LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT B

PROPOSED LABELING

Doxycycline Hyclate Tablets
(coated doxycycline hyclate tablets)

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

DESCRIPTION

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

CLINICAL PHARMACOLOGY

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

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

Hemodialysis does not alter serum half-life.

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

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

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

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

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

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

INDICATIONS AND USAGE

Doxycycline is indicated in infections caused by the following microorganisms:

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

Mycoplasma pneumoniae (PPLO, Eaton's agent)

Agents of psittacosis and ornithosis

Agents of lymphogranuloma venereum and granuloma inguinale

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

The following gram-negative microorganisms:

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

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

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

Escherichia coli
Enterobacter aerogenes (formerly *Aerobacter aerogenes*)
Shigella species
Mima species and *Herellea* species
Haemophilus influenzae (respiratory infections)
Klebsiella species (respiratory and urinary infections)

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

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

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

Diplococcus pneumoniae.

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

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

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

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

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

In severe acne, doxycycline may be useful adjunctive therapy.

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

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

Doxycycline is indicated for the treatment of uncomplicated urethral, endocervical or rectal infections in adults cause by *Chlamydia trachomatis.*[2]

Doxycycline is indicated for the treatment of nongonococcal urethritis caused by *Chlamydia trachomatis* and *Ureaplasma urealyticum* and for the treatment of acute epididymo-orchitis caused by *Chlamydia trachomatis.*[2]

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

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

CONTRAINDICATIONS

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

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN). This adverse reaction is more common during long term use of the drugs but has been observed following repeated short term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

Pregnancy: Teratogenic Effects.
Pregnancy Category D: There are no adequate and well-controlled studies on the use of doxycycline in pregnant women. The vast majority of reported experience with doxycycline during human pregnancy is short-term, first trimester exposure. There are no human data available to assess the effects of long-term therapy of doxycycline in pregnant women such as that proposed for the treatment of anthrax exposure. An expert review of published data on experiences with doxycycline use during pregnancy by TERIS – the Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (the quantity and quality of data were assessed as limited to fair) but the data are insufficient to state that there is no risk[3].

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[4].

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[5].

Nursing Mothers

Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines including doxycycline, by the breast-fed infant is not known. Short-term use by lactating women is not necessarily contraindicated; however, the effects of prolonged exposure to doxycycline in breast milk are unknown[6]. 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 doxcycline'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, entercolitis, 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 ADMINISTRAITON section)

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

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

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

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

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

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

DOSAGE AND ADMINISTRATION

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

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

For pediatric patients above eight years of age: The recommended dosage schedule for pediatric patients weighing 100 pounds or less is 2 mg/lb of body weight divided into two doses on the first day of treatment, followed by a 1 mg/lb of body weight given as a single daily dose or divided into two doses on subsequent days. For more severe

infections up to 2 mg/lb of body weight may be used. For pediatric patients over 100 pounds, the usual adult dose should be used.

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

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

Primary and secondary syphilis: 300 mg a day in divided doses for at least 10 days.[2]

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

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

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

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

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

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

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

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

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

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

HOW SUPPLIED

THE DESCRIPTION WILL BE INCLUDED IN THE ANDA LABELING.

STORAGE CONDITIONS

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

REFERENCES:

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2. CDC Sexuality Transmitted Diseases Treatment Guidelines 1982
3. Friedman JM and Polifka JE, *Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS).* Baltimore, MD: The John Hopkins University Press: 2000: 149-195.
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5. Horne HW Jr. and Kundsin RB. The role of mycoplasma among 81 consecutive pregnancies: a prospective study. *Int J Fertil* 1980; 25:315-317
6. Hale T. *Medications and Mothers Milk.* 9th edition, Amarillo, TX: Pharmasoft Publishing 2000; 225-226

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