CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205931Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ACTICLATE™ safely and effectively. See full prescribing information for ACTICLATE™.

ACTICLATE™ (doxycycline hyclate USP) Tablets for oral use

Initial U.S. Approval: 1967

----------INDICATIONS AND USAGE----------

ACTICLATE™ is a tetracycline-class antimicrobial indicated for:

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline hyclate and other antimicrobial drugs, ACTICLATE Tablets should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1)

----------DOSAGE AND ADMINISTRATION----------

- Adults: the usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg daily. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended. (2.1)
- For children above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg per kg of body weight may be used. For children over 45 kg, the usual adult dose should be used. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets, 75 mg and 150 mg (functionally scored) (3)

----------CONTRAINDICATIONS----------

Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines. (4)

----------WARNINGS AND PRECAUTIONS----------

- The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). (5.1)
- *Clostridium difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.2)
- Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Limit sun exposure. (5.3)
- Overgrowth of non-susceptible organisms, including fungi, may occur. Reevaluate therapy if superinfection occurs. (5.4)

----------ADVERSE REACTIONS----------

Adverse reactions observed in patients receiving tetracyclines include anorexia, nausea, vomiting, diarrhea, rash, photosensitivity, urticaria, and hemolytic anemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Aqua Pharmaceuticals at 1-866-665-2782, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage (7.1)
- Avoid coadministration of tetracyclines with penicillin (7.2)
- Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate and iron-containing preparations (7.3)
- Concurrent use of tetracycline may render oral contraceptives less effective (7.4)
- Barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline (7.5)

----------USE IN SPECIFIC POPULATIONS----------

- Tetracycline-class drugs can cause fetal harm when administered to a pregnant woman, but data for doxycycline are limited. (5.6, 8.1)
- Tetracyclines are excreted in human milk; however, the extent of absorption of doxycycline in the breastfed infant is not known. Doxycycline use during nursing should be avoided if possible. (8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

Doxycycline is a tetracycline-class antibacterial indicated in the following conditions or diseases:

1.1 Rickettsial Infections

Rocky Mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsial pox, and tick fevers caused by *Rickettsiae*.

1.2 Sexually Transmitted Infections

Uncomplicated urethral, endocervical or rectal infections caused by *Chlamydia trachomatis*.

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Granuloma inguinale caused by *Klebsiella granulomatis*.

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.

Chancroid caused by *Haemophilus ducreyi*.

1.3 Respiratory Tract Infections

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Psittacosis (ornithosis) caused by *Chlamydophila psittaci*.

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

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

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract infections caused by *Klebsiella species*.

Upper respiratory infections caused by *Streptococcus pneumoniae*.

1.4 Specific Bacterial Infections

Relapsing fever due to *Borrelia recurrentis*.

Plague due to *Yersinia pestis*.

Tularemia due to *Francisella tularensis*.

Cholera caused by *Vibrio cholerae*.

Campylobacter fetus infections caused by *Campylobacter fetus*.

Brucellosis due to *Brucella* species (in conjunction with streptomycin).

Bartonellosis due to *Bartonella bacilliformis*.

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

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

Escherichia coli

Enterobacter aerogenes

Shigella species

Acinetobacter species

Urinary tract infections caused by *Klebsiella* species.

1.5 Ophthalmic Infections

Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

1.6 Anthrax Including Inhalational Anthrax (Post-Exposure)

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

1.7 Alternative Treatment for Selected Infections when Penicillin is Contraindicated

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

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema 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*.

1.8 Adjunctive Therapy for Acute Intestinal Amebiasis and Severe Acne

In acute intestinal amebiasis, doxycycline may be a useful adjunct to amebicides. In severe acne, doxycycline may be useful adjunctive therapy.

1.9 Prophylaxis of Malaria

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (less than 4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains [see *Dosage and Administration* (2.2) and *Patient Counseling Information* (17)].

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage and Administration

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

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

For pediatric patients above eight years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg per kg of body weight divided into two doses on the first day of treatment, followed by 2.2 mg per kg of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe infections, up to 4.4 mg per kg of body weight may be used. For children over 45 kg, the usual adult dose should be used.

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline-class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration [see *Adverse Reactions* (6.1)].

If gastric irritation occurs, doxycycline may be given with food or milk [see *Clinical Pharmacology* (12.3)].

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

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

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.

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

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

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

Acute epididymo-orchitis caused by *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.

2.2 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 per kg given once daily up to the adult dose. Prophylaxis should begin 1 or 2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

2.3 Inhalational Anthrax (Post-Exposure)

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

CHILDREN: weighing less than 45 kg, 2.2 mg per kg of body weight, by mouth, twice-a-day for 60 days. Children weighing 45 kg or more should receive the adult dose.

3 DOSAGE FORMS AND STRENGTHS

ACTICLATE™ (doxycycline hyclate USP) Tablets, 75 mg are round, convex, light-teal, film-coated, tablets with "75" debossed on one side of the tablet and "AQ101" debossed on the other.

ACTICLATE™ (doxycycline hyclate USP) Tablets, 150 mg are oval-shaped, convex, mossy-green, film-coated tablets. Each side of the functionally scored tablet has two parallel score lines for splitting into 3 equal portions with "A" debossed on each portion of one side of the tablet, and no debossing on the other.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Tooth Development

The use of drugs of the tetracycline-class during tooth development (last half of pregnancy, infancy and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). This adverse reaction is more common during long-term use of the drugs but it has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Doxycycline should not be used in this age group, except for anthrax, including inhalational anthrax (post-exposure), unless other drugs are not likely to be effective or are contraindicated.

5.2 *Clostridium difficile* Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ACTICLATE, 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 antibacterial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

5.3 Photosensitivity

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

5.4 Superinfection

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

5.5 Intracranial Hypertension

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including ACTICLATE. 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 ACTICLATE 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.

5.6 Skeletal Development

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

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

5.7 Antianabolic Action

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

5.8 Malaria

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

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

5.9 Development of Drug-Resistant Bacteria

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

5.10 Laboratory Monitoring for Long-Term Therapy

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

6 ADVERSE REACTIONS

6.1 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of doxycycline hyclate tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

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. Hepatotoxicity has been reported. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline-class. Most of these patients took medications immediately before going to bed [see *Dosage and Administration* (2.1)].

Skin: Maculopapular and erythematous rashes, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme have been reported. Photosensitivity is discussed above [see *Warnings and Precautions* (5.3)].

Renal: Rise in BUN has been reported and is apparently dose-related [see *Warnings and Precautions* (5.7)].

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

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

Intracranial Hypertension: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines [see *Warnings and Precautions* (5.5)].

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

7 DRUG INTERACTIONS

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

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

7.3 Antacids and Iron Preparations
Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, or magnesium, bismuth subsalicylate, and iron-containing preparations.

7.4 Oral Contraceptives
Concurrent use of tetracycline may render oral contraceptives less effective.

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

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

7.7 Drug and Laboratory Test Interactions
False elevations of urinary catecholamines may occur due to interference with the fluorescence test.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects. Pregnancy Category D: [see *Warnings and Precautions* (5.6)]

There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS - the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair), but the data are insufficient to state that there is no risk.[1]

A case-control study (18,515 mothers of infants with congenital anomalies and 32,804 mothers of infants with no congenital anomalies) shows a weak but marginally statistically significant association with total malformations and use of doxycycline anytime during pregnancy. Sixty-three (0.19%) of the controls and 56 (0.30%) of the cases were treated with doxycycline. This association was not seen when the analysis was confined to maternal treatment during the period of organogenesis (that is, in the second and third months of gestation), with the exception of a marginal relationship with neural tube defect based on only two-exposed cases.[2]

A small prospective study of 81 pregnancies describes 43 pregnant women treated for 10 days with doxycycline during early first trimester. All mothers reported their exposed infants were normal at 1 year of age.[3]

Nonteratogenic effects: [see *Warnings and Precautions* (5.1, 5.6)].

8.3 Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breastfed infant is not known. Short-term use by lactating women is not necessarily contraindicated. The effects of prolonged exposure to doxycycline in breast milk are unknown[4]. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother [see *Warnings and Precautions* (5.1, 5.6)].

8.4 Pediatric Use

Because of the effects of drugs of the tetracycline-class on tooth development and growth, ACTICLATE should not be used in pediatric patients to the age of 8 years, unless the potential benefits are expected to outweigh the risks such as for anthrax, or when other drugs are not likely to be effective or are contraindicated [see *Warnings and Precautions* (5.1, 5.6) and *Dosage and Administration* (2.1, 2.3)].

8.5 Geriatric Use

Clinical studies of doxycycline hyclate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

ACTICLATE Tablets, 75 mg contain 0.34 mg (0.0146 mEq) of sodium.
ACTICLATE Tablets, 150 mg contain 0.68 mg (0.0295 mEq) of sodium.

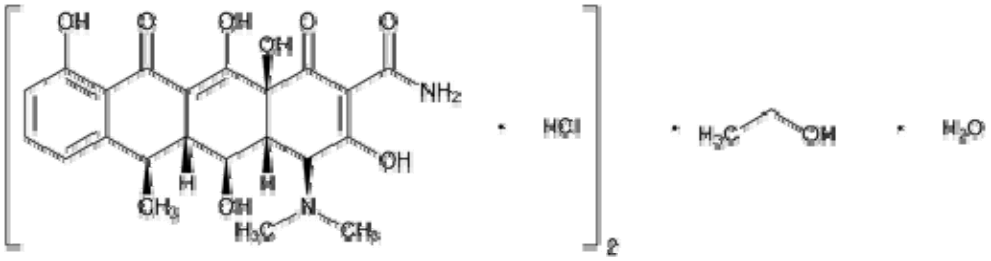
10 OVERDOSAGE

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

11 DESCRIPTION

ACTICLATE™ (doxycycline hyclate USP) Tablets contain doxycycline hyclate, a broad-spectrum antibacterial synthetically derived from oxytetracycline, in an immediate release formulation for oral administration.

The structural formula for doxycycline hyclate is:



with a molecular formula of $(C_{22}H_{24}N_2O_8, HCl)_2 \cdot C_2H_6O \cdot H_2O$ and a molecular weight of 1025.87.

The chemical designation for doxycycline hyclate 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 monohydrochloride, compound with ethyl alcohol (2:1), monohydrate.

Doxycycline hyclate is a yellow crystalline powder soluble in water and in solutions of alkali hydroxides and carbonates. Inactive ingredients in the tablet formulation are: microcrystalline cellulose, sodium lauryl sulfate, croscarmellose sodium and magnesium stearate. Film-coating contains: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue #1 (75 mg), FD&C Yellow #6 (75 mg), FD&C Blue #2 (150 mg) and yellow iron oxide (150 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Doxycycline is an antimicrobial drug [see *Microbiology* (12.4)].

12.3 Pharmacokinetics

Doxycycline is virtually completely absorbed after oral administration. Following administration of a single 300 mg dose to adult volunteers, average peak plasma doxycycline levels were 3.0 mcg per mL at 3 hours, decreasing to 1.18 mcg per mL at 24 hours. The mean C_{max} and AUC $_{0-\infty}$ of doxycycline are 24% and 15% lower, respectively, following single dose administration of ACTICLATE, 150 mg tablets with a high fat meal (including milk) compared to fasted conditions. The clinical significance of these decreases is unknown.

Tetracyclines are concentrated in bile by the liver and excreted in the urine and feces at high concentrations and in a biologically active form. Excretion of doxycycline by the kidney is about 40% per 72 hours in individuals with a creatinine clearance of about 75 mL per minute. This percentage may fall as low as 1% per 72 hours to 5% per 72 hours in individuals with a creatinine clearance below 10 mL per minute.

Studies have shown no significant difference in the serum half-life of doxycycline (range 18 to 22 hours) in individuals with normal and severely impaired renal function. Hemodialysis does not alter the serum half-life.

12.4 Microbiology

Mechanism of Action

Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. 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 ACTICLATE [see *Indications and Usage* (1).

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

Gram-Positive Bacteria
Bacillus anthracis
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 species
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 antibacterial 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 antibacterial.

Dilution techniques
Quantitative methods are used to determine antibacterial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized test method [5,6,7,8,9] (broth and/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 antibacterial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds.

The zone size should be determined using a standardized test method[5,7,10]. This procedure uses paper disks impregnated with 30 mcg 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[11]. 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

Pathogen*	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†									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Brucella species†									
Doxycycline	≤1	-	-	-	-	-	-	-	-
Tetracycline	≤1	-	-	-	-	-	-	-	-
Enterobacteriaceae									
Doxycycline	≤4	8	≥16	≥14	11 - 13	≤10	-	-	-
Tetracycline	≤4	8	≥16	≥15	12 - 14	≤11	-	-	-
Franciscella tularensis†									
Doxycycline	≤4	-	-	-	-	-	-	-	-
Tetracycline	≤4	-	-	-	-	-	-	-	-

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Pathogen*	Minimal Inhibitory Concentration (mcg per mL)			Zone Diameter (mm)			Agar Dilution (mcg per mL)		
	S	I	R	S	I	R	S	I	R
Haemophilus influenzae									
Tetracycline	≤2	4	≥8	≥29	26 - 28	≤25	-	-	-
Mycoplasma pneumoniae†									
Tetracycline	-	-	-	-	-	-	≤2	-	-
Nocardiae and other aerobic *Actinomyces* species†									
Doxycycline	≤1	2 - 4	≥8	-	-	-	-	-	-
Neisseria gonorrhoeae‡									
Tetracycline	-	-	-	≥38	31 - 37	≤30	≤0.25	0.5 - 1	≥2
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

* 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.

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

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

A report of *Susceptible* (S) indicates that the antibacterial is likely to inhibit growth of the pathogen if the antibacterial compound reaches the concentrations at the infection site necessary to inhibit growth of the pathogen. 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 antibacterial is not likely to inhibit growth of the pathogen if the antibacterial compound 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[5,6,7,8,9,10,11]. 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 Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution[b] (mcg per mL)
Enterococcus faecalis ATCC[a] 29212			

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

QC Strain	Minimal Inhibitory Concentration (mcg per mL)	Zone Diameter (mm)	Agar Dilution[b] (mcg per mL)
Doxycycline	2 - 8	-	-
Tetracycline	8 - 32	-	-
Escherichia coli ATCC 25922			
Doxycycline	0.5 - 2	18 - 24	-
Tetracycline	0.5 - 2	18 to 25	-
Eubacterium 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 pneumoniae ATCC 49619			
Doxycycline	0.015 - 0.12	25 - 34	-
Tetracycline	0.06 - 0.5	27 - 31	-
Bacteroides fragilis ATCC 25285			
Tetracycline	-	-	0.125 - 0.5
Bacteroides thetaiotaomicron ATCC 29741			
Doxycycline	2 - 8	-	-
Tetracycline	-	-	8 - 32
Mycoplasma hominis ATCC 23114			
Tetracycline	-	-	0.12 - 1
Mycoplasma pneumoniae ATCC 29342			
Tetracycline	0.06 - 5	-	0.06 - 0.5
Ureaplasma urealyticum ATCC 33175			
Tetracycline	-	-	≥8

[a] ATCC is the American Type Culture Collection

[b] For four-dilution ranges, results at the extremes of the acceptable ranges should be suspect. Verify with data from other control strains.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibacterials, oxytetracycline (adrenal and pituitary tumors) and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in *in vitro* mammalian cell assays have been reported for related antibacterials (tetracycline, oxytetracycline).

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

13.2 Animal Toxicology and/or Pharmacology

Hyperpigmentation of the thyroid has been produced by members of the tetracycline-class in the following species: in rats by oxytetracycline, doxycycline, tetracycline 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.

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

15 REFERENCES

1. Friedman JM, Polifka JE. *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The Johns Hopkins University Press: 2000: 149-195.
2. Cziezel AE and Rockenbauer M. Teratogenic study of doxycycline. Obstet Gynecol 1997; 89: 524-528.
3. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25: 315-317.
4. Hale T. *Medications and Mothers Milk.* 9th edition. Amarillo, TX: Pharmasoft Publishing 2000; 225-226.
5. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-fourth Informational Supplement*, CLSI document M100-S24, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2014.
6. Clinical and Laboratory Standards Institute (CLSI). *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard – Ninth Edition*. CLSI document M07-A9, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.
7. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – Second Edition.* CLSI document M45-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2010.
8. Clinical and Laboratory Standards Institute (CLSI). *Methods for Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes; Approved Standard – Second Edition*. CLSI document M24-A2, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2011.
9. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing for Human Mycoplasmas; Approved Guideline*. CLSI document M43-A, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2011.
10. Clinical and Laboratory Standards Institute (CLSI). *Performance Standards for Antimicrobial Disk Diffusion Susceptibility Tests; Approved Standard – Eleventh Edition*. CLSI document M02-A11, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

11. Clinical and Laboratory Standards Institute (CLSI). *Methods for Antimicrobial Susceptibility Testing of Anaerobic Bacteria; Approved Standard – Eighth Edition*. CLSI document M11-A8, Clinical Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087, USA, 2012.

16 HOW SUPPLIED/STORAGE AND HANDLING

ACTICLATE™ (doxycycline hyclate USP) Tablets, 75 mg

Bottles of 60 tablets: NDC 16110-501-01

ACTICLATE™ (doxycycline hyclate USP) Tablets, 150 mg

Bottles of 60 tablets: NDC 16110-502-01

Store at 20° to 25°C (68° to 77°F) excursions permitted to 15° to 30°C (59° to 86°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.

17 PATIENT COUNSELING INFORMATION

Advise patients taking doxycycline for malaria prophylaxis:

- 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 (for example, 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 day 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.

Advise all patients taking doxycycline:

- to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (for example, skin eruptions, etc.) occurs. Sunscreen or sunblock should be considered [see *Warnings and Precautions* (5.3)].
- to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration [see *Adverse Reactions* (6.1)].
- that the absorption of tetracyclines is reduced when taken with foods, especially those that contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk [see *Drug Interactions* (7.3)].
- that the absorption of tetracyclines is reduced when taken with antacids containing aluminum, calcium or magnesium, bismuth subsalicylate, and iron-containing preparations [see *Drug Interactions* (7.3)].
- that the use of doxycycline might increase the incidence of vaginal candidiasis.

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

Counsel patients that antibacterial drugs including ACTICLATE should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When ACTICLATE 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 ACTICLATE or other antibacterial drugs in the future.

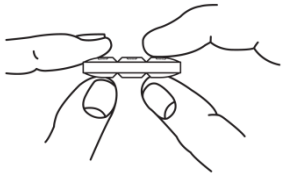
17.1 Instructions for Breaking the 150 mg Tablet

Your doctor may find it necessary to adjust your dosage of ACTICLATE to obtain the proper treatment response. The tablet is marked with separation lines (scored lines) and may be broken at these scored lines to provide any of the following doses.

150 mg treatment (take entire tablet)

Full Tablet Top View

Full Tablet Side View

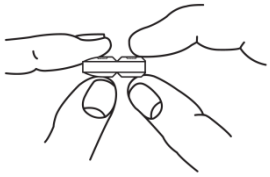


Full Tablet Side View
(with Thumb and Index Finger)

100 mg treatment (take two-thirds of the tablet or two 50 mg tablet segments)

Two-Thirds Tablet Top View

Two-Thirds Tablet Side View



Two-Thirds Tablet Side View
(with Thumb and Index Finger)

50 mg treatment (take one-third of the tablet)

One-Third Tablet Top View

One-Third Tablet Side View

One-Third Tablet Side View
(with Thumb and Index Finger)

To break the tablet, hold the tablet between your thumbs and index fingers close to the appropriate score line. Then, apply enough pressure to snap the tablet segments apart (do not use segments that do not break along the score line).

FDA-Approved Patient Labeling

ACTICLATE™ Tablets

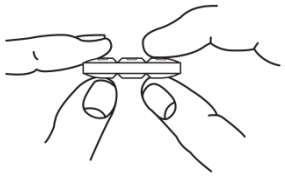
Instructions for Breaking the 150 mg Tablet

Your doctor may find it necessary to adjust your dosage of ACTICLATE to obtain the proper treatment response. The tablet is marked with separation lines (scored lines) and may be broken at these scored lines to provide any of the following doses.

150 mg treatment (take entire tablet)

Full Tablet Top View

Full Tablet Side View

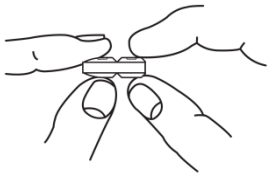


Full Tablet Side View
(with Thumb and Index Finger)

100 mg treatment (take two-thirds of the tablet or two 50 mg tablet segments)

Two-Thirds Tablet Top View

Two-Thirds Tablet Side View



Two-Thirds Tablet Side View
(with Thumb and Index Finger)

50 mg treatment (take one-third of the tablet)

One-Third Tablet Top View

One-Third Tablet Side View

One-Third Tablet Side View
(with Thumb and Index Finger)

To break the tablet, hold the tablet between your thumbs and index fingers close to the appropriate score line. Then, apply enough pressure to snap the tablet segments apart (do not use segments that do not break along the score line).

Revised: 07/2014

Rx only

Manufactured by Catalent Pharma Solutions, Winchester, KY 40391
For Aqua Pharmaceuticals, an Almirall Company West Chester, PA 19380

NDC 16110-**501**-02

Acticlate™

(Doxycycline Hyclate USP) Tablets

75 mg per tablet

Physician Sample Use Only. Not for Sale.

Manufactured by:
Catalent Pharma Solutions
Winchester, KY 40391
For: Aqua Pharmaceuticals
an Almirall Company
West Chester, PA 19380

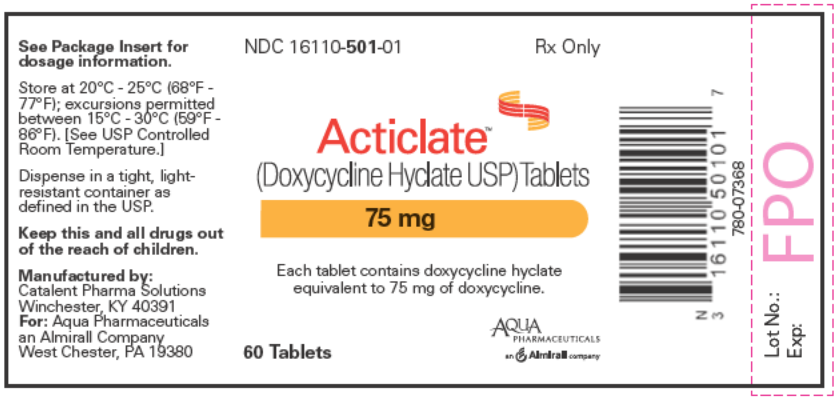
2 Tablets

Lot xxxxxxx FPO

Exp xx/20xx FPO

080-07369

UNVARNISHED AREA



2-7-14
Aqua AQ101 75mg Dumpbin

16 in x 14 in flat
3 in x 3.5 in x 5 in folded

Each tablet contains:
Doxycycline hyclate equivalent to 75 mg of doxycycline.

Net Quantity: 10 blisters of 2 tablets each

See Package Insert for dosage information.

Store at 20°C - 25°C (68°F - 77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F).
[See USP controlled room temperature.]

Keep this and all drugs out of the reach of children.

AQUA PHARMACEUTICALS
an Almirall company

Manufactured by:
Catalent Pharma Solutions
Winchester, KY 40391
For: Aqua Pharmaceuticals
an Almirall Company
West Chester, PA 19380

UNVARNISHED AREA →

FPO

Lot No.:
Exp:

700-07370

Acticlate™
(Doxycycline Hyclate USP) Tablets
75 mg per tablet

N 3 16110 50102 4

75 mg per tablet

Each tablet contains doxycycline hyclate equivalent to 75 mg of doxycycline.

Rx Only

Physician Sample Use Only.

Not For Sale.

Acticlate™
(Doxycycline Hyclate USP) Tablets
75 mg per tablet

NDC 16110-**501**-02

Acticlate™
(Doxycycline Hyclate USP) Tablets
75 mg per tablet

Each tablet contains doxycycline hyclate equivalent to 75 mg of doxycycline.

AQUA PHARMACEUTICALS
an Almirall company

Acticlate™
(Doxycycline Hyclate USP) Tablets
75 mg per tablet

Each tablet contains doxycycline hyclate equivalent to 75 mg of doxycycline.

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NDC 16110-**502**-02

Acticlate™

(Doxycycline Hyclate USP) Tablets

150 mg per tablet

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West Chester, PA 19380

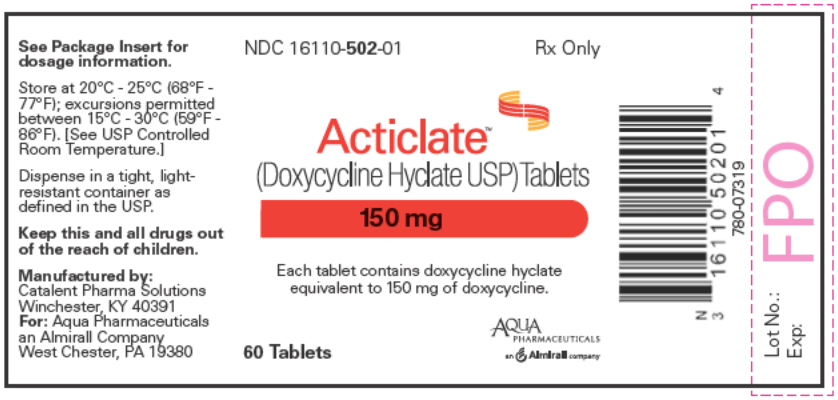
1 Tablet

Lot:xxxxxxx FPO

Exp xx/20xx FPO

080-07327

UNVARNISHED AREA



2-11-14
Aqua AQ101 150mg Dumpbin

16 in x 14 in flat
3 in x 3.5 in x 5 in folded

Each tablet contains:
Doxycycline hyclate equivalent to 150 mg of doxycycline.

Net Quantity: 10 blisters of 1 tablet each

See Package Insert for dosage information.

Store at 20°C - 25°C (68°F - 77°F) with excursions permitted to 15°C - 30°C (59°F - 86°F).
[See USP controlled room temperature.]

Keep this and all drugs out of the reach of children.

AQUA PHARMACEUTICALS an Almirall company

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For: Aqua Pharmaceuticals
an Almirall Company
West Chester, PA 19380

UNVARNISHED AREA →

FPO

Lot No.:
Exp:

700-07325

Acticlate™
(Doxycycline Hyclate USP) Tablets
150 mg per tablet

N 3 16110 50202 1

150 mg per tablet
Each tablet contains doxycycline hyclate equivalent to 150 mg of doxycycline.
Rx Only
Physician Sample Use Only.
Not For Sale.

Acticlate™
(Doxycycline Hyclate USP) Tablets
150 mg per tablet

NDC 16110-**502**-02

Acticlate™
(Doxycycline Hyclate USP) Tablets
150 mg per tablet

Each tablet contains doxycycline hyclate equivalent to 150 mg of doxycycline.

AQUA PHARMACEUTICALS an Almirall company

Acticlate™
(Doxycycline Hyclate USP) Tablets
150 mg per tablet

Each tablet contains doxycycline hyclate equivalent to 150 mg of doxycycline.

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SUMATHI NAMBIAR
07/25/2014