratory infections caused by *Streptococcus pneumoniae*
- Anthrax due to *Bacillus anthracis*, including Inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

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

- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
- Syphilis caused by *Treponema pallidum*.
- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Vincent's infection caused by *Fusobacterium fusiforme*.
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

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

In severe acne, doxycycline may be useful adjunctive therapy.

**Prophylaxis:**

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** section and Information for Patients subsection of the **PRECAUTIONS** section).

**CONTRAINDICATIONS**

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

**WARNINGS**

**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. Use doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

***Clostridium Difficile* Associated Diarrhea**

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

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

**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.

**Potential for Microbial Overgrowth**

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

**Severe Skin Reactions**

Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in

patients receiving doxycycline [See Adverse Reactions (6)]. If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

### **Intracranial Hypertension**

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including DORYX. Clinical manifestations of IH 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 tetracycline associated IH. Avoid concomitant use of isotretinoin and Doryx because isotretinoin is also known to cause pseudotumor cerebri.

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

### **Skeletal Development**

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryotoxicity 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 potential hazard to the fetus.

### **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.

## **PRECAUTIONS**

### **General**

As with other antibacterial preparations, use of this drug may result in overgrowth of non-susceptible organism, including fungi. If superinfection occurs, the antibacterial should be discontinued and appropriate therapy instituted.

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

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. 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.

### **Information for Patients**

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 to 2 days before travel to the malarious areas.
- 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**).
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration (see **ADVERSE REACTIONS**).
- 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**).
- that the absorption of tetracyclines is reduced when taking bismuth subsalicylate (see **DRUG INTERACTIONS**).
- 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 two or more months after having taken the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible.

Patients should be counselled 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.

**Laboratory tests:** In venereal disease when coexistent syphilis is suspected, dark-field examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

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

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

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

Absorption of tetracyclines is impaired by bismuth subsalicylate.

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

**Drug/Laboratory Test Interactions:** False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

**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, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

**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.<sup>a</sup>

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.<sup>b</sup>

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.<sup>c</sup>

Nonteratogenic effects: (see **WARNINGS**).

**Labor and Delivery:** The effect of tetracyclines on labor and delivery is unknown.

#### **Nursing Mothers**

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated. The effects of prolonged exposure to doxycycline in breast milk are unknown.<sup>d</sup> 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**).

**Pediatric use:** Because of the effects of drugs of the tetracycline-class on tooth development and growth, use doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies. (see **WARNINGS and DOSAGE AND ADMINISTRATION**).

**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 the decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### **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:

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region and pancreatitis. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Superficial discoloration of the adult permanent dentition, reversible upon drug discontinuation and professional dental cleaning has been reported. Permanent tooth discoloration and enamel hypoplasia may occur with drugs of the tetracycline class when used during tooth development (see **WARNINGS**). 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**).

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**).

Renal toxicity: Rise in BUN has been reported and is apparently dose-related (see **WARNINGS**).

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus, and drug reaction with eosinophilia and systemic symptoms (DRESS).

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

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebr) has been associated with the use of tetracyclines (see **WARNINGS**).

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.

## **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.

## **DOSAGE AND ADMINISTRATION**

The usual dosage and frequency of administration of doxycycline differs from that of the other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects.

### Adults:

The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours), followed by a maintenance dose of 100 mg daily. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

### Pediatric Patients:

For all pediatric patients weighing less than 45 kg with severe or life threatening infections (e.g., anthrax, Rocky Mountain spotted fever) the recommended dosage is 2.2 mg/kg of body weight administered every 12 hours. Children weighing 45 kg or more, should receive the adult dose. (see **WARNINGS and PRECAUTIONS**).

For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.2 mg per kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

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

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**).

If gastric irritation occurs, doxycycline may be given with food or milk.

Studies to date have indicated that administration of doxycycline at the usual recommended doses does not lead to excessive accumulation of the antibacterial in patients with renal impairment.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days. As an alternative single visit dose, administer 300 mg stat followed in an hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

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 *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 *N. gonorrhoeae*: 100 mg, by mouth, twice-a-day for at least 10 days.

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

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

Inhalational anthrax (post-exposure):

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

Children: weighing less than 45 kg; (2 mg/kg) of body weight, by mouth, twice-a day for 60 days. Children weighing 45 kg or more should receive the adult dose.

#### **Sprinkling the Capsule Contents on Applesauce**

DORYX Capsules may also be administered by carefully opening the capsule and sprinkling the capsule contents on a spoonful of applesauce. However, any loss of pellets in the transfer would prevent using the dose. The applesauce should be swallowed immediately without chewing and followed with a cool 8-ounce glass of water to ensure complete swallowing of the capsule contents. 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 pellets cannot be taken immediately, the mixture should be discarded and not stored for later use.

## **HOW SUPPLIED**

DORYX® (doxycycline hyclate) Delayed-Release Capsules, 100 mg have a dark yellow transparent body, with light blue opaque cap; the capsule bearing the inscription "DORYX" and "WC" in a circle, printed in white. Pellets are colored yellow. Each capsule contains specially coated pellets of doxycycline hyclate equivalent to 100 mg of doxycycline. Supplied in bottles of 50 capsules - N 51862-548-50

DORYX® (doxycycline hyclate) Delayed-Release Capsules, 75 mg have an orange transparent body, with green opaque cap: the capsule bearing the inscription "DORYX" and "75 mg" in black. Pellets are colored yellow. Each capsule contains specially coated pellets of doxycycline hyclate equivalent to 75 mg of doxycycline. Supplied in bottles of 60 tablets - N 51862-548-60

## **STORAGE CONDITIONS**

**Store at controlled room temperature below 25° C (77° F).**

## **ANIMAL PHARMACOLOGY AND TOXICOLOGY**

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO<sub>4</sub>, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO<sub>4</sub>, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO<sub>4</sub>, 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.

## **References:**

1. Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Susceptibility Testing; Twenty Sixth Informational Supplement*, CLSI document M100 S26 [2016], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.
2. Clinical Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, Approved Standard Tenth Edition*. CLSI document M07 A10 [2015], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.
3. Clinical Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Test; Approved Standard- Twelfth Edition*. CLSI document M02 A12 [2015]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.
4. Clinical Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline -Third Edition*. CLSI document M45 A3 [2015] Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.
5. Clinical Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard - Eighth Edition*. CLSI document M11-A8 [2012]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

6. Clinical Laboratory Standards Institute (CLSI). *Susceptibility Testing of Mycobacteria, Nocardiae, and other Aerobic Actinomycetes; Approved Standard - Second Edition*. CLSI document M24-A2 [2011]. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.
7. Clinical Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline - Second Edition*. CLSI document M43-A [2011], Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA.

<sup>a</sup>Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.

<sup>b</sup>Czietel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.

<sup>c</sup>Horne HW Jr. and Kundsinn RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.

<sup>d</sup>Drugs and Lactation Database (LactMed) [Internet], Bethesda (MD): National Library of Medicine (US); [Last Revision Date 2015 March 10, cited 2016 Jan]. Doxycycline; LactMed Record Number: 100; [about 3 screens]. Available from: <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>

## Rx only

Manufactured by:

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**To report SUSPECTED ADVERSE REACTIONS, contact Mayne Pharma at 1-844-825-8500 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

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