

**Important note.** *In vitro* sulfonamide sensitivity tests are not always reliable. The test must be carefully coordinated with bacteriologic and clinical response. When the patient is already taking sulfonamides, followup cultures should have aminobenzotic acid added to the culture media.

Currently, the increasing frequency of resistant organisms is a limitation of the usefulness of antibacterial agents including the sulfonamides, especially in the treatment of chronic and recurrent urinary tract infections.

Wide variation in blood levels may result with identical doses. Blood levels should be measured in patients receiving sulfonamides for serious infections. Free sulfonamide blood levels of 5-15 mg. per 100 ml. may be considered therapeutically effective for most infections, with blood levels of 12-15 mg. per 100 ml. optimal for serious infections; 20 mg. per 100 ml. should be the maximum total sulfonamide level, as adverse reactions occur more frequently above this level.

#### ADVERSE REACTIONS

**Blood dyscrasias.** Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia, and methemoglobinemia.

**Allergic reactions.** Erythema multiforme (Stevens-Johnson Syndrome), generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia, and allergic myocarditis.

**Gastrointestinal reactions.** Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis, and stomatitis.

**C.N.S. reactions.** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, and insomnia.

**Miscellaneous reactions.** Drug fever, chills, and toxic nephrosis with oliguria and anuria. Periarthritis nodosum and L.E. phenomenon have occurred.

The sulfonamides bear certain chemical similarities to some goitrogens, diuretics (acetazolamide and the thiazides), and oral hypoglycemic agents. Goiter production, diuresis, and hypoglycemia have occurred rarely in patients receiving sulfonamides. Cross-sensitivity may exist with these agents.

Rats appear to be especially susceptible to the goitrogenic effects of sulfonamides, and long-term administration has produced thyroid malignancies in the species.

6. Revising the first paragraph of the Warnings section (that follows "Use in Pregnancy") so that the entire section reads as follows:

#### WARNINGS

The sulfonamides should not be used for the treatment of group A beta-hemolytic streptococcal infections. In an established infection, they will not eradicate the streptococcus and, therefore, will not prevent sequelae such as rheumatic fever and glomerulonephritis.

Deaths associated with the administration of sulfonamides have been reported from hypersensitivity reactions, agranulocytosis, aplastic anemia, and other blood dyscrasias.

The presence of clinical signs such as sore throat, fever, pallor, purpura, or jaundice

may be early indications of serious blood disorders.

Complete blood counts should be done frequently in patients receiving sulfonamides.

The frequency of renal complications is considerably lower in patients receiving the more soluble sulfonamides. Urinalysis with careful microscopic examinations should be obtained frequently in patients receiving sulfonamides.

7. Adding a statement in the Precautions section so that the section reads as follows:

#### PRECAUTIONS

Sulfonamides should be given with caution to patients with impaired renal or hepatic function and to those with severe allergy or bronchial asthma.

Adequate fluid intake must be maintained in order to prevent crystalluria and stone formation.

In glucose-6-phosphate dehydrogenase deficient individuals, hemolysis may occur. This reaction is frequently dose-related.

The new-drug applications held by Parke, Davis & Co. (NDA 4-154), Abbott Laboratories (NDA 4-125), Ayerst Laboratories (NDA 8-565), Ciba Pharmaceutical Co. (NDA 8-070) and Roche Laboratories (NDA's 6-525, 6-917, 9-182 and 12-715) have been satisfactorily supplemented to delete those claims for which substantial evidence of effectiveness is lacking and to be in accord with this notice.

Other holders of applications approved for these drugs should submit, within 60 days following publication of this amended announcement in the FEDERAL REGISTER, supplements to their new-drug applications to provide for revised labeling in accord with the sections above. Such supplements should be submitted under the provisions of § 130.9 (d) and (e) of the new-drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest time.

Any such preparation, for human use, introduced into interstate commerce after 60 days following publication of this notice in the FEDERAL REGISTER with labeling bearing indications that lack substantial evidence of effectiveness may be subject to regulatory proceedings.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: March 16, 1972.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

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[DESI 7322]

### DOXYCYCLINE FOR ORAL USE

#### Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration published an announcement in the FEDERAL REGISTER of September 2, 1970 (35

F.R. 13897), regarding the efficacy of tetracycline, oxytetracycline, chlortetracycline, demethylchlortetracycline, and rolitetracycline for systemic use. A correction of that announcement, which extended the labeling guidelines for tetracycline to include doxycycline capsules and suspension and methacycline capsules and syrup, was published April 20, 1971 (36 F.R. 7473). Based upon new information and a reevaluation of available data, the Commissioner of Food and Drugs finds it appropriate to amend the labeling section of the September 2, 1970 and April 20, 1971 announcements insofar as they concern doxycycline as follows: (Revised labeling for tetracycline, oxytetracycline, chlortetracycline, demeclocycline, rolitetracycline, and methacycline is the subject of a separate notice.)

#### DESCRIPTION

(Descriptive information to be included by the manufacturer or distributor should be confined to an appropriate description of the physical and chemical properties of the drug and the formulation.)

#### ACTION

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. Microorganisms may be considered susceptible if the M.I.C. (minimum inhibitory concentration) is not more than 4.0 mcg./ml. and intermediate if the M.I.C. is 4.0 to 12.5 mcg./ml.

Susceptibility plate testing: A tetracycline disc may be used to determine microbial susceptibility to drugs in the tetracycline class. If the Kirby-Bauer method of disc susceptibility testing is used, a 30 mcg. tetracycline disc should give a zone of at least 19 mm. when tested against a tetracycline-susceptible bacterial strain.

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 percent/72 hours in individuals with normal function (creatinine clearance about 75 ml./min.). This percentage excretion may fall as low as 1-5 percent/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.

#### INDICATIONS

Doxycycline is indicated in infections caused by the following microorganisms:

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

*Mycoplasma pneumoniae* (PPLO, Eaton 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:

*Raemophilus ducreyi* (chancroid),  
*Pasteurella pestis* and *Pasteurella tularensis*,  
*Bartonella bacilliformis*,  
*Bacteroides* species,  
*Vibrio comma* and *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 bacteriologic 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 bacteriologic testing indicates appropriate susceptibility to the drug:

*Streptococcus pyogenes* (For upper respiratory infections due to Group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever),

Alpha-hemolytic streptococci (viridans group),

Enterococcus group (*Streptococcus faecalis*).

*Diplococcus pneumoniae*,  
*Staphylococcus aureus*, skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.

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

*Neisseria gonorrhoeae*,  
*Treponema pallidum* and *Treponema pertenue* (syphilis and yaws),  
*Listeria monocytogenes*,  
*Clostridium* species,  
*Bacillus anthracis*,  
*Fusobacterium justiforme* (Vincent's infection),  
*Actinomycin* species.

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

In severe acne, doxycycline may be a 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 oral and topical agents.

#### 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 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 unless other drugs are not likely to be effective or are contraindicated.

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

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

#### USAGE IN PREGNANCY

(See above "Warnings" about use during tooth development.)

Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues and can have toxic effects on the developing fetus (often related to retardation of skeletal development). Evidence of embryo-toxicity has also been noted in animals treated early in pregnancy.

#### USAGE IN NEWBORNS, INFANTS, AND CHILDREN

(See above "Warnings" about use during tooth development.)

As with other tetracyclines, doxycycline forms a stable calcium complex in any bone forming tissue. A decrease in the fibula growth rate has been observed in premature given oral tetracycline in doses of 25 mg./kg. every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

#### PRECAUTIONS

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

In venereal diseases when coexistent syphilis is suspected, darkfield examination should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

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

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

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

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

#### ADVERSE REACTIONS

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Skin: maculopapular and erythematous rashes. Exfoliative dermatitis has been reported but is uncommon. Photosensitivity is discussed above. (See "Warnings.")

Renal toxicity: rise in BUN has been reported and is apparently dose related. (See "Warnings.")

Hypersensitivity reactions: urticaria, angioneurotic edema, anaphylaxis, anaphylac-

toid purpura, pericarditis and exacerbation of systemic lupus erythematosus.

Bulging fontanels have been reported in young infants following full therapeutic dosage. This sign disappeared rapidly when the drug was discontinued.

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

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

#### DOXAGE 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.

(Adult and pediatric dose—to be supplied. Dosage for the treatment of gonorrhea should conform with recommendations of the U.S. Public Health Service.)

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.

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 impair absorption and should not be given to patients taking oral doxycycline.

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

Holders of applications approved for doxycycline for oral use are requested to submit, within 60 days following publication of this announcement in the FEDERAL REGISTER, amendments to their antibiotic applications to provide for revised labeling in accord with the labeling section above.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-51, as amended, 59 Stat. 463, as amended; 21 U.S.C. 352, 357) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: March 16, 1972.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

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#### LITHIUM CORP. OF AMERICA

#### Notice of Filing of Petition for Food Additive

Pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(b)(5)), 72 Stat. 1786; 21 U.S.C. 348 (b)(5)), notice is given that a petition (FAP 2H2732) has been filed by Lithium Corp. of America, a subsidiary of Gulf Resources & Chemical Corp., Post Office Box 795, Bessemer City, N.C. 28016, proposing that § 121.2547 *Sanitizing solutions* (21 CFR 121.2547) be amended to provide for the safe use of an aqueous