DOXYCYCLINE- doxycycline hyclate tablet, coated
Blenheim Pharmacal, Inc.

DOXYCYCLINE HYCLATE

TABLETS, USP

Rev. 11/14

Rx Only

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.

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% per 72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1 to 5% per 72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

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

Microbiology

Doxycycline inhibits bacterial protein synthesis by binding the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for doxycycline hyclate tablets.

Gram-Negative Bacteria
Acinetobacter species
Bartonella bacilliformis
Brucella species
Campylobacter fetus
Enterobacter aerogenes
Escherichia coli
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Klebsiella species

Klebsiella granulomatis
Neisseria gonorrhoeae
Shigella species
Vibrio cholerae
Yersinia pestis

Gram-Positive Bacteria
Bacillus anthracis
Streptococcus pneumoniae

Anaerobic Bacteria
Clostridium species
Fusobacterium fusiforme
Propionibacterium acnes

Other Bacteria
Nocardiae and other aerobic *Actinomyces* species
Borrelia recurrentis
Chlamydophila psittaci
Chlamydia trachomatis
Mycoplasma pneumoniae
Rickettsiae
Treponema pallidum
Treponema pallidum subspecies *pertenue*
Ureaplasma urealyticum

Parasites
Balantidium coli
Entamoeba species
*Plasmodium falciparum**

*Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

Susceptibility Testing Methods

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drugs used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method [1,2,4] (broth or agar). The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method. [1,3,4] This procedure uses paper disks impregnated with 30-µg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

Anaerobic Techniques:

For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method. [5] The MIC values obtained should be interpreted according to the criteria provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

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

[a] Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.

[b] The current absence of resistant isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.

[c] Gonococci with 30mcg tetracycline disk zone diameters of <19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥16mcg per mL).

A report of *Susceptible* (S) indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the bacteria 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 product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistant* (R) indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

Quality Control

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test. [1,2,3,4,5,6,7] Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk, the criteria noted in Table 2 should be achieved.

Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline

QC Strain	Minimal Inhibitory Contentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution (mcg per mL)
Enterococcus faecalis ATCC 29212			
Doxycycline	2-8	-	-
Tetracycline	8-32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5-2	18-24	-
Tetracycline	0.5-2	18-25	-
Eubacteria lentum ATCC 43055			
Doxycycline	2-16	-	-
Haemophilus influenzae ATCC 49247			
Tetracycline	4-32	14-22	-
Neisseria gonorrhoeae ATCC 49226			
Tetracycline	-	30-42	0.25-1
Staphylococcus aureus ATCC 25923			
Doxycycline	-	23-29	-
Tetracycline	-	24-30	-
Staphylococcus aureus ATCC			

29213			
Doxycycline	0.12-0.5	-	-
Tetracycline	0.12-1	-	-
Streptococcus pneumonia ATCC 49619			
Doxycycline	0.015-0.12	25-34	-
Tetracycline	0.06-0.5	27-31	-
Bacteroides fragilis ATCC 25285			
Tetracycline	-	-	0.12-0.5
Bacteroides thetaiotaomicron ATCC 29741			
Doxycycline	2-16	-	-
Tetracycline	-	-	8-32
Mycoplasma pneumoniae ATCC 29342			
Tetraycline	0.06-0.5	-	0.06-0.5
Ureaplasma urealyticum ATCC 33175			
Tetracycline	-	-	≥8

INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain effectiveness of Doxycycline Hyclate Tablets, USP and other antibacterial drugs, Doxycycline Hyclate Tablets, USP 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.

Treatment

Doxycycline is indicated for the treatment of the following infections:

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

Doxycycline 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.*
- Tularemia due to *Francisella tularensis.*
- Cholera caused by *Vibrio cholerae.*

- Campylobacter fetus infections caused by *Campylobacter fetus*.
- Brucellosis due to *Brucella* species (in conjunction with streptomycin).
- Bartonellosis due to *Bartonella bacilliformis*.
- Granuloma inguinale caused by *Klebsiella granulomatis*.

Because many strains of the following groups of microorganisms have been shown to be resistant to doxycycline, culture and susceptibility testing are recommended.

Doxycycline is indicated for treatment of infections caused by the following gram-negative bacteria, when bacteriologic testing indicates appropriate susceptibility to the drug:
- *Escherichia coli*.
- *Enterobacter aerogenes*.
- *Shigella* species.
- *Acinetobacter* species.
- Respiratory tract infections caused by *Haemophilus influenzae*.
- Respiratory tract and urinary tract infections caused by *Klebsiella* species.

Doxycycline is indicated for treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:
- Upper respiratory infections caused by *Streptococcus pneumoniae*.
- Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections:
- Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
- Syphilis caused by *Treponema pallidum*.
- Yaws caused by *Treponema pallidum* subspecies *pertenue*.
- Listeriosis due to *Listeria monocytogenes*.
- Vincent's infection caused by *Fusobacterium fusiforme*.
- Actinomycosis caused by *Actinomyces israelii*.
- Infections caused by *Clostridium* species.

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

In severe acne, doxycycline may be useful adjunctive therapy.

Prophylaxis

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains (See **DOSAGE AND ADMINISTRATION** section and **Information for Patients** subsection of the **PRECAUTIONS** section).

CONTRAINDICATIONS

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). This adverse reaction is more common during long-term use of the drugs, but it has been observed following

repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST-EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

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

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

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

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline hyclate tablets. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and doxycycline hyclate tablets should be avoided because isotretinoin is also known to cause pseudotumor cerebri.

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

All tetracyclines form a stable calcium complex in any bone-forming tissue. A decrease in fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

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

As with other antibacterial drugs, use of doxycycline hyclate tablets may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, doxycycline hyclate tablets should be discontinued and appropriate therapy instituted.

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

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum's* sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

Prescribing doxycycline hyclate tablets in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Patients taking doxycycline for malaria prophylaxis should be advised:

- that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.
- to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (e.g., staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent).
- that doxycycline prophylaxis:
  - should begin 1 to 2 days before travel to the malarious area.
  - should be continued daily while in the malarious area and after leaving the malarious area.
  - should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area.
  - should not exceed 4 months.

All patients taking doxycycline should be advised:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs. Sunscreen or sunblock should be considered (See **WARNINGS**).
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration (See **ADVERSE REACTIONS**).
- that the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk (See **Drug Interactions**).
- that the absorption of tetracyclines is reduced when taking bismuth subsalicylate (See **Drug Interactions**).
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

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 are prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by doxycycline hyclate or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs which usually ends when the antibacterials are discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

Laboratory Tests

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

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

Drug Interactions

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

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

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, and iron-containing preparations.

Absorption of tetracyclines is impaired by bismuth subsalicylate.

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibacterial drugs, 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 antibacterial drugs (tetracycline, oxytetracycline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy
Teratogenic Effects. Pregnancy Category D

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women, such as that proposed for 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. [a] 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 fifty-six (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. [b]

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. [c]

Nonteratogenic Effects

See **WARNINGS**.

Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers

Tetracyclines are excreted in human milk; however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown. [d] Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (See **WARNINGS**).

Pediatric Use

See **WARNINGS** and **DOSAGE AND ADMINISTRATION**

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects of 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. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of the drugs in the tetracycline class. Most of these patients took medications immediately before going to bed (See **DOSAGE AND ADMINISTRATION**).

Skin: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, 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**).

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

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

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 studies are known to occur.

To report SUSPECTED ADVERSE REACTIONS, contact West-Ward Pharmaceutical Corp. at 1-877-233-2001, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

OVERDOSAGE

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day.

In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by 1 mg/lb of body weight given as a single daily dose or divided into two doses, on subsequent days. For more severe infections up to 2 mg/lb of body weight may be used. For children over 100 lb the usual adult dose should be used.

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

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

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration (See **ADVERSE REACTIONS**).

If gastric irritation occurs, 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.

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

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an 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.

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

Nongonococcal urethritis (NGU) caused by *C. trachomatis* or *U. urealyticum*: 100 mg, by mouth, twice a day for 7 days.

Syphilis – early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg, by mouth, twice a day for 2 weeks.

Syphilis of more than one year’s duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg, by mouth, twice a day for 4 weeks.

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

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

For prophylaxis of malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1 to 2 days before travel to the malarious area. Prophylaxis should be continued daily

during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

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.

HOW SUPPLIED

Doxycycline Hyclate Tablets, USP equivalent to 100 mg doxycycline: Orange Coated, Round, Unscored Tablets; Debossed “WW 112”.

Bottles of 20 tablets
Bottles of 50 tablets
Bottles of 500 tablets

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

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

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 PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline 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.

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

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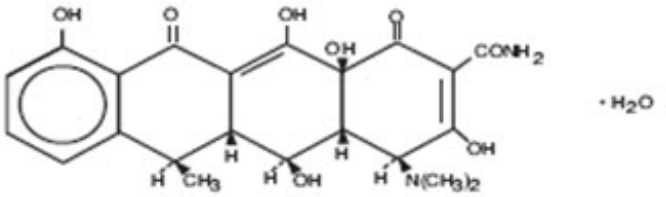
Manufactured by:
West-Ward Pharmaceutical Corp.
Eatontown, NJ 07724
Revised November 2014

DESCRIPTION

Doxycycline hyclate is an antibacterial drug synthetically derived from oxytetracycline. The structural formula of doxycycline monohydrate is



with a molecular formula of $C_{22}H_{24}N_2O_8 \cdot H_2O$ and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacenecarboxamide monohydrate. The molecular formula for doxycycline hydrochloride hemiethanolate hemihydrate is $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$ and the molecular weight is 1025.89. Doxycycline is a light yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

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.

Each tablet for oral administration contains doxycycline hyclate equivalent to 100 mg of doxycycline (anhydrous). Inactive ingredients are: Colloidal Silicon Dioxide, Corn Starch, Croscarmellose Sodium, Docusate Sodium, Sodium Benzoate, Magnesium Stearate, and Microcrystalline Cellulose. Film Coating and Polishing contains: FD&C Blue No. 2, FD&C Yellow No. 6, Hydroxypropyl Methylcellulose, Polyethylene Glycol, and Titanium Dioxide.

Principal Display Panel

Doxycycline Hyclate Tablets, USP 100mg

20 Tablets

NDC 10544-073-20

DOXYCYCLINE

doxycycline hyclate tablet, coated

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:10544-073(NDC:0143-2112)
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DOXYCYCLINE HYCLATE (UNII: 19XTS3T51U) (DOXYCYCLINE ANHYDROUS - UNII:334895S862)	DOXYCYCLINE ANHYDROUS	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
CROSCARMELLOSE SODIUM (UNII: M28OL1HH48)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
STARCH, CORN (UNII: O8232NY3SJ)	
DOCUSATE SODIUM (UNII: F05Q2T2JA0)	
FD&C BLUE NO. 2 (UNII: L06K8R7DQK)	
FD&C YELLOW NO. 6 (UNII: H77VEI93A8)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics			
Color	orange (Orange)	**Score**	no score
Shape	ROUND (ROUND)	**Size**	17mm
Flavor		**Imprint Code**	WW;112
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:10544-073-20	20 in 1 BOTTLE; Type 0: Not a Combination Product	05/24/2012	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA065095	05/09/2012	

Labeler - Blenheim Pharmacal, Inc. (171434587)

Registrant - Blenheim Pharmacal, Inc. (171434587)

Establishment

Name	Address	ID/FEI	Business Operations
Blenheim Pharmacal, Inc.		171434587	repack(10544-073)

Revised: 3/2015 Blenheim Pharmacal, Inc.