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WASHINGTON
NEW YORK
SAN FRANCISCO
BRUSSELS
PARIS

February 28, 2001

Dockets Management Branch
Food and Drug Administration (HFA-305)
Park Building, Room 1-23
5600 Fishers Lane
Rockville, MD 20857

SUITABILITY PETITION

The undersigned hereby submits this petition pursuant to 21CFR parts 10.20 and 10.30, as provided for in 21 CFR 314.93, and Section 505(j)(2)(c) of the Federal Food, Drug and Cosmetic Act to request the Commissioner of the Food and Drug Administration to declare that the drug product Doxycycline Monohydrate Capsules 75 mg is suitable for submission as an abbreviated new drug application (ANDA).

A. Action Requested

This petition is submitted for a change in dosage strength of Doxycycline Monohydrate Capsules to include a 75 mg strength. The listed drug products are Monodox® Capsules 50 mg and 100 mg manufactured by Oclassen Pharmaceuticals, Inc.. The proposed product would differ only in strength from Oclassen's marketed product. This difference in strength is permitted by 21 CFR 314.93 (b).

B. Statement of Grounds

In accordance with Section 505 (j)(2)(C) of the Food, Drug, and Cosmetic Act, a petition may be filed with the Agency seeking permission to file an Abbreviated New Drug Application for a new drug which differs from a "listed" drug in dosage strength. The Act stipulates that such a petition must be approved by the

Agency unless there is a finding that investigations are needed to demonstrate the safety and effectiveness of the proposed drug product.

The reference listed drug product, Oclassen's Monodox® Capsules 100mg, is identified in the Prescription Drug Product List of the 20th edition of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (refer to Attachment-1). We propose to develop Doxycycline Monohydrate Capsules in the 75 mg strength. We call to FDA's attention that a suspension is currently available and the reference listed drug product, Vibramycin®, is manufactured by Pfizer. Vibramycin® 25 mg/5 mL Powder for Reconstitution was approved under NDA 50-006 and Vibramycin® 50 mg/5 mL Oral Suspension was approved under NDA 50-480.

The 75 mg strength capsule would contain the same active ingredient in the same dosage form and would be used in the same route of administration (oral) as the reference listed product. The indicated patient population would be the same as is currently used for the listed product.

The new strength, 75 mg capsule, would allow for better dosing for pediatric patients above eight years of age and who are 100 pounds or less. These pediatric patients are dosed at 2 mg/lb of body weight the first day in two divided doses and thereafter dosed at 1 mg/lb per day.

This proposed 75 mg strength will allow practitioners to prescribe a solid, oral dosage form for the pediatric patient that requires this strength due to weight. There are currently two suspension products available, both a 25 mg/5 mL and a 50 mg/5 mL strength, but these products do not afford the convenience of a capsule.

As this strength falls within the two strengths already available commercially and it is consistent with the reference listed drug product's approved labeling, especially the dosage and administration section, there are no safety issues for this new proposed strength.

The proposed product is expected to have the same therapeutic effect as the listed product, when administered for use as indicated in the product labeling. The labeling for the proposed product would be identical to that of the reference listed product with the exception that appropriate references to the proposed additional strength would be included. Additionally, any changes needed to denote the difference in formulation of excipients and manufacturer would also be made to the labeling. A package insert of Oclassen's Monodox® is attached along with the draft package insert of the proposed Doxycycline Monohydrate 75 mg capsule.

C. Pediatric Use Information

As the package insert of Oclassen's Monodox® contains adequate dosing and administration information for the pediatric population, no additional studies are required.

D. Environmental Impact

An environmental assessment report on the action requested in this petition is not required under 21 CFR 25.24.

E. 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.

F. Certification

The undersigned certifies that to the best of its knowledge, 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.

Sincerely,

Nicholas M. Fleischer, R.Ph., Ph.D.
Director of Biopharmaceutics
THE WEINBERG GROUP INC.

Enclosures

NMF/cb

cc: Gary Buehler
Acting Director, Office of Generic Drugs

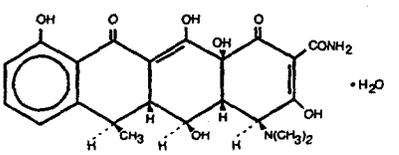
DOXYCYCLINE CAPSULES

Rx only

DESCRIPTION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline. The chemical designation of the yellow crystalline powder is 4-(Dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,-12,12a-pentahydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrate.

Structural formula:



$C_{22}H_{24}N_2O_8 \cdot H_2O$ 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.

Each capsule, for oral administration contains doxycycline monohydrate equivalent to 50mg, 75mg or 100mg of doxycycline.

Inactive ingredients will be furnished when the new strength is submitted as this is proprietary information. All inactive ingredients are GRAS and are used at appropriate levels.

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 (± 0.9 sd)
Time of Maximum Concentration	2.60 hr (± 1.10 sd)
Elimination Rate Constant	0.049 per hr (± 0.030 sd)
Half-Life	16.33 hr (± 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*)
Francisellea 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 pertenue
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 (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 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 *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.*

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

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

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF 8 YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH (YELLOW-GRAY-BROWN).

This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP 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 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.

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 Monohydrate Capsules 50mg, 75mg and 100mg

Package sizes to be determined.

Dispense in a tight, light-resistant container as defined in the USP/NF.

STORE AT CONTROLLED ROOM TEMPERATURE 15°- 30°C (59°- 86°F). [see USP]
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 PO_4, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO_4, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO_4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl and tetracycline HCl were goitrogenic in rats fed a low iodine diet. This goitrogenic effect was accompanied by high radioactive iodine uptake. Administration of minocycline also produced a large goiter with high radioiodine uptake in rats fed a relatively high iodine diet.

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

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

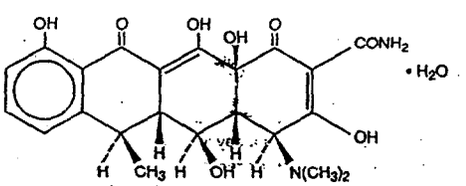
MONDOX® CAPSULES PACKAGE INSERT

Monodox®
Doxycycline Monohydrate Capsules

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:



$C_{22}H_{24}N_2O_8 \cdot H_2O$ 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.	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 (± 0.9 sd)
Time of Maximum Concentration	2.60 hr (± 1.10 sd)
Elimination Rate Constant	0.049 per hr (± 0.030 sd)
Half-Life	16.33 hr (± 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.

MONDOX® CAPSULES PACKAGE INSERT

GRAM-NEGATIVE BACTERIA:

Neisseria gonorrhoeae
Haemophilus ducreyi
Haemophilus influenzae
Yersinia pestis (formerly Pasteurella pestis)
Francisellea 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 pertenue
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.

MONDOX® CAPSULES PACKAGE INSERT

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) tetracycline	Interpretation 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 (mm) tetracycline	Diameter (mm) 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

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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:

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.

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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 nonsusceptible 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.

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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.

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
Bottles of 250 capsules .....NDC 55515-259-07

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PROTECT FROM LIGHT.

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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.

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Revised April 28, 1998
02-18391/R7

Attachment-1

Active Ingredient Search Results from "Rx" table for query on "doxycycline."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
065032	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE	EON
065032	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE	EON
065041	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE	HALSEY
065041	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE	HALSEY
050641	AB	Yes	DOXYCYCLINE	Capsule; Oral	EQ 100MG BASE	MONODOX	OCLASSEN
050641	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 50MG BASE	MONODOX	OCLASSEN
065053	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE	RANBAXY
065053	AB	No	DOXYCYCLINE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE	RANBAXY
050006	AB	Yes	DOXYCYCLINE	Powder For Reconstitution; Oral	EQ 25MG BASE/5ML	VIBRAMYCIN	PFIZER
061720	AB	No	DOXYCYCLINE	Powder For Reconstitution; Oral	EQ 25MG BASE/5ML	DOXYCHEL	RACHELLE
050480		Yes	DOXYCYCLINE CALCIUM	Suspension; Oral	EQ 50MG BASE/5ML	VIBRAMYCIN	PFIZER
050582	AB	Yes	DOXYCYCLINE HYCLATE	Capsule, Coated Pellets; Oral	EQ 100MG BASE	DORYX	FAULDING
063187	AB	No	DOXYCYCLINE HYCLATE	Capsule, Coated Pellets; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	SIDMAK LABS NJ
062653	AB	No	DOXYCYCLINE HYCLATE	Capsule, Coated Pellets; Oral	EQ 100MG BASE	DORYX	WARNER CHILCOTT
062142	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	CHELSEA LABS
062142	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	CHELSEA LABS
050744		Yes	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 20MG BASE	PERIOSTAT	COLLAGENEX
062031	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	DANBURY PHARMA
062031	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	DANBURY PHARMA
062418	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HALSEY

062418	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	HALSEY
061717	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HOUBA
061717	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	HOUBA
062676	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
062675	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
062337	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MYLAN
062337	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	MYLAN
050007	AB	Yes	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	VIBRAMYCIN	PFIZER
050007	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	VIBRAMYCIN	PFIZER
062497	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXY-LEMMON	TEVA
062497	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXY-LEMMON	TEVA
062396	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	WEST WARD
062396	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	WEST WARD
062500	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	ZENITH GOLDLINE
062500	AB	No	DOXYCYCLINE HYCLATE	Capsule; Oral	EQ 50MG BASE	DOXYCYCLINE HYCLATE	ZENITH GOLDLINE
062475	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	DOXY 100	AM PHARM PARTNERS
062475	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 200MG BASE/VIAL	DOXY 200	AM PHARM PARTNERS
062569	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	DOXYCYCLINE	BEDFORD
062569	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 200MG BASE/VIAL	DOXYCYCLINE	BEDFORD
062450	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	DOXYCYCLINE	ELKINS SINN
062450	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 200MG BASE/VIAL	DOXYCYCLINE	ELKINS SINN
062992	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	DOXYCYCLINE HYCLATE	LEDERLE
062992	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 200MG BASE/VIAL	DOXYCYCLINE HYCLATE	LEDERLE
050442	AP	Yes	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	VIBRAMYCIN	PFIZER

050442	AP	Yes	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 200MG BASE/VIAL	VIBRAMYCIN	PFIZER
061953	AP	No	DOXYCYCLINE HYCLATE	Injectable; Injection	EQ 100MG BASE/VIAL	DOXYCHEL HYCLATE	RACHELLE
050751		Yes	DOXYCYCLINE HYCLATE	Liquid, Extended Release; Periodontal	EQ 10% W/W	ATRIDOX	ATRIX
062421	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	DANBURY PHARMA
062391	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HALSEY
062269	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HOUBA
062269	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	HOUBA
062677	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MUTUAL PHARM
062432	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	MYLAN
050533	AB	Yes	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	VIBRA-TABS	PFIZER
062581	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXY-LEMMON	TEVA
062538	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	VINTAGE PHARMS
062505	AB	No	DOXYCYCLINE HYCLATE	Tablet; Oral	EQ 100MG BASE	DOXYCYCLINE HYCLATE	ZENITH GOLDLINE

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