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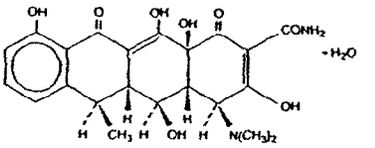
Part Number: 02-18391/R8 Package Insert for Trade Products

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	2.83	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.

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 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) tetracycline-	Zone Diameter (mm) doxycycline	Interpretation
≥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	Zone Diameter (mm) doxycycline
E. coli ATCC 25922	18-25	18-24
S. aureus ATCC 25923	19-28	20-29

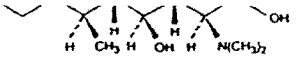
DILUTION TECHNIQUES

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	[illegible]



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GRAM-NEGATIVE BACTERIA:

Neisseria gonorrhoeae	*Francisella tularensis (formerly Pasteurella tularensis)*
Haemophilus ducreyi	*Vibrio cholerae (formerly Vibrio comma)*
Haemophilus influenzae	*Bartonella bacilliformis*
Yersinia pestis (formerly Pasteurella pestis)	*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	*Shigella species*
Klebsiella species	*Acinetobacter species (formerly Mima species and Herellea species)*
Enterobacter aerogenes	*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	*Enterococcus group (Streptococcus faecalis and Streptococcus faecium)*
Streptococcus pneumoniae	*Alpha-hemolytic Streptococci (viridans group)*

OTHER MICROORGANISMS:

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

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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 israeli*
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 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

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, [illegible] Approved Standard NCCLS Document [illegible]

[illegible] early in pregnancy. If any tetracycline is used during pregnancy or if the [illegible] 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.

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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

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

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.

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PHARMACEUTICALS, INC.
A Division of Watson Labs.
Inc., Corona, CA 91720
by Heritage Pharm. Inc.
Charlotte, NC 28206

Revised January 12, 1999

02-16391/R6

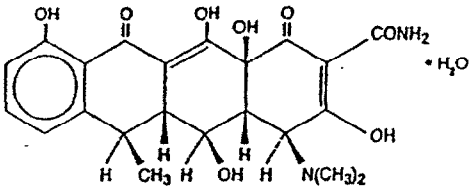
Monodox®

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. (mcg/mL)	1.02	2.26	2.87	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 pyo-*

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) tetracycline	Zone Diameter (mm) doxycycline	Interpretation
≥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	Zone Diameter 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

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	2.28	2.87	3.01	3.16	3.03	2.03	1.62	0.95	0.37	0.15

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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.

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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

	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

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Psittacosis (ornithosis) caused by *Chlamydia psittaci*.

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Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

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

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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*.

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.

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%.

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MONODOX® 100 mg is available in:

Bottles of 50 capsules .....NDC 55515-259-04
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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 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 Standard for Antimicrobial Disk Susceptibility Tests*, Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April 1990.

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 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 drug 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.)

Long-term use in prolonged periods, tetracyclines have been

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.

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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

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

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A Division of Watson Labs, Inc. Corona, CA 91720
by Vintage Pharm., Inc.
Charlotte, NC 28208

Revised January 14, 1998.

02-1357/R1

[illegible] 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.

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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.

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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.

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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.)

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[illegible] 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%.

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

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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.

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In acute intestinal amebiasis, cline 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.

NINGS

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

his adverse reaction is more common during long-term use f the drugs but has been observed following repeated short- rm courses. Enamel hypoplasia has also been reported. ETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE SED IN THIS AGE GROUP UNLESS OTHER DRUGS ARE OT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED.

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

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

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Pregnancy Category D. (See WARNINGS.)

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

g mothers: Tetracyclines are present in the milk of lac- women who are taking a drug in this class. Because of tential for serious adverse reactions in nursing infants e tetracyclines, a decision should be made whether to tinue nursing or discontinue the drug, taking into

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.

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REFERENCES

proteins of 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	2.28	2.87	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 (± 0.000 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

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*.

7

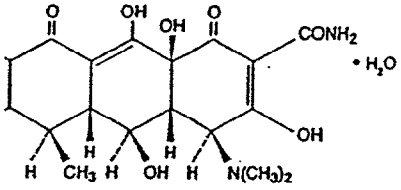
Monodox®

oxycycline Monohydrate Capsules

TION

line is a broad-spectrum antibiotic synthetically rom oxytetracycline. Monodox® 100 mg and 50 mg contain doxycycline monohydrate equivalent to 100 mg of doxycycline for oral administration. The chemnation of the light-yellow crystalline powder is alpha-5-oxytetracycline.

l formula:



$_{22}N_2O_8 \cdot H_2O$ M.W.= 462.46

e has a high degree of lipid solubility and a low affincium binding. It is highly stable in normal human xycycline will not degrade into an epianhydro form.

dients: colloidal silicon dioxide; hard gelatin capmesium stearate; microcrystalline cellulose; and arch glycolate.

PHARMACOLOGY

es are readily absorbed and are bound to plasma varying degrees. They are concentrated by the liver and excreted in the urine and feces at high cons in a biologically active form. Doxycycline is virtuetely absorbed after oral administration.

a 200 mg dose of doxycycline monohydrate, 24 volunteers averaged the following serum con-

s:

.0	1.5	2.0	3.0	4.0	8.0	12.0	24.0	48.0	72.0
2.26	2.67	3.01	3.16	3.03	2.03	1.62	0.95	0.37	0.15

Average Observed Values

Concentration	3.61 mcg/mL (± 0.9 sd)
laximum Concentration	2.60 hr (± 1.10 sd)
n Rate Constant	0.049 per hr (± 0.030 sd)
	18.33 hr (± 4.53 sd)

f doxycycline by the kidney is about 40%/72 hours ts with normal function (creatinine clearance about L. This percentage excretion may fall as low as 1-rs in individuals with severe renal insufficiency (creance below 10 mL/min). Studies have shown no difference in serum half-life of doxycycline (range s) in individuals with normal and severely impaired on.

is does not alter serum half-life.

gy: The tetracyclines are primarily bacteriostatic ought to exert their antimicrobial effect by the inhitein synthesis. The tetracyclines, including doxyve a similar antimicrobial spectrum of activity vide range of gram-positive and gram-negative Cross-resistance of these organisms to tetracynmon.

studies have demonstrated the susceptibility of of the following microorganisms, clinical efficaions other than those included in the INDICA USAGE section has not been documented.

ATIVE BACTERIA:

onorrhoeae

us ducreyi

us influenzae

stis (formerly *Pasteurella pestis*)

tularensis (formerly *Pasteurella tularensis*)

rae (formerly *Vibrio comma*)

bacilliformis

ecies

trains of the following groups of gram-nega-s have been shown to be resistant to tetra-nd susceptibility testing are recommended:

coli

pecies

r aerogenes

cies

er species (formerly *Mima* species and 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 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) tetracycline	Zone Diameter (mm) doxycycline	Interpretation
≥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	Zone Diameter 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

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Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

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Doxycycline is indicated for treatment of infections caused by the following gram-negative microorganisms, when bacterio-

tion 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

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 55515-260-08

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

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 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 Standard 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.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

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PHARMACEUTICALS, INC.
A Division of Watson Labs., Inc., Corona, CA 91720
by Vintage Pharm., Inc.
Charlotte, NC 28208

Revised January 14, 1998.

02-1357/R1

WATSON Laboratories, Inc.
A subsidiary of Watson Pharmaceuticals, Inc.

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Form FDA 2252

June 17, 2003

Janice M. Soreth, M.D., Director
Division of Anti-Infective Drug Products (HFD-520)
Office of Drug Evaluation IV
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Annual Report

RE: **NDA# 50-641**, Monodox® Capsules (Doxycycline Monohydrate) 50 mg and 100 mg
Annual Report

Dear Dr. Soreth:

In accordance with 21 CFR §314.81, enclosed please find the annual report for Monodox® Capsules. This report covers the period from **December 31, 2001 to December 30, 2002.**

If you have any questions concerning this submission, please contact me by telephone at (801) 588-6200 or by fax at (801) 588-6232.

Sincerely,

Wendy DeSpain

Wendy DeSpain, R.A.C.
Associate, Regulatory CMC
U.S. Proprietary Products

ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/588-6212