

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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(516) 222-6222 • FAX (516) 683-1887

November 8, 2001

OVERNIGHT COURIER 11/8/01

Dockets Management Branch
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act, and in accordance with 21 CFR 10.30, on behalf of a client requesting the Commissioner of the Food and Drug Administration to declare that the drug product, Doxycycline Monohydrate Tablets, 75 mg, is suitable for consideration in abbreviated new drug applications (ANDAs).

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration declare that Doxycycline Monohydrate Tablets, 75 mg, are suitable for submission as an ANDA. The listed reference drug product, upon which this petition is based, is Monodox® Capsules (Doxycycline Monohydrate), 100 mg (Oclassen Pharmaceuticals). The petitioner also references Monodox Capsules, 50 mg, in support of this petition. Therefore, the petitioner seeks a change in dosage form (from capsule to tablet), and change in strength (from 100 mg to 75 mg), from that of the listed drug product.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an Abbreviated New Drug Application for a drug product that differs in dosage strength and/or dosage form from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The reference-listed drug (RLD), Monodox Capsules manufactured by Oclassen Pharmaceuticals, is a capsule product containing 100 mg of Doxycycline Monohydrate.

OIP-0515

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CP 1

See listing on page 3-135 of the Twenty-First Edition of the Approved Drug Products with Therapeutic Equivalence Evaluations (Attachment 1). The proposed drug product represents a tablet dosage form containing 75 mg of Doxycycline Monohydrate. The petition is thus seeking a change in dosage form (from capsule to tablet), and change in strength (from 100 mg to 75 mg), from that of the reference listed drug.

In support of the change in dosage form requested in this petition, we refer to other FDA-approved "doxycycline" drug products that are available in a tablet dosage form (i.e., Doxycycline Hyclate). Additionally, we also refer to an approved petition (99P-4958/CP1) for Doxycycline Monohydrate Tablets, 50 mg and 100 mg (Note that the issue of pediatric safety and effectiveness was also addressed in that petition. A copy of that petition approval letter is enclosed, as Attachment 2). The petitioner is seeking this change in dosage form in an effort to make an alternate dosage form (tablet) available for those individuals that either have difficulty in swallowing a capsule, or who prefer a tablet dosage form.

This petition also seeks a change in strength for the proposed drug from that of the listed drug. Doxycycline Monohydrate is indicated for use in pediatric patients eight years and above. The recommended doses in this population, and who are 100 pounds or less, is 2 mg/lb body weight divided into two divided doses on the first day of treatment, and 1 mg/lb of body weight given as a single dose or a divided dose on subsequent days. For severe infections in this population, up to 2 mg/lb of body weight may be used. The availability of a 75 mg strength dosage unit provides the health care practitioner additional flexibility in dosing pediatric patients who may more appropriately be treated with a 75 mg dose. Presently, only 50 mg and 100 mg strengths of Doxycycline Monohydrate are commercially available. However, the approved labeling of the listed drug clearly contemplates doses titrated based on body weight and thus the 75 mg tablet will aid the physician to select a dose most appropriate for his/her patient.

The proposed strength may also be used in the treatment of primary and secondary syphilis. The approved labeling of the listed drug states that 300 mg of Doxycycline Monohydrate should be administered in divided doses. A 75 mg strength provides additional flexibility in dosage regimens to those currently available. A 75 mg strength would allow dosing at 75 mg four times daily, or two 75 mg tablets twice daily.

In accordance with the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, Final Rule (Pediatric Rule) published December 2, 1998, the petitioner claims the following:

The listed drug product provides dosing recommendations for the pediatric population down to eight years of age. The "Warnings" section of approved labeling for the listed drug product contains the following statement: "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. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

Due to the restrictions associated with drugs of the tetracycline class in the approved labeling of the listed drug, the petitioner certifies its belief that the requested change in dosage form (from capsule to tablet): A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in the age group not covered in existing labeling; and B) Due to the problem associated with permanent staining of the teeth, is not likely to be used in a substantial number of patients in that age group; and C) The absence of adequate labeling for this similar oral dosage form (tablet) could not pose significant risks to pediatric patients. In that regard, the petitioner requests a waiver under 21 CFR 201.23 for the need to conduct pediatric studies. The waiver is requested in accordance with the citation referenced above. The referenced product labeling contains the appropriate dosing recommendations for the pediatric age group for which the product is indicated. It is the petitioner's belief that the introduction of a tablet dosage form will not create any additional usage in the existing pediatric population for whom the product is recommended, and based on the labeled warnings will not likely be used in any substantial sub age group of pediatric patients.

There are no proposed changes in labeling with the exception of the obvious changes in dosage form and strength sought in this petition. Draft labeling for the proposed product is included in Attachment 3 and labeling of the reference-listed drug is provided in Attachment 4. Additionally, a copy of the November 2, 2001 Federal Register Notice (66FR55679) is included to support the FDA's approval for use of Doxycycline in the treatment of anthrax (Attachment 5).

Therefore, the petitioner's request for the Commissioner to find that a change in dosage form from capsule to tablet and a change in strength from 100 mg to 75 mg for Doxycycline Monohydrate should raise no questions of safety or effectiveness, and the Agency should approve the petition.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

D. Economic Impact

The petitioner does not believe that this is applicable in this case, but will agree to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Robert W. Pollock
Vice President

RP/pk

Attachments: 1. Prescription Drug Product List
 2. FDA Letter dated April 13, 2000
 3. Draft Insert Labeling Proposed for Doxycycline Tablets 75 mg
 4. Labeling for Monodox®, Revised April 28, 1998
 5. Federal Register Notice

cc: G. Davis (OGD)
 L. Lachman (LCS)

49P1312

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

PRESCRIPTION DRUG PRODUCT LIST

3-135

DOXORUBICIN HYDROCHLORIDE

INJECTABLE; INJECTION

AP RUBEX
BRISTOL MYERS SQUIBB 50MG/VIAL
100MG/VIAL

N62926 002
APR 13, 1989
N62926 003
APR 13, 1989

INJECTABLE, LIPOSOMAL; INJECTION

DOXIL
+ ALZA 2MG/ML

N50718 001
NOV 17, 1995

DOXYCYCLINE

CAPSULE; ORAL

DOXYCYCLINE

AB EON EQ 50MG BASE
AB EQ 100MG BASE
AB HALSEY EQ 50MG BASE
AB EQ 100MG BASE
AB PAR PHARM EQ 50MG BASE
AB EQ 100MG BASE
AB RANBAXY EQ 50MG BASE
AB EQ 100MG BASE
→ AB MONODOX
OCLASSEN EQ 50MG BASE
AB + EQ 100MG BASE

N65032 001
JUN 30, 2000
N65032 002
JUN 30, 2000
N65041 001
APR 28, 2000
N65041 002
APR 28, 2000
N65055 001
DEC 01, 2000
N65055 002
DEC 01, 2000
N65053 001
NOV 22, 2000
N65053 002
NOV 22, 2000

FOR SUSPENSION; ORAL

DOXYCHEL

AB RACHELLE EQ 25MG BASE/5ML
AB + VIBRAMYCIN
PFIZER EQ 25MG BASE/5ML

N61720 001
N50006 001

TABLET; ORAL
DOXYCYCLINE
PAR PHARM

EQ 50MG BASE

N65070 001
DEC 15, 2000

DOXYCYCLINE

TABLET; ORAL

DOXYCYCLINE
+ PAR PHARM

EQ 100MG BASE

N65070 002
DEC 15, 2000

DOXYCYCLINE CALCIUM

SUSPENSION; ORAL

VIBRAMYCIN
+ PFIZER

EQ 50MG BASE/5ML

N50480 001

DOXYCYCLINE HYCLATE

CAPSULE; ORAL

DOXY-LEMMON

AB TEVA EQ 50MG BASE
AB EQ 100MG BASE
AB DOXYCYCLINE HYCLATE
CHELSEA LABS EQ 50MG BASE
AB EQ 100MG BASE
AB DANBURY PHARMA EQ 50MG BASE
AB EQ 100MG BASE
AB HALSEY EQ 50MG BASE
AB EQ 100MG BASE
AB HOUBA EQ 50MG BASE
AB EQ 100MG BASE
AB MUTUAL PHARM EQ 50MG BASE
AB EQ 100MG BASE
AB MYLAN EQ 50MG BASE
AB EQ 100MG BASE
AB WEST WARD EQ 50MG BASE
AB EQ 100MG BASE
AB ZENITH GOLDLINE EQ 50MG BASE

N62497 001
AUG 23, 1984
N62497 002
JUN 15, 1984

N62142 001
N62142 002
N62031 002
OCT 13, 1982
N62031 001
N62418 001
JAN 28, 1983
N62418 002
JAN 28, 1983
N61717 001
N61717 002
N62675 001
JUL 10, 1986
N62676 001
JUL 10, 1986
N62337 001
MAR 29, 1982
N62337 002
MAR 29, 1982
N62396 002
NOV 07, 1984
N62396 001
MAY 07, 1984
N62500 001
SEP 11, 1984

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

3 0 5 4 '00 APR 24 AM 0:33

Lachman Consultant Services, Inc.
Attention: Robert W. Pollock
1600 Stewart Avenue
Westbury, New York 11590

APR 13 2000

Docket No. 99P-4958/CP1

Dear Mr. Pollock:

This is in response to your petition filed on November 16, 1999, requesting permission to file an Abbreviated New Drug Application (ANDA) for the following drug products: Doxycycline Tablets, 50 mg and 100 mg. The listed drug products to which you refer in your petition are Monodox® (Doxycycline) Capsules, 50 mg and 100 mg, manufactured by Oclassen Pharmaceuticals Inc.

Your request involves a change in dosage form from that of the listed drug products (i.e., from capsules to tablets). The change you request is the type of change that is authorized under the Act.

We have reviewed your petition under Section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (Act) and have determined that it is approved. This letter represents the Agency's determination that an ANDA may be submitted for the above-referenced drug products.

In addition, this petition and your waiver request were evaluated with respect to the Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients; Final Rule, published in the Federal Register (Pediatric Rule)(63 FR 66632). The agency has determined that your proposed change in dosage form is subject to the Pediatric Rule, but has concluded that investigations are not necessary to demonstrate the safety and effectiveness of your proposed product in the pediatric population, because this specific drug product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients below the age of eight.

Under Section 505(j)(2)(C)(i) of the Act, the Agency must approve a petition seeking a dosage form which differs from the dosage form of the listed drug product unless it finds that investigations must be conducted to show the safety and effectiveness of the differing dosage form.

99P-4958

PAV1

The Agency finds that the change in dosage form for the specific proposed drug products does not pose questions of safety or effectiveness because the uses, dose, and route of administration of the proposed drug products are the same as that of the listed drug products. The Agency concludes, therefore, that investigations are not necessary in this instance. In addition, if shown to meet bioavailability requirements, the proposed drug products can be expected to have the same therapeutic effect as the listed reference drug products.

The approval of this petition to allow an ANDA to be submitted for the above-referenced drug products does not mean that the Agency has determined that an ANDA will be approved for the drug products. The determination of whether an ANDA will be approved is not made until the ANDA itself is submitted and reviewed by the Agency.

To permit review of your ANDA submission, you must submit all information required under Sections 505(j)(2)(A) and (B) of the Act. To be approved, the drug products will, among other things, be required to meet current bioavailability requirements under Section 505(j)(2)(A)(iv) of the Act. We suggest that you submit your protocol to the Office of Generic Drugs, Division of Bioequivalence for these drug products prior to the submission of your ANDA. During the review of your application, the Agency may require the submission of additional information.

The listed drug products to which you refer in your ANDA must be the drug products upon which you based this petition. In addition, you should refer in your ANDA to the appropriate petition docket number cited above, and include a copy of this letter in the ANDA submission.

A copy of this letter approving your petition will be placed on public display in the Dockets Management Branch, Room 1061, Mail Stop HFA-305, 5630 Fishers Lane, Rockville, MD 20852.

Sincerely yours,



Gary J. Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

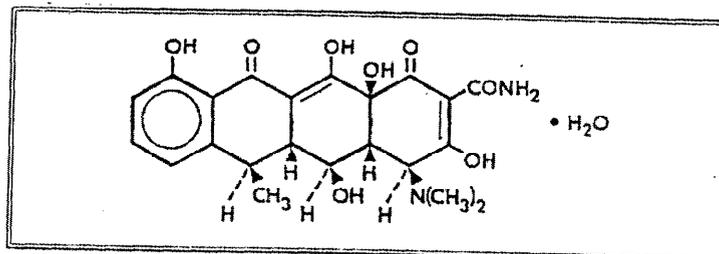
Copy of Draft Insert Labeling Proposed for Doxycycline Tablets 75 mg

DOXYCYCLINE TABLETS

DESCRIPTION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. Doxycycline 75 mg tablets contain doxycycline monohydrate equivalent to 75 mg of doxycycline for oral administration. The chemical designation of the light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline.

Structural formula:



M.W. = 462.45

Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inactive ingredients:

CLINICAL PHARMACOLOGY

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

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

Time (hr):	0.5	1.0	1.5	2.0	3.0	4.0	8.0	12.0	24.0	48.0	72.0
Conc:	1.02	2.26	2.67	3.01	3.16	3.03	2.03	1.62	0.95	0.37	0.15 (mcg/mL)

Average Observed Values

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

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

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

tetracyclines is common.

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:

<i>Neisseria gonorrhoeae</i>	<i>Francisella tularensis</i> (formerly <i>Pasteurella tularensis</i>)
<i>Haemophilus ducreyi</i>	<i>Vibrio cholerae</i> (formerly <i>Vibrio comma</i>)
<i>Haemophilus influenzae</i>	<i>Bartonella bacilliformis</i>
<i>Yersinia pestis</i> (formerly <i>Pasteurella pestis</i>)	<i>Brucella</i> species

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

<i>Escherichia coli</i>	<i>Shigella</i> species
<i>Klebsiella</i> species	<i>Acinetobacter</i> species (formerly <i>Mima</i> species and <i>Herellea</i> species)
<i>Enterobacter aerogenes</i>	<i>Bacteroides</i> species

GRAM-POSITIVE BACTERIA:

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended. Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used to treat streptococcal infections unless the organism has been demonstrated to be susceptible.

<i>Streptococcus pyogenes</i>	<i>Enterococcus</i> group (<i>Streptococcus faecalis</i> and <i>Streptococcus faecium</i>)
<i>Streptococcus pneumoniae</i>	<i>Alpha-hemolytic Streptococci</i> (<i>viridans</i> group)

OTHER MICROORGANISMS:

<i>Chlamydia psittaci</i>	<i>Fusobacterium fusiforme</i>
<i>Chlamydia trachomatis</i>	<i>Actinomyces</i> species
<i>Ureaplasma urealyticum</i>	<i>Bacillus anthracis</i>
<i>Borrelia recurrentis</i>	<i>Propionibacterium acnes</i>
<i>Treponema pallidum</i>	<i>Entamoeba</i> species
<i>Treponema pertenue</i>	<i>Balantidium coli</i>
<i>Clostridium</i> species	

Susceptibility tests:

DIFFUSION TECHNIQUES:

Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents.

One such standard procedure¹ which has been recommended for use with disks to test susceptibility of organisms to doxycycline uses the 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline

or doxycycline, respectively.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should be interpreted according to the following criteria:

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

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "intermediate" suggests that the organism would be susceptible if a high dose is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should give the following zone diameters:

Organism	Zone Diameter (mm)	
	tetracycline	doxycycline
E. coli ATCC 25922	18-25	18-24
S. aureus ATCC 25923	19-28	23-29

DILUTION TECHNIQUES:

Use a standardized dilution method² (broth, agar, microdilution) or equivalent with tetracycline powder. The MIC values obtained should be interpreted according to the following criteria:

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

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard tetracycline powder should provide the following MIC values:

Organism	MIC (mcg/mL)
S. aureus ATCC 29213	0.25-1
E. faecalis ATCC 29212	8-32
E. coli ATCC 25922	1-4
P. aeruginosa ATCC 27853	8-32

INDICATIONS AND USAGE

Doxycycline is indicated for the treatment of the following infections:

Rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsialpox, and tick fevers caused by *Rickettsiae*.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.
Psittacosis (ornithosis) caused by *Chlamydia psittaci*.
Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.
Inclusion conjunctivitis caused by *Chlamydia trachomatis*.
Uncomplicated urethral, endocervical or rectal infections in adults caused by *Chlamydia trachomatis*.
Nongonococcal urethritis caused by *Ureaplasma urealyticum*.
Relapsing fever due to *Borrelia recurrentis*.

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms:

Chancroid caused by *Haemophilus ducreyi*.
Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*).
Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).
Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*).
Campylobacter fetus infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).
Brucellosis due to *Brucella* species (in conjunction with streptomycin).
Bartonellosis due to *Bartonella bacilliformis*.
Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

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

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

Escherichia coli
Enterobacter aerogenes (formerly *Aerobacter aerogenes*)
Shigella species
Acinetobacter species (formerly *Mima* species and *Herellea* species)
Respiratory tract infections caused by *Haemophilus influenzae*.
Respiratory tract and urinary tract infections caused by *Klebsiella* species.

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

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

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

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

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

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

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.
Syphilis caused by *Treponema pallidum*.
Yaws caused by *Treponema pertenue*.
Listeriosis due to *Listeria monocytogenes*.

Vincent's infection caused by *Fusobacterium fusiforme*.
Actinomycosis caused by *Actinomyces 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.

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, EXCEPT FOR ANTHRAX, INCLUDING INHALATIONAL ANTHRAX (POST EXPOSURE), UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

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

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

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

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

PRECAUTIONS

General: 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.

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

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

indicated.

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

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

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

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

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

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/Laboratory Test Interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

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

Pregnancy: Pregnancy Category D. (See WARNINGS.)

Labor and Delivery: The effect of tetracyclines on labor and delivery is unknown.

Nursing Mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

Pediatric Use: See WARNINGS and DOSAGE AND ADMINISTRATION sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

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

administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See **DOSAGE AND ADMINISTRATION**.)

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

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See **WARNINGS**.)

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

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

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg, by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose.

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

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

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

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

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

Inhalational anthrax (post exposure):

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

CHILDREN: weighing less than 100 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.

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

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS**.) If gastric irritation occurs, doxycycline may be given with food. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5% and the area under the curve by 5.7%.

HOW SUPPLIED

Doxycycline Tablets 75 mg are XXXXXXXXXX tablets, debossed "XXX" on one side and "XXX" on the other side. Each tablet contains doxycycline monohydrate equivalent to 75 mg of doxycycline. They are supplied as follows:

Bottles of 100 NDC XXXXX-XXX-XX

Store at controlled room temperature 15-30° C (59-86° F).

Protect from light.

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY

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

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

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

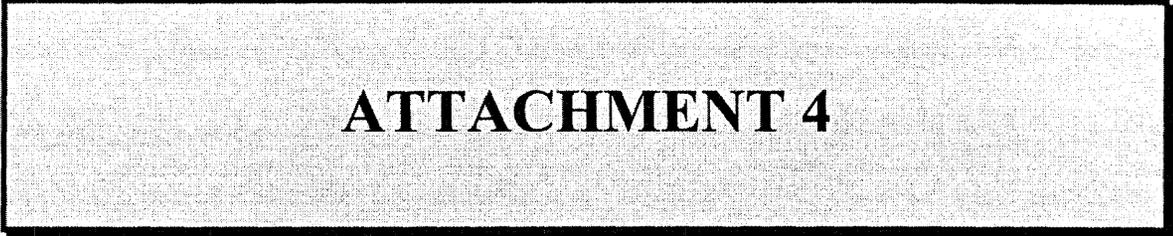
REFERENCES

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April 1990.
2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, Second Edition. Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8 NCCLS, Villanova, PA, April 1990.

Manufactured by:

Issued:

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590



ATTACHMENT 4

Copy of the Labeling for Monodox[®], Revised April 28, 1998

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Physician's Desk Reference

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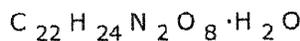
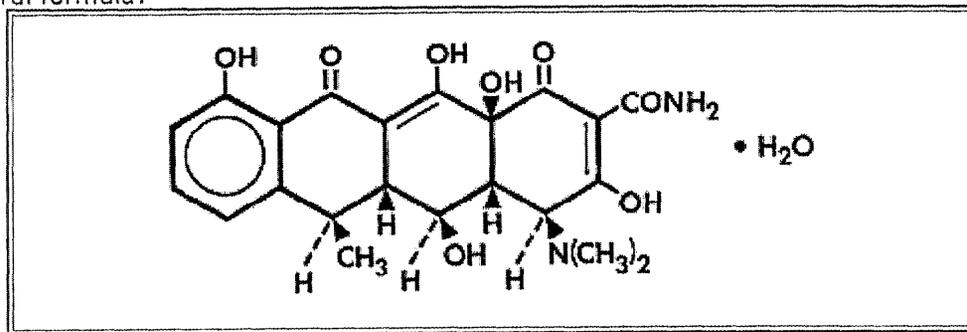
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PDR® entry for
Monodox Capsules (Oclassen)

DESCRIPTION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. Monodox® 100 mg and 50 mg capsules contain doxycycline monohydrate equivalent to 100 mg or 50 mg of doxycycline for oral administration. The chemical designation of the light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline.

Structural formula:



M.W.=462.46

Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

Inert Ingredients: colloidal silicon dioxide; hard gelatin capsule; magnesium stearate; microcrystalline cellulose; and sodium starch glycolate.

CLINICAL PHARMACOLOGY

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

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

Time (hr):	0.5	1.0	1.5	2.0	3.0	4.0	8.0	12.0	24.0	48.0	72.0
Conc. (mcg/mL)	1.02	2.26	2.67	3.01	3.16	3.03	2.03	1.62	0.95	0.37	0.15

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

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal function (creatinine clearance about 75 mL/min). This percentage excretion may fall as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in serum half-life of doxycycline (range 18-22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

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

While *in vitro* studies have demonstrated the susceptibility of most strains of the following microorganisms, clinical efficacy for infections other than those included in the INDICATIONS AND USAGE section has not been documented.

GRAM-NEGATIVE BACTERIA:

- *Neisseria gonorrhoeae*
- *Haemophilus ducreyi*
- *Haemophilus influenzae*
- *Yersinia pestis* (formerly *Pasteurella pestis*)
- *Francisella tularensis* (formerly *Pasteurella tularensis*)
- *Vibrio cholerae* (formerly *Vibrio comma*)
- *Bartonella bacilliformis*
- *Brucella species*

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

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

GRAM-POSITIVE BACTERIA:

Because many strains of the following groups of gram-positive microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing are recommended. Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Therefore, tetracyclines should not be used to treat streptococcal infections unless the organism has been demonstrated to be susceptible.

- *Streptococcus pyogenes*
- *Streptococcus pneumoniae*
- *Enterococcus* group (*Streptococcus faecalis* and *Streptococcus faecium*)
- *Alpha-hemolytic streptococci* (*viridans* group)

OTHER MICROORGANISMS:

- *Chlamydia psittaci*
- *Chlamydia trachomatis*
- *Ureaplasma urealyticum*
- *Borrelia recurrentis*
- *Treponema pallidum*
- *Treponema pertenu*
- *Clostridium* species
- *Fusobacterium fusiforme*
- *Actinomyces* species
- *Bacillus anthracis*
- *Propionibacterium acnes*
- *Entamoeba* species
- *Balantidium coli*

Susceptibility tests: Diffusion Techniques: Quantitative methods that require measurement of zone diameters give the most precise estimate of the susceptibility of bacteria to antimicrobial agents.

One such standard procedure ¹ which has been recommended for use with disks to test susceptibility of organisms to doxycycline uses the 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline or doxycycline, respectively.

Reports from the laboratory giving results of the standard single-disk susceptibility test with a 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should be interpreted according to the following criteria.

Zone Diameter (mm)		Interpretation
tetracycline	doxycycline	
>/=19	>/=16	Susceptible
15-18	13-15	Intermediate
</=14	</=12	Resistant

A report of "susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "intermediate" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected.

Standardized procedures require the use of laboratory control organisms. The 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should give the following zone diameters:

Organism	Zone Diameter	
	tetracycline	doxycycline

E. coli ATCC 25922	18-25	18-24
S. aureus ATCC 25923	19-28	23-29

Dilution Techniques:

Use a standardized dilution method ² (broth, agar, microdilution) or equivalent with tetracycline powder. The MIC values obtained should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
</=4	Susceptible
8	Intermediate
>/=16	Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard tetracycline powder should provide the following MIC values:

Organism	MIC (mcg/mL)
S. aureus ATCC 29213	0.25-1
E. faecalis ATCC 29212	8-32
E. coli ATCC 25922	1-4
P. aeruginosa ATCC 27853	8-32

INDICATIONS AND USAGE

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 *Rickettsia*.

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) caused by *Chlamydia psittaci*.

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

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

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

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Relapsing fever due to *Borrelia recurrentis*.

Doxycycline is also indicated for the treatment of infections caused by the following gram-negative microorganisms:

Chancroid caused by *Haemophilus ducreyi*.

Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*).

Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).

Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*).

Campylobacter fetus infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).

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

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

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

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

Escherichia coli

Enterobacter aerogenes (formerly *Aerobacter aerogenes*)

Shigella species

Acinetobacter species (formerly *Mima* species and *Herellea* species)

Respiratory tract infections caused by *Haemophilus influenzae*.

Respiratory tract and urinary tract infections caused by *Klebsiella* species.

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

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

Skin and skin structure infections caused by *Staphylococcus aureus*. Doxycycline is not the drug of choice in the treatment of any type of staphylococcal infections.

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

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.

Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

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.

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.

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

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

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

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

should be discontinued at the first evidence of skin erythema.

PRECAUTIONS

General:

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.

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

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

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

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

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

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

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

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

Drug/laboratory test interactions: False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

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

Pregnancy: Pregnancy Category D. (See **WARNINGS**).

Labor and Delivery: The effect of tetracyclines on labor and delivery is unknown.

Nursing mothers: Tetracyclines are present in the milk of lactating women who are taking a drug in this class. Because of the potential for serious adverse reactions in nursing infants from the tetracyclines, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS**).

Pediatric Use: See **WARNINGS** and **DOSAGE AND ADMINISTRATION** sections.

ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects to the lower bowel, particularly diarrhea, have been infrequent. The following adverse reactions have been observed in patients receiving tetracyclines.

Gastrointestinal: Anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, and inflammatory lesions (with monilial overgrowth) in the anogenital region. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Rare instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class. Most of these patients took medications immediately before going to bed. (See **DOSAGE AND ADMINISTRATION**).

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

Renal toxicity: Rise in BUN has been reported and is apparently dose related. (See **WARNINGS**.)

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

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

Uncomplicated gonococcal infections in adults (except anorectal infections in men): 100 mg by mouth, twice a day for 7 days. As an alternate single visit dose, administer 300 mg stat followed in one hour by a second 300 mg dose.

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

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

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

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

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

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

Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to wash down the drugs and reduce the risk of esophageal irritation and ulceration. (See **ADVERSE REACTIONS**). If gastric irritation occurs, doxycycline may be given with food. Ingestion of a high fat meal has been shown to delay the time to peak plasma concentrations by an average of one hour and 20 minutes. However, in the same study, food enhanced the average peak concentration by 7.5% and the area under the curve by 5.7%.

HOW SUPPLIED

MONODOX® 50 mg Capsules have a white opaque body with a yellow opaque cap. The capsule bears the inscription "MONODOX 50" in brown and "M 260" in brown. Each capsule contains doxycycline monohydrate equivalent to 50 mg doxycycline.

MONODOX® 50 mg is available in: Bottles of 100 capsules, NDC 55515-260-06.
MONODOX® 100 mg Capsules have a yellow opaque body with a brown opaque cap. The capsule bears the inscription "MONODOX 100" in white and "M 259" in brown. Each capsule contains doxycycline monohydrate equivalent to 100 mg of doxycycline. MONODOX® 100 mg is available in: Bottles of 50 capsules, NDC 55515-259-04 and in bottles of 250 capsules, NDC 55515-259-07.

STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°

F). PROTECT FROM LIGHT.**ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY**

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

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

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

REFERENCES:

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April 1990.
2. National Committee for Clinical Laboratory Standards, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*, Second Edition. Approved Standard NCCLS Document M7-A2, Vol. 10, No. 8 NCCLS, Villanova, PA, April 1990.

Rx Only

Manufactured for

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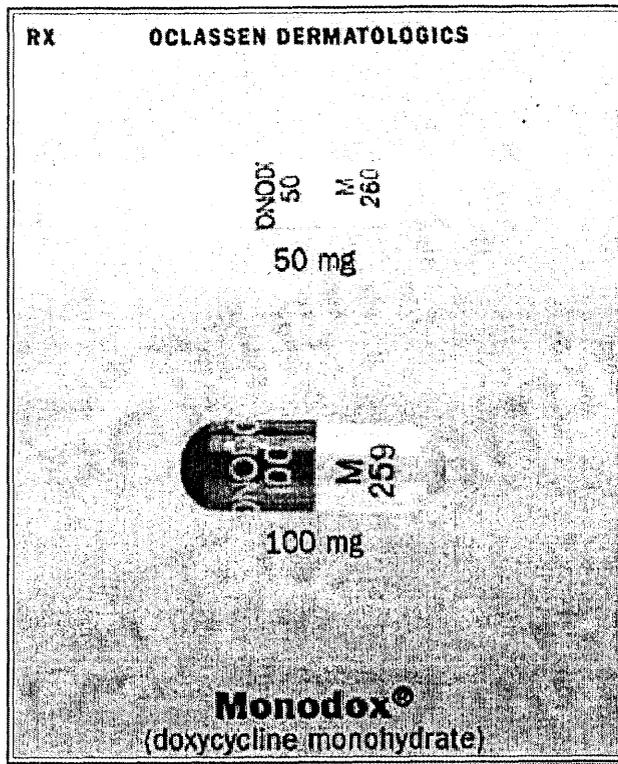
Revised April 28, 1998

02-18391/R7

PRODUCT PHOTO(S):

NOTE: These photos can be used only for identification by shape, color, and imprint. They do not depict actual *or relative* size.

The product samples shown here have been supplied by the manufacturer and reproduced in full color by PDR as a quick-reference identification aid. While every effort has been made to assure accurate reproduction, please remember that any visual identification should be considered preliminary. In cases of poisoning or suspected overdose, the drug's identity should be verified by chemical analysis.



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LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 5

Federal Register Notice

IV. Response to Comments

Because of the large number of items of correspondence we normally receive on Federal Register documents published for comment, we are not able to acknowledge or respond to them individually. We will consider all comments we receive, and, if we proceed with a subsequent document, we will respond to the major comments in the preamble to that document.

V. Regulatory Impact Statement

This notice does not require an impact analysis because it does not have an economic impact on small entities, small rural hospitals, or State, local, or tribal governments.

In accordance with the provisions of Executive Order 12866, this notice was not reviewed by the Office of Management and Budget.

(Catalog of Federal Domestic Assistance Program No. 93.778, Medical Assistance Program)

(Catalog of Federal Domestic Assistance Program No. 93.773, Medicare—Hospital Insurance; and Program No. 93.774, Medicare—Supplementary Medical Insurance Program)

Dated: September 7, 2001.

Thomas A Scully,
Administrator, Centers for Medicare & Medicaid Services.

[FR Doc. 01-27700 Filed 11-1-01; 8:45 am]
BILLING CODE 4120-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

[Program Announcement No. ACYF-PA-HS-02-01A]

Discretionary Announcement of the Availability of Funds and Request for Applications for Select Service Areas of Early Head Start; Correction

AGENCY: Administration for Children, Youth and Families, ACF, DHHS.

ACTION: Correction.

SUMMARY: This document contains a correction to the Notice that was published in the Federal Register on September 20, 2001.

On page 48475, Appendix A, Part II, in the State of Missouri, in the County of St. Charles, in the FY 2002 funding level column, delete "1,470,549" and add "1,497,549".

On page 48476, Appendix A, Part II, in the State of New York, in the County of Bronx, in the FY 2002 funding level column, delete "1,334,471" and add "1,322,291". In the State of New York,

in the County of Cattaraugus, in the FY 2002 funding level column, delete "468,962" and add "511,079". In the State of New York, in the County of Cattaraugus, in the FY 2002 funding level column, delete "450,808" and add "568,205". In the State of New York, in the County of Chenango, in the FY 2002 funding level column, delete "468,962" and add "511,079". In the State of New York, in the County of Monroe, in the FY 2002 funding level column, delete "1,995,614" and add "2,173,928". In the State of New York, in the County of Rensselaer, in the FY 2002 funding level column, delete "670,221" and add "732,234". In the State of New York, in the County of Steuben, in the FY 2002 funding level column, delete "329,700" and add "349,700". In the State of New York, in the County of Westchester, in the FY 2002 funding level column, delete "941,224" and add "1,033,799". In the State of New York, in the County of Erie, in the FY 2002 funding level column, delete "1,277,058" and add "1,381,901". In the State of New York, in the County of Schenectady, in the FY 2002 funding level column, delete "1,057,663" and add "743,672".

FOR FURTHER INFORMATION CONTACT: The ACYF Operations Center at 1-800-351-2293 or send an e-mail to ehs@lcnnet.com. You can also contact Sherri Ash, Early Head Start, Head Start Bureau at (202) 205-8562.

Dated: October 29, 2001.

James A. Harrell,
Acting Commissioner, Administration on Children, Youth and Families.

[FR Doc. 01-27810 Filed 11-1-01; 8:45 am]
BILLING CODE 4184-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N-0336]

Schering Corp. et al.; Withdrawal of Approval of 51 New Drug Applications and 25 Abbreviated New Drug Applications; Correction

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting a notice that appeared in the Federal Register of August 16, 2001 (66 FR 43017). The document announced the withdrawal of approval of 51 new drug applications (NDAs) and 25 abbreviated new drug applications (ANDAs). The document inadvertently withdrew

approval of NDA 17-255 for DTPA (chelate) Multidose (kit for the preparation of Tc-99m pentetate injection) held by Nycomed Amersham Imaging, 101 Carnegie Center, Princeton, NJ 08540. FDA confirms that approval of NDA 17-255 is still in effect.

EFFECTIVE DATE: August 16, 2001.

FOR FURTHER INFORMATION CONTACT: Florine P. Purdie, Center for Drug Evaluation and Research (HFD-7), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-2041.

In FR Doc. 01-20605 appearing on page 43017 in the Federal Register of Thursday, August 16, 2001, the following correction is made: On page 43018, in the table, the entry for NDA 17-255 is removed.

Dated: October 11, 2001.

Janet Woodcock,
Director, Center for Drug Evaluation and Research.

[FR Doc. 01-27520 Filed 11-01-01; 8:45 am]
BILLING CODE 4180-01-8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 01N-0494]

Prescription Drug Products; Doxycycline and Penicillin G Procaine Administration for Inhalational Anthrax (Post-Exposure)

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is clarifying that the currently approved indications for doxycycline and penicillin G procaine drug products include use in cases of inhalational exposure to *Bacillus anthracis* (the bacterium that causes anthrax). We also are providing dosing regimens that we have determined are appropriate for these products for this use. We encourage the submission of supplemental new drug applications (labeling supplements) to add the dosage information to the labeling of currently marketed drug products.

ADDRESSES: Submit labeling supplements to the Center for Drug Evaluation and Research, Food and Drug Administration, Central Document Room, 12229 Wilkins Ave., Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dianne Murphy, Center for Drug Evaluation and Research (HFD-950),

55680

Federal Register / Vol. 66, No. 213 / Friday, November 2, 2001 / Notices

Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2350.

SUPPLEMENTARY INFORMATION:

I. Anthrax

Anthrax is caused by the spore-forming bacterium *Bacillus anthracis*. There are three types of anthrax infection in humans: Cutaneous, gastrointestinal, and inhalational.

Until recently, most human experience with anthrax was associated with exposure to infected animals or animal products. Anthrax is reported annually among livestock. In areas where these animal cases occur, most human cases are the cutaneous form. Such cases occur among workers who have handled infected hooved animals or products from these animals. Gastrointestinal anthrax has been reported following the ingestion of undercooked or raw meat from infected animals. Inhalational anthrax, resulting from inhalation of aerosolized spores, was associated with industrial processing of infected wool, hair, or hides in the United States in the past. Before October 2001, no case of inhalational anthrax had been reported in the United States since 1978. In 1979, at least 64 people died in Sverdlovsk (currently Ekaterinburg), Russia, of inhalational anthrax after *Bacillus anthracis* spores were accidentally released from a Soviet military laboratory.

Administration of certain antimicrobial agents may prevent or reduce the incidence of disease following inhalational exposure to *Bacillus anthracis*.

II. Approved Drug Products

Drug products containing doxycycline, doxycycline calcium, doxycycline hyclate,¹ and penicillin G procaine are currently approved with indications for anthrax.² The approved labeling for the doxycycline products states that the drugs are indicated in infections caused by *Bacillus anthracis*. The approved labeling for penicillin G procaine drug products states that the drugs are indicated for anthrax.

¹ Doxycycline hyclate tablets, equivalent to 20 milligrams (mg) base, and doxycycline hyclate 10 percent for controlled release in subgingival application are not subjects of this notice because they have periodontal indications and do not have indications for anthrax or infections caused by *Bacillus anthracis*.

² Other drug products are currently approved with indications for anthrax or infections caused by *Bacillus anthracis*, i.e., minocycline, tetracycline, oxytetracycline, demeclocycline, and penicillin G potassium. We have not completed a review on these other drugs. We will not discuss these other drugs further in this notice.

Presently, the labeling for these drug products does not specify a dosing regimen for inhalational exposure to *Bacillus anthracis*. The indication sections of approved labeling for these drug products does not specify cutaneous, gastrointestinal, or inhalational anthrax. We have determined that the language in the labeling of drug products containing doxycycline, doxycycline calcium, doxycycline hyclate, and penicillin G procaine is intended to, and does, cover all forms of anthrax, including inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

On August 30, 2000, we approved supplements to provide an indication for inhalational anthrax (post-exposure) for ciprofloxacin hydrochloride tablets and ciprofloxacin intravenous (IV) solution, IV in 5 percent dextrose, IV in 0.9 percent saline, and oral suspension. The approved labeling for these ciprofloxacin products provides for a 60-day dosing regimen. Because ciprofloxacin drug products are already specifically indicated for inhalational anthrax (post-exposure) and their approved labeling provides a regimen for inhalational anthrax (post-exposure), we do not discuss ciprofloxacin any further in this notice. It is relevant, however, that the rhesus monkey study supporting the approval of ciprofloxacin for inhalational anthrax also included separate doxycycline and penicillin G procaine treatment arms. Each of these arms showed a survival advantage over placebo.³ No other antimicrobial drugs were tested in this study.

III. Doxycycline Drug Products

We have determined that 100 mg of doxycycline, taken orally twice daily for 60 days, is an appropriate dosing regimen for administration to adults who have inhalational exposure to *Bacillus anthracis*. The corresponding oral dosing regimen for children under 100 pounds (lb) is 1 mg per (1) lb of body weight (2.2 mg/kilogram (kg)), given twice daily for 60 days.

We have determined that IV doxycycline can be administered to adults in a 100 mg dose twice daily for inhalational anthrax (post-exposure). The corresponding IV dosing regimen for children under 100 lb is 1 mg /lb of body weight (2.2 mg/kg), twice daily. Intravenous therapy is indicated only when oral therapy is not indicated.

³ Friedlander, A. M. et al., "Postexposure Prophylaxis Against Experimental Inhalation Anthrax," *Journal of Infectious Diseases*, 167:1230-1243, 1993.

Intravenous therapy should not be given over a prolonged period of time. Patients should be switched to oral doxycycline, or another antimicrobial drug product, as soon as possible, to complete a 60-day course of therapy.

A. Safety

Doxycycline drug products have been used for over 30 years, and the literature on the products is voluminous. We have reviewed the literature dealing with the long-term administration of doxycycline for treatment of diseases other than anthrax. Several articles report the results of studies involving the administration of doxycycline in amounts comparable to the doses recommended in this notice. They also involve administration of doxycycline for 60 days and periods approaching and exceeding 60 days. We have also reviewed data from our Adverse Event Reporting System (AERS). Analysis of these articles and data indicates no pattern of unlabeled adverse events has been associated with the long-term use of doxycycline.

Doxycycline and other members of the tetracycline class of antibiotics are not generally indicated for the treatment of any patients under the age of 8 years. Tetracyclines are known to be associated with teeth discoloration and enamel hypoplasia in children and delays in bone development in premature infants after prolonged use. We have balanced the nature of the effect on teeth and the fact that this delay in bone development is apparently reversible against the lethality of inhalational anthrax, and concluded that doxycycline drug products can be labeled with a pediatric dosing regimen for inhalational anthrax (post-exposure).

We are not recommending that IV doxycycline be administered for prolonged periods because of the possibility of thrombophlebitis and other complications of IV therapy. Thrombophlebitis as a possible adverse reaction is already described in the approved labeling for IV doxycycline drug products. Patients administered IV doxycycline for inhalational anthrax (post-exposure) should be switched to oral doxycycline or another antimicrobial drug product as soon as possible to complete a 60-day course of therapy.

B. Effectiveness

We have reviewed minimal inhibitory concentration (MIC) data for the tetracycline class and *Bacillus anthracis*, pharmacokinetic data, data from the Sverdlovsk incident, and the outcome data from a study of

inhalational exposure to *Bacillus anthracis* in rhesus monkeys.⁴ We have concluded that 100 mg of doxycycline, administered twice a day for 60 days, is an effective dosing regimen for adults who have inhalational exposure to *Bacillus anthracis*. The corresponding dosing regimen for children under 100 lb of 1 mg/lb of body weight (2.2 mg/kg), given twice daily for 60 days, is also effective.

C. Labeling for Oral Doxycycline

We encourage the submission of labeling supplements for orally administered doxycycline, doxycycline calcium, and doxycycline hyclate drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to use in children, and other information described below. The following specific changes to the current approved labeling are recommended:

- **Indications and Usage.** The indication for anthrax should be revised from "Anthrax due to *Bacillus anthracis*" to "Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure); to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*." This indication should be removed from the paragraph of the "Indications and Usage" section that begins "When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of the following infections;" and inserted at the end of the preceding paragraph that begins "Doxycycline is indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug:"

- **Warnings.** The last sentence in the first paragraph of the "Warnings" section should be revised to read as follows: "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."

- **Dosage and Administration.** The following text should be inserted as the last item of the "Dosage and Administration" section:

"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."

D. Labeling for IV Doxycycline

We encourage the submission of labeling supplements for doxycycline hyclate injectable drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to use in children and prolonged use, and other information described below. We recommend that labeling supplements for doxycycline hyclate injectable drug products include the following specific changes:

- **Indications.** The indication for anthrax should be revised from "*Bacillus anthracis*" to "Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure); to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*." This indication should be removed from the paragraph of the "Indications" section that begins "When penicillin is contraindicated, doxycycline is an alternative drug in the treatment of infections due to;" and inserted at the end of the preceding paragraph that begins "Doxycycline is indicated for the treatment of infections caused by the following gram-positive microorganisms when bacteriologic testing indicates appropriate susceptibility to the drug."

- **Warnings.** The last sentence in the first paragraph of the "Warnings" section should be revised to read as follows: "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."

- **Dosage and Administration.** The following paragraph should be inserted in the "Dosage and Administration" section after the paragraph describing the treatment for syphilis:

"In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days."

The following paragraph should be inserted in the "Dosage and Administration" section after the paragraph describing the dosages for children above 8 years of age:

"In the treatment of inhalational anthrax (post-exposure) the recommended dose is 1 mg/lb (2.2 mg/kg) of body weight, twice a day in children weighing less than 100 lb (45 kg). Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days."

IV. Penicillin G Procaine Drug Products

We have determined that 1,200,000 units of penicillin G procaine, administered every 12 hours, is an appropriate dosing regimen for adults who have inhalational exposure to *Bacillus anthracis*. The corresponding dosing regimen for children is 25,000 units/kg of body weight (maximum 1,200,000 units) every 12 hours.

A. Safety

Penicillin drug products have been used for over 50 years. The amount of literature on penicillin is correspondingly large. We have reviewed published literature on the safety of penicillin G procaine. We have also reviewed data from AERS. Analysis of these articles and data indicates that no pattern of unexpected adverse events is associated with the use of penicillin G procaine as described in the recommended dosing regimen. All adverse events that we have identified are described in the approved labeling. We note that there may be an increased risk of neutropenia and an increased incidence of serum sickness-like reactions associated with use of penicillin for more than 2 weeks. Because prescribing health care professionals should take those factors into consideration when continuing administration of penicillin G procaine for longer than 2 weeks for inhalational anthrax (post-exposure), we are suggesting that the labeling for the drug products reflect these concerns about neutropenia and serum sickness-like reactions.

B. Effectiveness

We have reviewed MIC data for penicillin G and *Bacillus anthracis*, pharmacokinetic data, data from the Sverdlovsk incident, clinical data regarding the use of penicillins in treatment of primarily cutaneous anthrax, and the outcome data from a study of inhalational exposure to *Bacillus anthracis* in rhesus monkeys.⁵ We have concluded that the recommended dosing regimens are effective for adults and children who

⁴ Friedlander.

⁵ Friedlander.

have inhalational exposure to *Bacillus anthracis*.

C. Labeling

We encourage the submission of labeling supplements for penicillin G procaine injectable drug products. The revised labeling should contain a specific indication for inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to prolonged use and use in children, and other information described below. The following specific changes to the current approved labeling are recommended:

- **Indications.** In the "Indications" section, the indication for anthrax should be revised from "Anthrax" to "Anthrax due to *Bacillus anthracis*, including inhalational anthrax (post-exposure); to reduce the incidence or progression of the disease following exposure to aerosolized *Bacillus anthracis*."

- **Precautions.** In the "Precautions" section, at the end of the paragraph that begins "In prolonged therapy with penicillin, and particularly with high-dosage schedules, periodic evaluation of the renal and hematopoietic systems is recommended," the following text should be added: "In such situations, use of penicillin for more than 2 weeks may be associated with an increased risk of neutropenia and an increased incidence of serum sickness-like reactions."

- **Dosage and Administration.** In the "Dosage and Administration" section, immediately following "Anthrax—cutaneous: 600,000 to 1,000,000 units/day," the following text should be inserted:

"Anthrax—inhalational (post-exposure): 1,200,000 units every 12 hours in adults, 25,000 units per kilogram of body weight (maximum 1,200,000 unit) every 12 hours in children. The available safety data for penicillin G procaine at this dose would best support a duration of therapy of 2 weeks or less. Treatment for inhalational anthrax (post-exposure) must be continued for a total of 80 days. Physicians must consider the risks and benefits of continuing administration of penicillin G procaine for more than 2 weeks or switching to an effective alternative treatment."

V. Conclusions

Drug products containing the following active ingredients are currently approved for administration in cases of inhalational anthrax:

- Doxycycline
- Doxycycline calcium
- Doxycycline hyclate
- Penicillin G procaine

We encourage the submission of labeling supplements for these drug

products. The revised labeling should specifically mention inhalational anthrax (post-exposure), the recommended dosing regimen, safety information relevant to prolonged exposure (60 days or longer), and other information described in this notice. The requirement for data to support these labeling changes may be met by citing the published literature we relied on in publishing this notice. A list of the published literature and reprints of the reports will be available for public inspection in the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. It is unnecessary to submit copies and reprints of the reports from the listed published literature. We invite applicants to submit any other pertinent studies and literature of which they are aware.

VI. Published Literature

The published literature we have relied on in making our recommendations will be placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. A list of this published literature will be on display in the Dockets Management Branch and on the Internet at www.fda.gov/cder/drug/infopage/penG_doxy/bibliolist.htm.

Dated: October 26, 2001.
 Bernard A. Schwetz,
 Acting Principal Deputy Commissioner.
 [FR Doc. 01-27493 Filed 10-29-01; 4:35 pm]
 BILLING CODE 4180-01-5

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the Advisory Committee to the Director, National Cancer Institute.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: Advisory Committee to the Director, National Cancer Institute.
Date: November 20, 2001.

Time: 11 am to 1 pm.

Agenda: The purpose of the meeting will be to discuss the Gynecologic Cancers Progress Review, Group Report.

Place: National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Building 31, Room 11A03, Bethesda, MD 20892 (Telephone Conference Call).

Contact Person: Chitra Mohla, Executive Secretary, Office of Scientific Opportunities, National Cancer Institute, National Institutes of Health, Bldg. 31, Rm. 11A03, Bethesda, MD 20892. (301) 496-1458.

This notice is being published less than 15 days prior to the meeting due to scheduling conflicts.

Any interested person may file written comments with the committee by forwarding the statement to the Contact Person listed on this notice. The statement should include the name, address, telephone number and when applicable, the business or professional affiliation of the interested person.

Information is also available on the Institute's/Center's homepage: deainfo.nci.nih.gov/advisory/joint/htm, where an agenda and any additional information for the meeting will be posted when available.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)

Dated: October 26, 2001.

LaVerne Y. Stringfield,
 Director, Office of Federal Advisory Committee Policy.
 [FR Doc. 01-27505 Filed 11-1-01; 8:45 am]
 BILLING CODE 4140-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Meeting

Pursuant to section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of a meeting of the National Cancer Institute Director's Consumer Liaison Group.

The meeting will be open to the public, with attendance limited to space available. Individuals who plan to attend and need special assistance, such as sign language interpretation or other reasonable accommodations, should notify the Contact Person listed below in advance of the meeting.

Name of Committee: National Cancer Institute Director's Consumer Liaison Group.
Date: November 8, 2001.
Time: 2 pm to 4 pm.

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