

**LACHMAN CONSULTANT SERVICES, INC.**  
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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August 31, 2004

**OVERNIGHT COURIER 8/31/04**

Division of Dockets Management  
Food and Drug Administration (HFA-305)  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Citizen Petition**

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug products, Doxycycline Hyclate Tablets 75 mg and 100 mg, are suitable for consideration in an abbreviated new drug application (ANDA).

**A. Action Requested**

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Doxycycline Hyclate Tablets, 75 mg and 100 mg are suitable for submission in an ANDA. The listed reference drug product (RLD) upon which this petition is based is Doryx® (doxycycline hyclate), Capsules (coated pellets) 100 mg. Doryx® is also approved in a 75 mg strength. Therefore, the petitioner seeks a change in dosage form (from capsule to tablet) from that of the listed drug product.

**B. Statement of Grounds**

The RLD product is a capsule product containing (coated pellets) 75 mg or 100 mg of doxycycline hyclate. The listing for Doryx® Capsules appears on page 3-135 of the 24<sup>th</sup> edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (better known as the Orange Book) (Attachment A). The proposed drug product represents a tablet dosage form of the same strengths and same active ingredient. The petition is thus seeking a change in dosage form (from capsule to tablet) from that of the RLD.

In support of the change in dosage form requested in this petition, we refer to other FDA **approved** "doxycycline" drug products that are available in a tablet dosage form (i.e., other doxycycline hyclate tablet products). However, in this instance, citing any of those products as the RLD would not be appropriate, since the purpose of this petition is to seek the ability to file a different dosage form (tablet) that is bioequivalent to Doryx® (doxycycline hyclate) Capsules (coated pellets). The petitioner is seeking this change in dosage form in an effort to make an alternate dosage form (tablet) available for those individuals that either have difficulty in

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swallowing a capsule or who prefer a tablet dosage form as an alternative to Doryx® (doxycycline hyclate), Capsules (coated pellets).

In further support of our proposed product, the petitioner would like to point out that the Agency has previously approved ANDA suitability petitions allowing for a change in dosage form (from capsule to tablet) in many instances. The labeling of the proposed product will be the same as that of the RLD with the exception of the obvious change in dosage form sought in this petition. The uses, doses and indications for the proposed product are also the same as those of the RLD. Draft labeling for the proposed product is included in Attachment B and labeling of the RLD is included in Attachment C.

Therefore, the petitioner's request for the Commissioner to find that a change in dosage form from capsule to tablet for Doxycycline Hyclate 75 mg and 100 mg should raise no questions of safety or effectiveness, and the Agency should approve the petition.

### **Pediatric Waiver Request**

In any petition seeking a change in dosage form, it is necessary to address the provisions of the Pediatric Research Equity Act (PREA) of 2003. PREA amended the Federal Food, Drug and Cosmetic Act, to provide the Agency authority to require drug firms to study certain drugs in pediatric patients if the Agency felt that such study would provide beneficial health data for that patient population. In that regard, please consider this request for a full waiver for the need to conduct pediatric studies for the proposed drug product under PREA for the reasons outlined below.

The act provides a provision for a waiver from such requirement if:

(iii) the drug or biological product,

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) is not likely to be used in a substantial number of pediatric patients.

The petitioner hereby requests that a waiver from the conduct of pediatric patient be granted for the approval of this petition to permit subsequent ANDA filing.

The labeling of the RLD clearly supports the use of the doxycycline hyclate in pediatric patients above 8 years of age.

"The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by a 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 pediatric patients over 100 pounds, the usual adult dose should be used."

However, the lack of dosing recommendations for pediatric patients under 8 years of age should not be construed as a need to study this drug in lower age groups since the product contains warnings against use in younger patients.

"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 drug but 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." (Emphasis added)

Clearly then, this drug product should not be utilized in other than the pediatric population for whom it is currently labeled (age 8 or older) and based on the fact that inhalational anthrax is an extremely rare disease, the product would not likely be used in a substantial number of pediatric patients. Therefore, a waiver should be granted exempting pediatric studies on the proposed product.

**C. Environmental Impact**

The petitioner claims a categorical exclusion under 21 CFR 25.31.

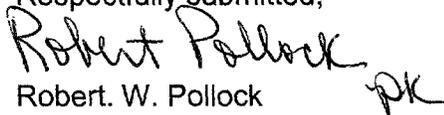
**D. Economic Impact**

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

**E. Certification**

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

pk

Robert W. Pollock  
Vice President  
Lachman Consultant Services, Inc.  
1600 Stewart Avenue  
Westbury, New York 11590

RWP/pk

- Attachments: A. page 3-135 of the 24<sup>th</sup> edition of the Approved Drug Products with Therapeutic Equivalence Evaluations  
B. Proposed Labeling  
C. Doryx (RLD) Labeling

cc: Emily Thomas (OGD)

P04P4244

LACHMAN CONSULTANT SERVICES, INC.  
Westbury, NY 11590

# ATTACHMENT A

PRESCRIPTION DRUG PRODUCT LIST

3-135

DOXYCYCLINE

TABLET; ORAL  
DOXYCYCLINE  
PAR PHARM

EQ 75MG BASE N65070 003  
DEC 30, 2002  
+ EQ 100MG BASE N65070 002  
DEC 15, 2000

DOXYCYCLINE CALCIUM

SUSPENSION; ORAL  
VIBRAMYCIN  
+ PFIZER

EQ 50MG BASE/5ML N50480 001

DOXYCYCLINE HYCLATE

CAPSULE; ORAL

DOXYCYCLINE HYCLATE

<u>AB</u>	AXIOM PHARM	<u>EQ 50MG BASE</u>	N61717 001
<u>AB</u>		<u>EQ 100MG BASE</u>	N61717 002
<u>AB</u>	IVAX PHARMS	<u>EQ 50MG BASE</u>	N62500 001
			SEP 11, 1984
<u>AB</u>		<u>EQ 100MG BASE</u>	N62500 002
			SEP 11, 1984
<u>AB</u>	MUTUAL PHARM	<u>EQ 50MG BASE</u>	N62675 001
			JUL 10, 1986
<u>AB</u>		<u>EQ 100MG BASE</u>	N62676 001
			JUL 10, 1986
<u>AB</u>	MYLAN	<u>EQ 50MG BASE</u>	N62337 001
			MAR 29, 1982
<u>AB</u>		<u>EQ 100MG BASE</u>	N62337 002
			MAR 29, 1982
<u>AB</u>	WATSON LABS	<u>EQ 50MG BASE</u>	N62031 002
			OCT 13, 1982
<u>AB</u>		<u>EQ 100MG BASE</u>	N62031 001
			NOV 07, 1984
<u>AB</u>	WEST WARD	<u>EQ 50MG BASE</u>	N62396 002
			NOV 07, 1984
<u>AB</u>		<u>EQ 100MG BASE</u>	N62396 001
			MAY 07, 1984
	<u>VIBRAMYCIN</u>		
<u>AB</u>	PFIZER	<u>EQ 50MG BASE</u>	N50007 001
<u>AB</u>	+	<u>EQ 100MG BASE</u>	N50007 002

CAPSULE, COATED PELLETS; ORAL

DORYX

AB + MAYNE PHARMA USA EQ 100MG BASE N50582 001  
JUL 22, 1985

DOXYCYCLINE HYCLATE

CAPSULE, COATED PELLETS; ORAL

DORYX

MAYNE PHARMA USA EQ 75MG BASE N50582 002  
AUG 13, 2001  
AB WARNER CHILCOTT EQ 100MG BASE N62653 001  
OCT 30, 1985

INJECTABLE; INJECTION  
DOXY 100

+ AM PHARM PARTNERS EQ 100MG BASE/VIAL N62475 001  
DEC 09, 1983

DOXY 200

+ AM PHARM PARTNERS EQ 200MG BASE/VIAL N62475 002  
DEC 09, 1983

LIQUID, EXTENDED RELEASE; PERIODONTAL  
ATRIDOX

+ ATRIX EQ 10% W/W N50751 001  
SEP 03, 1998

TABLET; ORAL

DOXYCYCLINE HYCLATE

<u>AB</u>	AXIOM PHARM	<u>EQ 100MG BASE</u>	N62269 002
			NOV 08, 1982
<u>AB</u>	IVAX PHARMS	<u>EQ 100MG BASE</u>	N62505 001
			SEP 11, 1984
<u>AB</u>	MUTUAL PHARM	<u>EQ 100MG BASE</u>	N62677 001
			JUL 10, 1986
<u>AB</u>	MYLAN	<u>EQ 100MG BASE</u>	N62432 001
			FEB 15, 1983
<u>AB</u>	VINTAGE PHARMS	<u>EQ 100MG BASE</u>	N62538 001
			APR 07, 1986
<u>AB</u>	WATSON LABS	<u>EQ 100MG BASE</u>	N62421 001
			FEB 02, 1983
<u>AB</u>	WEST WARD	<u>EQ 100MG BASE</u>	N65095 001
			JUL 02, 2003
	PERIOSTAT		
	+ COLLAGENEX PHARMS	20MG	N50783 001
			FEB 02, 2001
	<u>VIBRA-TABS</u>		
<u>AB</u>	+ PFIZER	<u>EQ 100MG BASE</u>	N50533 001

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**ATTACHMENT B**

## PROPOSED LABELING

### **Doxycycline Hyclate Tablets (coated doxycycline hyclate tablets)**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate tablets and other antibacterial drugs, doxycycline hyclate tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

### **DESCRIPTION**

**Doxycycline Hyclate Tablet** is a coated tablet of doxycycline hyclate for oral administration. **INACTIVE INGREDIENTS WILL BE PROVIDED IN THE ANDA LABELING.** Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline hyclate. The chemical designation of this light yellow crystalline powder is alpha-6-desoxy-5-oxytetra-cycline. Doxycycline has a high degree of lipoid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

### **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 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

**Microbiology:** Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common.

**Susceptibility Tests: Diffusion Techniques:** The use of antibiotic disc susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to doxycycline hyclate tablets. One such standard procedure<sup>1</sup> has been recommended for use with discs for testing antimicrobials. Doxycycline 30 mcg discs should be used for the determination of the susceptibility of organisms to doxycycline.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (e.g., urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a zone of 16 mm or greater indicates susceptibility, zone sizes of 12 mm or less indicate resistance and zone sizes of 13 to 15 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disc should give zone diameters between 19 and 28 mm for *S. aureus* ATCC 25923 and between 18 and 25 mm for *E. coli* ATCC 25922. The 30 mcg doxycycline disc should give zone diameters between 23 and 29 mm for *S. aureus* ATCC 25923, and between 18 and 24 mm for *E. coli* ATCC 25922.

**Dilution Techniques:** A bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) value for doxycycline is less than 4 mcg/mL. Organisms are considered resistant if the MIC is greater than 12.5 mcg/mL. MICs greater than 4.0 mcg/mL and less than 12.5 mcg/mL indicate intermediate susceptibility.

As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms. Standard doxycycline powder should give MIC values in the range of 0.25 mcg/mL and 1.0 mcg/mL for *S. aureus* ATCC 25923. For *E. coli* ATCC 25922 the MIC range should be between 1.0 mcg/mL and 4.0 mcg/mL.

## INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and typhus group, Q fever, rickettsialpox and tick fevers.

*Mycoplasma pneumoniae* (PPLQ, Eaton's agent)

Agents of psittacosis and ornithosis

Agents of lymphogranuloma venereum and granuloma inguinale

The spirochetal agent of relapsing fever (*Borrelia recurrentis*)

The following gram-negative microorganisms:

*Haemophilus ducreyi* (chancroid)  
*Yersinia pestis* (formerly *Pasteurella pestis*)  
*Francisella tularensis* (formerly *Pasteurella tularensis*)  
*Bartonella bacilliformis*  
*Bacteroides* species  
*Vibrio cholerae* (formerly *Vibrio comma*)  
*Campylobacter fetus* (formerly *Vibrio fetus*)  
*Brucella* species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, 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* (formerly *Aerobacter aerogenes*)  
*Shigella* species  
*Mima* species and *Herellea* species  
*Haemophilus influenzae* (respiratory infections)  
*Klebsiella* species (respiratory and urinary infections)

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

*Streptococcus* species:

Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

*Diplococcus pneumoniae*.

*Staphylococcus aureus* (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

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 infections due to:

*Treponema pallidum* and *Treponema pertenue* (syphilis and yaws)  
*Listeria monocytogenes*  
*Clostridium* species  
*Fusobacterium fusiforme* (Vincent's infection)  
*Actinomyces* species

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

In severe acne, doxycycline may be useful adjunctive therapy.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxycycline alone, or with a combination of topical agents.

Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.<sup>2</sup>

Doxycycline is indicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum* and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis*.<sup>2</sup>

Doxycycline is indicated for the treatment of uncomplicated gonococcal infections in adults (except for anorectal infections in men), the gonococcal arthritis-dermatitis syndrome and acute epididymo-orchitis caused by *N. gonorrhoeae*.<sup>2</sup>

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate tablets and other antibacterial drugs, doxycycline hyclate tablets 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 empiric selection of therapy.

## CONTRAINDICATIONS

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

## WARNINGS

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 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.

**"Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.**

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile colitis*."

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.

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone-forming tissue. A decrease in the 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.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individual 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.

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

## PRECAUTIONS

**General:** Prescribing doxycycline hyclate 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.

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.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

**Information for Patients:** Patients should be counseled that antibacterial drugs including doxycycline hyclate tablets should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When doxycycline hyclate tablets 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 be not treatable by doxycycline hyclate tablets 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.

For concomitant therapy with antacids or iron-containing preparations and food see DOSAGE AND ADMINISTRATION section.

**Carcinogenesis, mutagenesis, impairment of fertility:** Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell assays (L51784 mouse lymphoma and Chinese hamster lung cells *in vitro*), positive responses for mutagenicity occurred at concentrations of 60 and 10 mcg/mL,

respectively. In humans, no association between tetracyclines and these effects have been made.

#### **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>3</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>4</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>5</sup>.

#### **Nursing Mothers**

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breast-fed 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<sup>6</sup>. Because of the potential for 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:** (See WARNINGS and DOSAGE AND ADMINISTRATION sections.)

#### **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, and inflammatory lesions (with monilial overgrowth) in the anogenital region. 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 section)

Skin: Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

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

Hypersensitivity reactions: Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, and exacerbation of systemic lupus erythematosus.

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.

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

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.

## **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 pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by a 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 pediatric patients over 100 pounds, the usual adult dose should be used.

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice-a-day for 7 days.<sup>2</sup> As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose. The dose may be administered with food, including milk or carbonated beverage, as required.

Acute epididymo-orchitis caused by *N. gonorrhoeae*: 100 mg, by mouth, twice-a-day for at least 10 days.<sup>2</sup>

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.<sup>2</sup>

Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis*: 100 mg by mouth, twice-a-day for at least 7 days.<sup>2</sup>

Nongonococcal urethritis caused by *C. trachomatis* and *U. urealyticum*: 100 mg, by mouth, twice-a-day for at least 7 days.<sup>2</sup>

Acute epididymo-orchitis caused by *C. trachomatis*: 100 mg, by mouth, twice-a-day for at least 10 days.<sup>3</sup>

Inhalational anthrax (post exposure):

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

CHILDREN: weighing less than 100 lb (45 kg); 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice-a-day for 60 days. Children weighing 100 lb or more should receive the adult dose.

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 section).

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

**Concomitant therapy:** Antacids containing aluminum, calcium or magnesium, sodium bicarbonate, and iron-containing preparations should not be given to patients taking oral tetracyclines.

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

#### **HOW SUPPLIED**

THE DESCRIPTION WILL BE INCLUDED IN THE ANDA LABELING.

#### **STORAGE CONDITIONS**

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

#### **REFERENCES:**

1. NCCLS Approved Standard: M2-A3, Vol. 4, Performance Standards for Antimicrobial Disk Susceptibility Tests, Third Edition: available from the National Committee for Clinical Laboratory Standards, 771 East Lancaster Avenue, Villanova, PA 19085
2. CDC Sexually Transmitted Diseases Treatment Guidelines 1982
3. Friedman JM and Polifka JE, *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS)*. Baltimore, MD: The John Hopkins University Press: 2000: 149-195.
4. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997;89:524-528.
5. Horne HW Jr. and Kundsinn RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317
6. Hale T. *Medications and Mothers Milk*. 9<sup>th</sup> edition, Amarillo, TX: Pharmasoft Publishing 2000; 225-226

Manufactured by:  
**PAR PHARMACEUTICAL, INC.**  
Spring Valley, N Y 10977

**LACHMAN CONSULTANT SERVICES, INC.**  
Westbury, NY 11590

**ATTACHMENT C**

**DORYX®**  
(coated doxycycline  
hydrate pellets)

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 hydrate for oral administration. Also contains lactose, NF; microcrystalline cellulose, NF; povidone, USP. The capsule shell and/or band contains FD and C blue No. 1; FD and C yellow No. 8; D and C yellow No. 10; gelatin, NF; silicon dioxide; sodium lauryl sulfate, NF; titanium dioxide, USP. Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and available as doxycycline hydrate. The chemical designation of this light-yellow crystalline powder is alpha-6-desoxy-5-oxotetra-cycline. 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.

**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 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

**Microbiology:** Doxycycline is primarily bacteriostatic and is thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms. The drugs in the tetracycline class have closely similar antimicrobial spectra and cross resistance among them is common.

**Susceptibility Tests: Diffusion Techniques:** The use of antibiotic disc susceptibility test methods which measure zone diameter gives an accurate estimation of susceptibility of organisms to DORYX. One such standard procedure has been recommended for use with discs for testing antimicrobials. Doxycycline 30 mcg discs should be used for the determination of the susceptibility of organisms to doxycycline.

With this type of procedure, a report of "susceptible" from the laboratory indicates that the infecting organism is likely to respond to therapy. A report of "intermediate susceptibility" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissue and fluids (e.g., urine) in which high antibiotic levels are obtained. A report of "resistant" indicates that the infecting organism is not likely to respond to therapy. With the doxycycline disc, a zone of 16 mm or

greater indicates susceptibility, zone size of 12 mm or less indicates resistance, and zone sizes of 13 to 15 mm indicate intermediate susceptibility.

Standardized procedures require the use of laboratory control organisms. The 30 mcg tetracycline disc should give zone diameters between 19 and 29 mm for *S. aureus* ATCC 25923 and between 18 and 25 mm for *E. coli* ATCC 25922. The 30 mcg doxycycline disc should give zone diameters between 23 and 29 mm for *S. aureus* ATCC 25923, and between 18 and 24 mm for *E. coli* ATCC 25922.

**Dilution Techniques:** A bacterial isolate may be considered susceptible if the MIC (minimal inhibitory concentration) value for doxycycline is less than 11 mcg/mL. Organisms are considered resistant if the MIC is greater than 12.5 mcg/mL. MICs greater than 4.0 mcg/mL and less than 12.5 mcg/mL indicate intermediate susceptibility.

As with standard diffusion methods, dilution procedures require the use of laboratory control mechanisms. Standard doxycycline powder should give MIC values in the range of 0.25 mcg/mL and 1.0 mcg/mL for *S. aureus* ATCC 25923. For *E. coli* ATCC 25922 the MIC range should be between 1.0 mcg/mL and 4.0 mcg/mL.

**INDICATIONS AND USAGE**

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox and tick fever).

*Mycoplasma pneumoniae* (P.P.L.O., Eaton's agent).

Agents of psittacosis and ornithosis.

Agents of lymphogranuloma venereum and granuloma inguinale.

The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

- Hemophilus ducreyi* (chancroid)
- Yersinia pestis* (formerly *Pseudotuberculosis pestis*)
- Francisella tularensis* (formerly *Pasteurella tularensis*)
- Bartonella bacilliformis*
- Bacteroides* species
- Vibrio cholerae* (formerly *Vibrio comma*)
- Campylobacter fetus* (formerly *Vibrio fetus*)
- Brucella* species (in conjunction with streptomycin)

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, 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* (formerly *Aerobacter aerogenes*)
- Shigella* species
- Mirna* species and *Flavobacterium* species
- Haemophilus influenzae* (respiratory infections)
- Klebsiella* species (respiratory and urinary infections)

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

**Streptococcus** species:  
Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used for streptococcal disease unless the organism has been demonstrated to be susceptible.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

*Diplococcus pneumoniae*.

*Staphylococcus aureus* (respiratory, skin and soft-tissue infections). Tetracyclines are not the drug of choice in the treatment of any type of staphylococcal infection.

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 infections due to:

- Treponema pallidum* and *Treponema parvum* (syphilis and yaws)
- Listeria monocytogenes*
- Clostridium* species
- Fusobacterium fusiforme* (Vincent's infection)
- Actinomyces* species

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

In severe acne, doxycycline may be useful adjunctive therapy.

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

Inclusion conjunctivitis may be treated with oral doxycycline alone, or with a combination of topical agents.

Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.

Doxycycline is indicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum*; and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis*.

Doxycycline is indicated for the treatment of uncomplicated gonococcal infections in adults (except for anorectal infections in men), the gonococcal arthritis-dermatitis syndrome and acute epididymo-orchitis caused by *N. gonorrhoeae*.

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. Where 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.

**CONTRAINDICATIONS**

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

**WARNINGS**

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 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.

"Pseudo-membranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.



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DORYX®

DORYX®  
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## DORYX®

(coated doxycycline hyclate pellets)

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

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.

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

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.

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:** 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.

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.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

**Information for Patients:** 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.

**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.

For concomitant therapy with antacids or iron-containing preparations and food see DOSAGE AND ADMINISTRATION section.

**Carcinogenic, mutagenesis, impairment of fertility:** Long-term studies are currently being conducted to determine whether tetracyclines have carcinogenic potential. Animal studies conducted in rats and mice have not provided conclusive evidence that tetracyclines may be carcinogenic or that they impair fertility. In two mammalian cell assays (L5178Y mouse lymphoma and Chinese hamster lung cells *in vitro*), positive responses for mutagenicity occurred at concentrations of 80 and 10 mcg/mL, respectively. In humans, no association between tetracyclines and these effects have been made.

**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 experiences 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 (in 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.

A case-control study (18,515 mothers of infants with congenital anomalies and 32,604 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. (Study: 100 (0.18%) of the controls and 68 (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 defects based on only two exposed cases.

A small prospective study of 81 pregnancies described 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.

### Nursing Mothers

Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines including doxycycline, by the breast-fed infants 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. Because of the potential for 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:** See WARNINGS and DOSAGE AND ADMINISTRATION sections.

### 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, and inflammatory lesions (with monilial overgrowth) in the oropharyngeal region. These reactions have been caused by both the oral and parenteral administra-

tion 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 section).

**Skin:** Maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above (see WARNINGS section).

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

**Hypersensitivity reactions:** Urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, perivascularitis, and exfoliation of systemic lupus erythematosus.

**Bulging fontanelle in infants and benign intracranial hypertension in adults:** have been reported in individuals receiving tetracyclines. These conditions disappeared when the drug was discontinued.

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

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopically discoloration of thyroid glands. No abnormalities of thyroid function are known to occur.

### 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), 160 mg every 12 hours is recommended.

**For pediatric patients above eight years of age:** The recommended dosage schedule for pediatric patients 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 pediatric patients over 100 pounds, the usual adult dose should be used.

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

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

**Primary and secondary syphilis:** 300 mg a day in divided doses for at least 10 days.

**Uncomplicated urethral, endocervical, or rectal infection in adults caused by *Chlamydia trachomatis*:** 100 mg by mouth, twice-a-day for at least 7 days.

**Nongonococcal urethritis caused by *C. trachomatis* and *U. urealyticum*:** 100 mg, by mouth, twice-a-day for at least 7 days.

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

**Inhalational anthrax (post-exposure):** ADULTS: 100 mg, of doxycycline, by mouth, twice-a-day for 60 days. CHILDREN: weighing less than 100 lb (45 kg): 1 mg/lb (2.2 mg/kg) of body weight, by mouth, twice-a-day for 60 days. Children weighing 100 lb or more should receive the adult dose.

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 section).

If gastric irritation occurs, it is recommended that doxycycline be given with food or milk. The absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk.

### 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 6-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 can not be taken immediately, the mixture should be discarded and not stored for later use.

**Concomitant therapy:** Antacids containing aluminum, calcium or magnesium, sodium bicarbonate, and iron-containing preparations should not be given to patients taking oral tetracyclines.

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

### HOW SUPPLIED

100-mg DORYX® (coated doxycycline hyclate pellets) Capsules 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 60 capsules . . . N 0430-0838-19

75 mg DORYX® (coated doxycycline hyclate pellets) Capsules 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 capsules . . . N 0430-0838-20

### STORAGE CONDITIONS

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

### References:

1. NCCCLS Approved Standard; M2-A3, Vol. 4, Performance Standards for Antimicrobial Disk Susceptibility Tests, Third Edition; available from the National Committee for Clinical Laboratory Standards, 77 East Lancaster Avenue, Villanova, Pa. 19085
2. CDC Sexually Transmitted Diseases Treatment Guidelines, 1992
3. Friedman JM and Pollack JE, *Teratogenic Effects of Drugs: A Resource for Clinicians* (TERIS), Baltimore, MD: The Johns Hopkins University Press; 2000: 149-195.
4. Czeizel AE and Rockenbauer M, *Teratogenicity study of doxycycline. Obstet Gynecol* 1997;89:524-528.
5. Horne HW Jr, and Kurdaini RB, *The role of mycoplasma among 81 consecutive pregnancies: a prospective study. Int J Fertil* 1980;25:315-317.
6. Haid T, *Medications and Mothers Milk*, 9th, edition; Amarillo, TX: Pharmasoft Publishing; 2000; 225-226

### Rx only

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