ATTACHMENT 2

ADOXA®

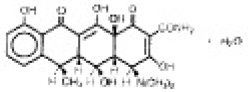
DOXYCYCLINE TABLETS

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

DESCRIPTION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. Doxycycline 150 mg, 100 mg, 75 mg and 50 mg tablets contain doxycycline monohydrate equivalent to 150 mg, 100 mg, 75 mg or 50 mg of doxycycline for oral administration. Inactive ingredients include colloidal silicon dioxide, FD&C yellow #6, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and titanium dioxide. In addition, doxycycline 100 mg and 50 mg tablets contain hypromellose 3cP, hypromellose 6cP, D&C yellow #10 lake, polyethylene glycol 400, polysorbate 80; doxycycline 150 mg and 75 mg tablets contain hypromellose, lactose monohydrate, synthetic yellow iron oxide and triethyl citrate. Its molecular weight is 462.46. The chemical designation of the light-yellow crystaline powder is alpha-6-deoxy-5-oxytetracycline.

Structural formula:



$C_{22}H_{24}N_2O_8 \cdot H_2O$

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 degrees. They are concentrated by the liver in the bile and excreted in the urine and feces at high concentrations in a biologically active form. Doxycycline is virtually completely absorbed after oral administration.

Following a 200 mg dose of doxycycline monohydrate, 24 normal adult volunteers averaged the following serum concentration values:

Time (hr):	0.5	1	1.5	2	3	4	8	12	24	48	72
Conc: (mcg/mL)	1.02	2.26	2.67	3.01	3.16	3.03	2.03	1.62	0.95	0.37	0.15

Average Observed Values

Maximum Concentration	3.61 mcg/mL (± 0.9 sd)
Time of Maximum Concentration	2.60 hr (± 1.10 sd)
Elimination Rate Constant	0.049 per hr (± 0.030 sd)
Half-Life	16.33 hr (± 4.53 sd)

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: The tetracyclines are primarily bacteriostatic and are thought to exert their antimicrobial effect by the inhibition of protein synthesis. The tetracyclines, including doxycycline, have a similar antimicrobial spectrum of activity against a wide range of gram-positive and gram-negative microorganisms. Cross-resistance of these microorganisms to tetracyclines is common.

Doxycycline has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section.

Aerobic Gram-Positive Microorganisms:

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Bacillus anthracis
Listeria monocytogenes
*Staphylococcus aureus**

*Doxycycline is not the drug of choice in the treatment of any type of staphylococcal infection.

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 to treat streptococcal infections unless the microorganism has been demonstrated to be susceptible.

Streptococcus pneumoniae

Aerobic Gram-Negative Microorganisms:

Bartonella bacilliformis
Brucella species
Calymmatobacterium granulomatis
Campylobacter fetus
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Neisseria gonorrhoeae
Vibrio cholerae
Yersinia pestis

Because many strains of the following groups of gram-negative microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended:

Acinetobacter species
Enterobacter aerogenes
Escherichia coli
Klebsiella species
Shigella species

Anaerobic Microorganisms:

Actinomyces israelii
Clostridium species
Fusobacterium fusiforme

Other Microorganisms:

Borrelia recurrentis
Chlamydia psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema pertenue

Susceptibility Tests:

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,3] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of tetracycline powder. The MIC values should be interpreted according to the following criteria for indicated aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae*:

MIC (mcg/mL)	Interpretation
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

When testing *Haemophilus spp.*[a]

MIC (mcg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

When testing *Neisseria gonorrhoeae*[b]

MIC (mcg/mL)	Interpretation
≤0.25	Susceptible (S)
0.5-1	Intermediate (I)
≥2	Resistant (R)

When testing *Streptococcus pneumoniae*[c]

MIC (mcg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[a] Interpretative criteria applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1,3]

[b] Interpretative criteria applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[1,3]

[c] Interpretative criteria applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1,3]

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard tetracycline powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
Enterococcus faecalis	ATCC 29212	8-32
Escherichia coli	ATCC 25922	0.5-2
Haemophilus influenzae[a]	ATCC 49247	4-32
Neisseria gonorrhoeae[b]	ATCC 49226	0.25-1
Pseudomonas aeruginosa	ATCC 27853	8-32
Staphylococcus aureus	ATCC 29213	0.12-1
Streptococcus pneumoniae[c]	ATCC 49619	0.12-0.5

[a] Range applicable only to tests performed by broth microdilution method using *Haemophilus* Test Medium (HTM).[1,3]

[b] Range applicable only to tests performed by agar dilution method using GC agar base with 1% defined growth supplement.[1,3]

[c] Range applicable only to tests performed by broth microdilution method using cation-adjusted Mueller-Hinton broth with 2 to 5% lysed horse blood.[1,3]

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 30-mcg tetracycline or 30-mcg doxycycline to test the susceptibility of microorganisms to doxycycline.

Reports from the laboratory providing results of the standard single-disk susceptibility test with 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should be interpreted according to the following criteria for indicated aerobic microorganisms other than *Haemophilus* species, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae*:

Zone Diameter (mm) tetracycline	Zone Diameter (mm) doxycycline	Interpretation
≥19	≥16	Susceptible (S)
15-18	13-15	Intermediate (I)
≤14	≤12	Resistant (R)

When testing *Haemophilus spp.*[a]

Zone Diameter (mm) tetracycline	Interpretation
≥29	Susceptible (S)
26-28	Intermediate (I)
≤25	Resistant (R)

When testing *Neisseria gonorrhoeae*[b]

Zone Diameter (mm) tetracycline	Interpretation
≥38	Susceptible (S)
31-37	Intermediate (I)
≤30	Resistant (R)

Zone diameters ≤19 mm may indicate a plasmid-mediated tetracycline-resistant *Neisseria gonorrhoeae* (TRNG) isolate. These TRNG strains should be confirmed by the dilution test (MIC ≥16 mcg/mL).

When testing *Streptococcus pneumoniae*[c]

Zone Diameter (mm) tetracycline	Interpretation
≥23	Susceptible (S)
19-22	Intermediate (I)
≤18	Resistant (R)

[a] Interpretative criteria applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using *Haemophilus* Test Medium (HTM).[2,3]

[b] Interpretative criteria applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using GC agar base with 1% defined growth supplement.[2,3]

[c] Interpretative criteria applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2.[2,3]

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for tetracycline or doxycycline, respectively.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm) tetracycline	Zone Diameter (mm) doxycycline
Escherichia coli	ATCC 25922	18-25	18-24
Haemophilus influenzae[a]	ATCC 49247	14-22	---
Neisseria gonorrhoeae[b]	ATCC 49226	30-42	---
Staphylococcus aureus	ATCC 25923	24-30	23-29
Streptococcus pneumoniae[c]	ATCC 49619	27-31	---

[a] Range applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using *Haemophilus* Test Medium (HTM).[2,3]

[b] Range applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using GC agar base with 1% defined growth supplement.[2,3]

[c] Range applicable only to tests performed by disk diffusion method using a 30-mcg tetracycline-class disk and using Mueller-Hinton agar with 5% defibrinated sheep blood and incubated in 5% CO_2.[2,3]

Anaerobic techniques:

For anaerobic bacteria, the susceptibility to tetracycline as MICs can be determined by standardized test methods.[4] The MIC values obtained should be interpreted according to the following criteria.

MIC (mcg/mL)	Interpretation
≤4	Susceptible (S)
8	Intermediate (I)
≥16	Resistant (R)

Interpretation is identical to that stated above for results using dilution techniques.

As with other susceptibility techniques, the use of laboratory control microorganisms is required to control the technical aspects of the laboratory standardized procedures. Standardized tetracycline powder should provide the following MIC values:

Microorganism		MIC (mcg/mL)
Bacteroides fragilis[a]	ATCC 25285	0.12-0.5
Bacteroides thetaiotaomicron[a]	ATCC 29741	8-32

[a] Range applicable only to tests performed by the reference agar dilution method.

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline tablets and other antibacterial drugs, doxycycline tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Doxycycline is 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 *Rickettsiae*.
- Respiratory tract infections caused by *Mycoplasma pneumoniae*.
- Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
- Psittacosis (ornithosis) caused by *Chlamydia 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 is also indicated for the treatment of infections caused by the following gram-negative microorganisms:

- Chancroid caused by *Haemophilus ducreyi*.
- Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*).
- Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).
- Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*).
- *Campylobacter fetus* infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).
- Brucellosis due to *Brucella* species (in conjunction with streptomycin).
- Bartonellosis due to *Bartonella bacilliformis*.
- Granuloma inguinale caused by *Calymmatobacterium 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 bacteriologic testing indicates appropriate susceptibility to the drug:

- *Escherichia coli*
- *Enterobacter aerogenes* (formerly *Aerobacter aerogenes*)
- *Shigella* species
- *Acinetobacter* species (formerly *Mima* species and *Herellea* 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-

040728-07

ADOXA® DOXYCYCLINE TABLETS
R 06/05

040728-07

positive microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Upper respiratory infections caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*).

Skin and skin structure infections caused by *Staphylococcus aureus*.

Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

Doxycycline is not the drug of choice in the treatment of any type of staphylococcal infections.

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 pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israeli*.

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.

CONTRAINDICATIONS

This 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).

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.

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.

All tetracyclines form 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.

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 embryo toxicity has been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy or if the patient becomes pregnant while taking these drugs, the patient should be apprised of the potential hazard to the fetus.

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.

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.

PRECAUTIONS

General: Prescribing doxycycline 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 nonsusceptible organisms, including fungi. If superinfection occurs, the antibiotic should be discontinued and appropriate therapy instituted.

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.

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

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

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

In long-term therapy, periodic laboratory evaluations 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 antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

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

The concurrent use of tetracycline and 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 catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate the carcinogenic potential of doxycycline have not been conducted.

However, there has been evidence of oncogenic activity in rats in studies with related antibiotics, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy: Teratogenic Effects. Pregnancy Category D: There are no adequate and well-controlled studies on the use of doxycycline in pregnant 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 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.5

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.6

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.7

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; however, the effects of prolonged exposure to doxycycline in breast milk are unknown.8 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**.)

Skin: Maculopapular and erythematous rashes. 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, pericarditis, and exacerbation of systemic lupus erythematosus.

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

Other: Bulging fontanels in infants and intracranial hypertension in adults. (See **PRECAUTIONS-General**.)

When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of the thyroid gland. 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 it 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 or 50 mg every 6 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 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 visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose.

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

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. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5% and the area under the curve by 5.7%.

HOW SUPPLIED

Doxycycline Tablets 50 mg are a yellow, film coated, round, biconvex tablet, debossed "B" on one side and "728" on the other side. Each tablet contains doxycycline monohydrate equivalent to 50 mg of doxycycline. They are supplied as follows:

Bottles of 100	NDC 10337-800-01

Doxycycline Tablets 75 mg are a light orange, film coated, round, biconvex tablet, debossed "B" on one side and "730" on the other side. Each tablet contains doxycycline monohydrate equivalent to 75 mg of doxycycline. They are supplied as follows:

Bottles of 100	NDC 10337-801-01
Bottles of 500	NDC 10337-801-50

Doxycycline Tablets 100 mg are a yellow, film coated, round, biconvex tablet, debossed "B" on one side and "729" on the other side. Each tablet contains doxycycline monohydrate equivalent to 100 mg of doxycycline. They are supplied as follows:

Bottles of 50	NDC 10337-802-05
Bottles of 250	NDC 10337-802-25

Doxycycline Tablets 150 mg are a peach colored, film coated, round, scored, biconvex tablet debossed "D/D" on one side and "150" on the other side. Each tablet contains doxycycline monohydrate equivalent to 150 mg of doxycycline. They are supplied as follows:

Bottles of 50	NDC 10337-814-05
Bottles of 100	NDC 10337-814-01
Bottles of 250	NDC 10337-814-25
Bottles of 500	NDC 10337-814-50

Store at 20°-25°C (68°-77°F). [See USP].

PROTECT FROM LIGHT.

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

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

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

REFERENCES

1. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically - Fifth Edition.* Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January, 2000.

2. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Disk Susceptibility Tests - Seventh Edition.* Approved Standard NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.

3. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing - Eleventh Informational Supplement.* NCCLS Document M100-S11, Vol. 21, No. 1, NCCLS, Wayne, PA, January, 2001.

4. National Committee for Clinical Laboratory Standards. *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria - Fourth Edition.* Approved Standard NCCLS Document M11-A4, Vol. 17, No. 22, NCCLS, Wayne, PA, December, 1997.

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

6. Czeizel AE and Rockenbauer M. Teratogenic study of doxycycline. *Obstet Gynecol* 1997; 89: 524-528.

7. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.

8. Hale T. *Medications and Mothers Milk.* 9th edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.

Manufactured for:

DERM*arts* DIVISION

DOAK DERMATOLOGICS

A SUBSIDIARY OF HEALTHY PHARMACEUTICALS, INC.

383 Route 46 West
Fairfield, NJ 07004-2402 USA
1-800-405-DOAK • www.doakderm.com

Manufactured by:
PAR PHARMACEUTICAL, INC.
Spring Valley, NY 10977 USA

Revised: 06/05

IL227-R1
OS728-01-31-06