



[www.pdr.net](http://www.pdr.net)

---

PHYSICIANS'

---

DESK

---

REFERENCE®

---

Dr. Reddy's Laboratories, Ltd., et al.  
v.  
Galderma Laboratories, Inc.  
IPR2015-\_\_\_\_\_  
**Exhibit 1073**

RECEIVED FEB 15 2000



## PDR.net Content and Features:

### Physicians' Desk Reference®\*

More than 10,000 full text  
articles from Medical Economics  
Company publications including:  
*Medical Economics*®, *Patient Care*®  
and much more...

### Free MEDLINE/AIDSLINE/ CANCERLIT

### PDR.net for Consumers

### PDR's Getting Well Network™

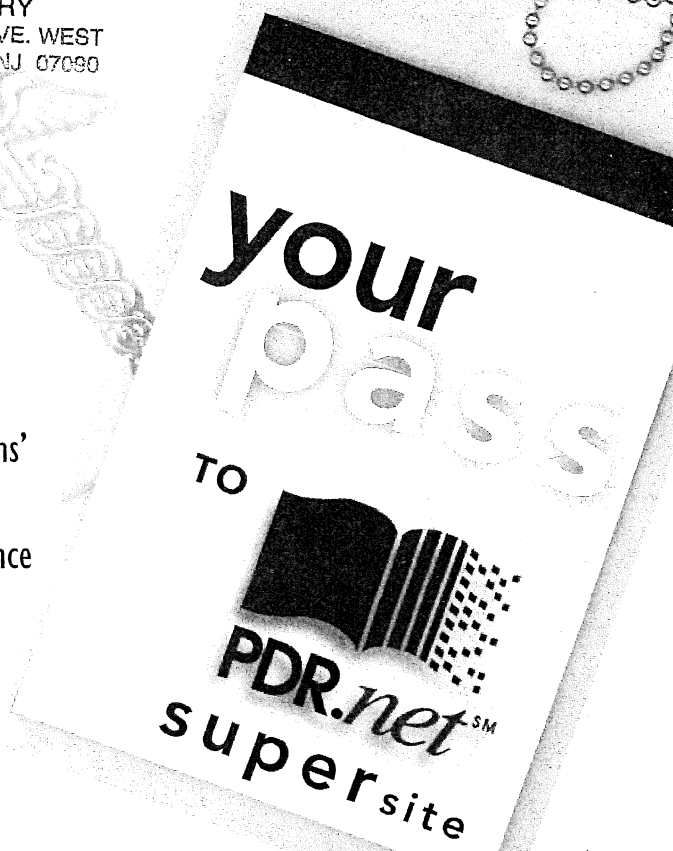
### Online CME/CE

Medical Economics Company

\*Access to the full, professional version of the PDR® on PDR.net is free for practicing U.S.-based physicians and physician assistants. Consumers can access drug information from the PDR Family Guide to Prescription Drugs® which is available for free through the PDR.net Supersite consumers' area.

LDL&M  
LIBRARY  
600 SOUTH AVE. WEST  
WESTFIELD, NJ 07090

The Official  
Home of  
the Physicians'  
Desk Reference  
on the Web

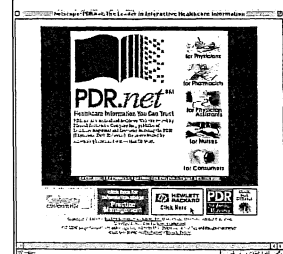


## healthcare information you can trust

When you need healthcare information visit the one site that offers the most – the PDR.net Supersite. Sponsored and maintained by one of the most respected names in health care, you can access the *Physicians' Desk Reference*® as well as thousands of professional healthcare articles from the pages of Medical Economics Company publications. Physicians also benefit from online CME, daily medical news from Reuters, and Stedman's Medical Dictionary. Consumers can take advantage of the *PDR Family Guide to Prescription Drugs*®, daily healthcare news from Reuters, as well as PDR's Getting Well Network – individual, disease-specific sites covering allergy, arthritis, breast cancer, depression, hypertension, osteoporosis, and ear infection/otitis media.

From the office, your home, or the road, the healthcare information you can trust is always within your reach.

[www.pdr.net](http://www.pdr.net)





# PHYSICIANS' DESK REFERENCE®

Senior Vice President, Directory Services: Paul Walsh

**Director of Product Management:** Mark A. Friedman

**Associate Product Manager:** Bill Shaughnessy

**Senior Business Manager:** Mark S. Ritchin

**Financial Analyst:** Wayne M. Soltis

**Director of Sales:** Dikran N. Barsamian

**National Sales Manager, Pharmaceutical Sales:** Anthony Sorce

**National Account Manager:** Don Bruccoleri

**Senior Account Manager:** Frank Karkowsky

**Account Managers:**

Marion Gray, RPh

Lawrence C. Keary

Jeffrey F. Pfohl

Suzanne E. Yarrow, RN

**Electronic Sales Account Manager:** Stephen M. Silverberg

**National Sales Manager, Medical Economics Trade Sales:** Bill Gaffney

**Director of Direct Marketing:** Michael Bennett

**List and Production Manager:** Lorraine M. Loening

**Senior Marketing Analyst:** Dina A. Maeder

**Director, New Business Development and Professional Support Services:** Mukesh Mehta, RPh

**Manager, Drug Information Services:** Thomas Fleming, RPh

**Drug Information Specialist:** Maria Deutsch, MS, RPh, CDE

**Editor, Directory Services:** David W. Sifton

**Senior Associate Editor:** Lori Murray

**Director of Production:** Carrie Williams

**Manager of Production:** Kimberly H. Vivas

**Senior Production Coordinator:** Amy B. Brooks

**Production Coordinators:** Gianna Caradonna, Maria Volpati

**Data Manager:** Jeffrey D. Schaefer

**Senior Format Editor:** Gregory J. Westley

**Index Editors:** Johanna M. Mazur, Robert N. Woerner

**Art Associate:** Joan K. Akerlind

**Senior Digital Imaging Coordinator:** Shawn W. Cahill

**Digital Imaging Coordinator:** Frank J. McElroy, III

**Electronic Publishing Designer:** Livio Udina

**Fulfillment Manager:** Stephanie DeNardi



Copyright © 2000 and published by Medical Economics Company, Inc. at Montvale, NJ 07645-1742. All rights reserved. None of the content of this publication may be reproduced, stored in a retrieval system, resold, redistributed, or transmitted in any form or by any means (electronic, mechanical, photocopying, recording, or otherwise) without the prior written permission of the publisher. PHYSICIANS' DESK REFERENCE®, PDR®, PDR For Ophthalmology®, Pocket PDR®, and The PDR® Family Guide to Prescription Drugs® are registered trademarks used herein under license. PDR For Nonprescription Drugs and Dietary Supplements™, PDR Companion Guide™, PDR® for Herbal Medicines™, PDR® Medical Dictionary™, PDR® Nurse's Drug Handbook™, PDR® Nurse's Dictionary™, The PDR® Family Guide Encyclopedia of Medical Care™, The PDR® Family Guide to Natural Medicines and Healing Therapies™, The PDR® Family Guide to Common Ailments™, The PDR® Family Guide to Over-the-Counter Drugs™, and PDR® Electronic Library™ are trademarks used herein under license.

**Officers of Medical Economics Company:** President and Chief Executive Officer: Curtis B. Allen; Vice President, New Media: L. Suzanne BeDell; Vice President, Corporate Human Resources: Pamela M. Bilash; Vice President and Chief Information Officer: Steven M. Bressler; Chief Financial Officer: Christopher Caridi; Vice President and Controller: Barry Gray; Vice President, New Business Planning: Linda G. Hope; Vice President, Business Integration: David A. Pitler; Vice President, Finance: Donna Santaripa; Senior Vice President, Directory Services: Paul Walsh; Senior Vice President, Operations: John R. Ware; Senior Vice President, Internet Strategies: Raymond Zoeller



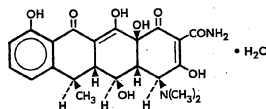
Printed on recycled paper

ISBN: 1-56363-330-2

# **MONODOX®** DOXYCYCLINE MONOHYDRATE CAPSULES [mon 'o-dox]

## 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:



$C_{22}H_{33}N_5O_8 \cdot H_2O$

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 epianhydride 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:  
[See table below]

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

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

Hemodialysis does not alter serum half-life.

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

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

### GRAM-NEGATIVE BACTERIA:

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

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

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

### GRAM-POSITIVE BACTERIA:

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

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

### OTHER MICROORGANISMS:

- *Chlamydia psittaci*
- *Chlamydia trachomatis*
- *Ureaplasma urealyticum*
- *Borrelia recurrentis*
- *Treponema pallidum*
- *Treponema pertenue*
- *Clostridium* species
- *Fusobacterium fusiforme*
- *Actinomyces* species
- *Bacillus anthracis*
- *Propionibacterium acnes*
- *Entamoeba* species
- *Balanitidum 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<sup>1</sup> which has been recommended for use with disks to test susceptibility of organisms to doxycycline uses the 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk. Interpretation involves the correlation of the diameter obtained in the disk test with the minimum inhibitory concentration (MIC) for tetracycline or doxycycline, respectively.

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

Zone Diameter (mm)		Interpretation
tetracycline	doxycycline	
$\geq 19$	$\geq 16$	Susceptible
15-18	13-15	Intermediate
$\leq 14$	$\leq 12$	Resistant

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

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

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

### Dilution Techniques:

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

MIC (mcg/mL)	Interpretation
$\leq 4$	Susceptible
8	Intermediate
$\geq 16$	Resistant

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

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

## INDICATIONS AND USAGE

Doxycycline is indicated for the treatment of the following infections:

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

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) caused by *Chlamydia psittaci*. Trachoma caused by *Chlamydia trachomatis*, although the infectious agent is not always eliminated as judged by immunofluorescence.

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

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Relapsing fever due to *Borrelia recurrentis*.

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

Chancroid caused by *Haemophilus ducreyi*. Plague due to *Yersinia pestis* (formerly *Pasteurella pestis*). Tularemia due to *Francisella tularensis* (formerly *Pasteurella tularensis*).

Cholera caused by *Vibrio cholerae* (formerly *Vibrio comma*). Campylobacter fetus infections caused by *Campylobacter fetus* (formerly *Vibrio fetus*).

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

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

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

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

*Escherichia coli*

*Enterobacter aerogenes* (formerly *Aerobacter aerogenes*)

*Shigella* species

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

Respiratory tract infections caused by *Haemophilus influenzae*.

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

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

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

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

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

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*. Syphilis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

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

In severe acne, doxycycline may be useful adjunctive therapy.

## CONTRAINDICATIONS

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 premature 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.

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 performed in conjunction indicated.

**Laboratory tests:** In venereal syphilis is suspected, a dark-field examination before treatment is started monthly for at least five months.

In long-term therapy, periodic systems, including hematology studies should be performed.

**Drug interactions:** Because tetracyclines depress plasma prothrombin levels, patients receiving anticoagulant therapy may require adjustment of dosage.

Since bacteriostatic drugs may delay action of penicillin, it is recommended that tetracyclines be given in conjunction with penicillin preparations.

Barbiturates, carbamazepine, and other anticonvulsants may alter the half-life of doxycycline.

The concurrent use of tetracyclines has been reported to result in fat necrosis of the breast.

Concurrent use of tetracyclines with oral contraceptives may be less effective.

**Drug/laboratory test interactions:** Tetracyclines may interfere with the fluorescence test for urinary catecholamine levels.

**Carcinogenesis, mutagenesis, and teratogenicity:** Studies in animals to evaluate the carcinogenicity of doxycycline have not been conducted, but there has been evidence of oncogenicity with related antibiotics, oxytetracycline, and minocycline.

Although mutagenicity studies have been conducted, positive results have been reported for oxytetracycline. Doxycycline levels as high as 250 mg/kg have been reported in the fetuses of female rats.

**Pregnancy:** Pregnancy Category C. The results of animal reproduction studies are inconclusive.

**Labor and Delivery:** The results of animal reproduction studies are inconclusive.

**Nursing mothers:** Tetracyclines are excreted in breast milk. Lactating women who are taking tetracyclines should be advised of the potential for serious effects on the infant.

Infants from the breast should be discontinued if the mother is taking tetracyclines.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

See WARNINGS section for information on the potential for serious effects on the infant.

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

Information will be superseded by supplements and subsequent editions



ed for the treatment of infections am-negative microorganisms: *nophilus ducreyi*, *stis* (formerly *Pasteurella pestis*), *ella tularensis* (formerly *Pasteu-*

*holerae* (formerly *Vibrio comma*), tions caused by *Campylobacter fe-*

*lla* species (in conjunction with

*nella bacilliformis*, ed by *Calymmatobacterium gran-*

the following groups of microor- to be resistant to doxycycline, cul- ting are recommended.

or treatment of infections caused ative microorganisms, when bac- appropriate susceptibility to the

rmerly *Aerobacter aerogenes*)

erly *Mima* species and *Herellea*

ms caused by *Haemophilus in-*

ary tract infections caused by

or treatment of infections caused tie microorganisms when bacte- appropriate susceptibility to the

ns caused by *Streptococcus pneu-* *cus pneumoniae*).

ections caused by *Staphylococcus* : the drug of choice in the treat- *thococcal* infections.

adicated, doxycycline is an alter- nt of the following infections: caused by *Neisseria gonorrhoeae*, *ma pallidum*.

*1 pertussis*, *monocytogenes*, *thracis*.

by *Fusobacterium fusiforme*, *ctinomyces israelii*, *ridium* species.

sis, doxycycline may be a useful

e may be useful adjunctive ther-

d in persons who have shown hy- : tetracyclines.

' THE TETRACYCLINE CLASS

LOPMENT (LAST HALF OF

AND CHILDHOOD TO THE

CAUSE PERMANENT DISCOL-

H (YELLOW-GRAY-BROWN).

re common during long-term use

beerved following repeated short-

plasia has also been reported.

, THEREFORE, SHOULD NOT

BE GROUP UNLESS OTHER

Y TO BE EFFECTIVE OR ARE

ble calcium complex in any bone

in the fibula growth rate has

ures given oral tetracycline in

hours. This reaction was shown

drug was discontinued.

indicate that tetracyclines cross

fetal tissues, and can have toxic

sis (often related to retardation

Evidence of embryo toxicity has

ed early in pregnancy. If any tes-

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

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

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

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

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

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

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

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

Concurrent use of tetracycline may render oral contraceptives less effective.

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

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

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

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

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

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

**ADVERSE REACTIONS**

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

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

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

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

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

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

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

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

**OVERDOSAGE**

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

**DOSAGE AND ADMINISTRATION**

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

**Adults:** The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every 6 hours) followed by a maintenance dose of

100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours. In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

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

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

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

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

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

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

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

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

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

**HOW SUPPLIED**

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

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

**STORE AT CONTROLLED ROOM TEMPERATURE 15°-30°C (59°-86°F). PROTECT FROM LIGHT.**

**ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY**

Hyperpigmentation of the thyroid has been produced by members of the tetracycline class in the following species: in rats by oxytetracycline, doxycycline, tetracycline PO<sub>4</sub>, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO<sub>4</sub>, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO<sub>4</sub>, 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 radiiodine uptake in rats fed a relatively high iodine diet.

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

**REFERENCES:**

1. National Committee for Clinical Laboratory Standards, *Performance Standards for Antimicrobial Disk Susceptibility Tests*, Fourth Edition. Approved Standard NCCLS Document M2-A4, Vol. 10, No. 7 NCCLS, Villanova, PA, April 1990.

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

**Rx Only**  
Manufactured for  
**OCLASSEN**  
**PHARMACEUTICALS**

A Division of Watson Labs. Inc., Corona, CA 91720  
by Vintage Pharmaceuticals, Inc., Charlotte, N.C.

Revised April 28, 1998 02-18391/R7  
*Shown in Product Identification Guide, page 327*

## OHMEDA

Pharmaceutical Products Division Inc.  
(see BAXTER PHARMACEUTICAL PRODUCTS INC.)

## Organon Inc.

375 MT. PLEASANT AVE.  
WEST ORANGE, NJ 07052

Direct Inquiries to:  
(973) 325-4500

Currently available products are listed below. For complete product line information and price lists, direct inquiries to Organon Inc. Customer Service. For specific product information, contact Organon Inc. Medical Services Department.

**ARDUAN®**  
(pipecuronium bromide) for injection

### HOW SUPPLIED

10 mL vials/10 mg—boxes of 6 vials—NDC-0052-0446-36

**TICE® BCG, BCG Live**  
**BCG VACCINE USP**  
(for intravesical use)

Distributed by Organon Inc.  
(See page 2111 complete product information.)

**CALDEROL®**  
[kal-dah'rol]  
(calcifediol capsules, USP)

### HOW SUPPLIED

20 µg (white, soft elastic capsules) bottle of 60  
50 µg (orange, soft elastic capsules) bottle of 60  
*Shown in Product Identification Guide, page 327*

**CORTROSYN®**  
[cōr-trō-sin]  
(cosyntropin) for injection  
**FOR DIAGNOSTIC USE ONLY**

### DESCRIPTION

Cortrosyn® (cosyntropin) for injection is a sterile lyophilized powder in vials containing 0.25mg of Cortrosyn® and 10mg of mannitol to be reconstituted with 1mL sodium chloride for injection, USP as solvent. Administration is by intravenous or intramuscular injection. Cosyntropin is a 1-24 corticotropin, a synthetic subunit of ACTH. It is an open chain polypeptide containing, from the N terminus, the first 24 of the 39 amino acids of natural ACTH. The sequence of amino acids in the 1-24 compound is as follows:

Ser—Tyr—Ser—Met—Glu—His—Phe—Arg—Trp—Gly—Lys—  
1. 2 3 4 5 6 7 8 9 10 11

Pro—Val—Gly—Lys—Lys—Arg—Arg—Pro—Val—Lys—Val  
12 13 14 15 16 17 18 19 20 21 22

Tyr—Pro  
23 24

### CLINICAL PHARMACOLOGY

Cortrosyn® (cosyntropin) for injection exhibits the full corticosteroidogenic activity of natural ACTH. Various studies have shown that the biologic activity of ACTH resides in the N-terminal portion of the molecule and that the 1-20 amino acid residue is the minimal sequence retaining full activity. Partial or complete loss of activity is noted with progressive shortening of the chain beyond 20 amino acid residue. For example, the decrement from 20 to 19 results in a 70% loss of potency.

The pharmacologic profile of Cortrosyn® is similar to that of purified natural ACTH. It has been established that 0.25 mg of Cortrosyn® will stimulate the adrenal cortex maximally and to the same extent as 25 units of natural ACTH. This dose of Cortrosyn® will produce maximal secretion of 17-OH corticosteroids, 17-ketosteroids and/or 17-ketogenic steroids.

The extra-adrenal effects which natural ACTH and Cortrosyn® have in common include increased melanotropic activity, increased growth hormone secretion and an adipokinetic effect. These are considered to be without physiological or clinical significance.

Animal, human and synthetic ACTH (1-39) which all contain 39 amino acids exhibit similar immunologic activity.

*Continued on next page*

Consult 2000 PDR® supplements and future editions for revisions

## Viagra—Cont.

ritonavir's marked effects on a broad range of P450 substrates. VIAGRA had no effect on ritonavir pharmacokinetics (see **DOSAGE AND ADMINISTRATION**).

Although the interaction between other protease inhibitors and sildenafil has not been studied, their concomitant use is expected to increase sildenafil levels.

It can be expected that concomitant administration of CYP3A4 inducers, such as rifampin, will decrease plasma levels of sildenafil.

Single doses of antacid (magnesium hydroxide/aluminum hydroxide) did not affect the bioavailability of VIAGRA. Pharmacokinetic data from patients in clinical trials showed no effect on sildenafil pharmacokinetics of CYP2C9 inhibitors (such as tolbutamide, warfarin), CYP2D6 inhibitors (such as selective serotonin reuptake inhibitors, tricyclic antidepressants), thiazide and related diuretics, ACE inhibitors, and calcium channel blockers. The AUC of the active metabolite, N-desmethyl sildenafil, was increased 62% by loop and potassium-sparing diuretics and 102% by nonspecific beta-blockers. These effects on the metabolite are not expected to be of clinical consequence.

**Effects of VIAGRA on Other Drugs**

**In vitro studies:** Sildenafil is a weak inhibitor of the cytochrome P450 isoforms 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4 (IC<sub>50</sub> >150 µM). Given sildenafil peak plasma concentrations of approximately 1 µM after recommended doses, it is unlikely that VIAGRA will alter the clearance of substrates of these isoenzymes.

**In vivo studies:** When VIAGRA 100 mg oral was coadministered with amlodipine, 5 mg or 10 mg oral, to hypertensive patients, the mean additional reduction on supine blood pressure was 6 mmHg systolic and 7 mmHg diastolic. No significant interactions were shown with tolbutamide (250 mg) or warfarin (40 mg), both of which are metabolized by CYP2C9.

VIAGRA (50 mg) did not potentiate the increase in bleeding time caused by aspirin (150 mg).

VIAGRA (50 mg) did not potentiate the hypotensive effect of alcohol in healthy volunteers with mean maximum blood alcohol levels of 0.08%.

In a study of healthy male volunteers, sildenafil (100 mg) did not affect the steady state pharmacokinetics of the HIV protease inhibitors, saquinavir and zalcitabine, both of which are CYP3A4 substrates.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Sildenafil was not carcinogenic when administered to rats for 24 months at a dose resulting in total systemic drug exposure (AUCs) for unbound sildenafil and its major metabolite of 29- and 42-times, for male and female rats, respectively, the exposures observed in human males given the Maximum Recommended Human Dose (MRHD) of 100 mg. Sildenafil was not carcinogenic when administered to mice for 18-21 months at dosages up to the Maximum Tolerated Dose (MTD) of 10 mg/kg/day, approximately 0.6 times the MRHD on a mg/m<sup>2</sup> basis.

Sildenafil was negative in *in vitro* bacterial and Chinese hamster ovary cell assays to detect mutagenicity, and *in vitro* human lymphocytes and *in vivo* mouse micronucleus assays to detect clastogenicity.

There was no impairment of fertility in rats given sildenafil up to 60 mg/kg/day for 36 days to females and 102 days to males, a dose producing an AUC value of more than 25 times the human male AUC.

There was no effect on sperm motility or morphology after single 100 mg oral doses of VIAGRA in healthy volunteers.

**Pregnancy, Nursing Mothers and Pediatric Use**

VIAGRA is not indicated for use in newborns, children, or women.

**Pregnancy Category B.** No evidence of teratogenicity, embryotoxicity or fetotoxicity was observed in rats and rabbits which received up to 200 mg/kg/day during organogenesis. These doses represent, respectively, about 20 and 40 times the MRHD on a mg/m<sup>2</sup> basis in a 50 kg subject. In the rat pre- and postnatal development study, the no observed adverse effect dose was 30 mg/kg/day given for 36 days. In the nonpregnant rat the AUC at this dose was about 20 times human AUC. There are no adequate and well-controlled studies of sildenafil in pregnant women.

**Geriatric Use:** Healthy elderly volunteers (65 years or over) had a reduced clearance of sildenafil (see **CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations**). Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered (see **DOSAGE AND ADMINISTRATION**).

**ADVERSE REACTIONS****PRE-MARKETING EXPERIENCE:**

VIAGRA was administered to over 3700 patients (aged 19-87 years) during clinical trials worldwide. Over 550 patients were treated for longer than one year.

In placebo-controlled clinical studies, the discontinuation rate due to adverse events for VIAGRA (2.5%) was not sig-

nificantly different from placebo (2.3%). The adverse events were generally transient and mild to moderate in nature. In trials of all designs, adverse events reported by patients receiving VIAGRA were generally similar. In fixed-dose studies, the incidence of some adverse events increased with dose. The nature of the adverse events in flexible-dose studies, which more closely reflect the recommended dosage regimen, was similar to that for fixed-dose studies. When VIAGRA was taken as recommended (on an as-needed basis) in flexible-dose, placebo-controlled clinical trials, the following adverse events were reported:

**TABLE 2. ADVERSE EVENTS REPORTED BY ≥2% OF PATIENTS TREATED WITH VIAGRA AND MORE FREQUENT ON DRUG THAN PLACEBO IN PRN FLEXIBLE-DOSE PHASE II/III STUDIES**

Adverse Event	Percentage of Patients Reporting Event	
	VIAGRA N = 734	PLACEBO N = 725
Headache	16%	4%
Flushing	10%	1%
Dyspepsia	7%	2%
Nasal Congestion	4%	2%
Urinary Tract Infection	3%	0%
Abnormal Vision†	3%	0%
Diarrhea	3%	1%
Dizziness	2%	1%
Rash	2%	1%

† Abnormal Vision: Mild and transient, predominantly color tinge to vision, but also increased sensitivity to light or blurred vision. In these studies, only one patient discontinued due to abnormal vision.

Other adverse reactions occurred at a rate of >2%, but equally common on placebo: respiratory tract infection, back pain, flu syndrome, and arthralgia.

In fixed-dose studies, dyspepsia (17%) and abnormal vision (11%) were more common at 100 mg than at lower doses. At doses above the recommended dose range, adverse events were similar to those detailed above but generally were reported more frequently.

The following events occurred in <2% of patients in controlled clinical trials; a causal relationship to VIAGRA is uncertain. Reported events include those with a plausible relation to drug use; omitted are minor events and reports too imprecise to be meaningful:

**Body as a whole:** face edema, photosensitivity reaction, shock, asthenia, pain, chills, accidental fall, abdominal pain, allergic reaction, chest pain, accidental injury.

**Cardiovascular:** angina pectoris, AV block, migraine, syncope, tachycardia, palpitation, hypotension, postural hypotension, myocardial ischemia, cerebral thrombosis, cardiac arrest, heart failure, abnormal electrocardiogram, cardiomyopathy.

**Digestive:** vomiting, glossitis, colitis, dysphagia, gastritis, gastroenteritis, esophagitis, stomatitis, dry mouth, liver function tests abnormal, rectal hemorrhage, gingivitis.

**Hemic and Lymphatic:** anemia and leukopenia.

**Metabolic and Nutritional:** thirst, edema, gout, unstable diabetes, hyperglycemia, peripheral edema, hyperuricemia, hypoglycemic reaction, hypernatremia.

**Musculoskeletal:** arthritis, arthrosis, myalgia, tendon rupture, tenosynovitis, bone pain, myasthenia, myositis.

**Nervous:** ataxia, hypertension, neuralgia, neuropathy, paresthesia, tremor, vertigo, depression, insomnia, somnolence, abnormal dreams, reflexes decreased, hypesthesia.

**Respiratory:** asthma, dyspnea, laryngitis, pharyngitis, sinusitis, bronchitis, sputum increased, cough increased.

**Skin and Appendages:** urticaria, herpes simplex, pruritus, sweating, skin ulcer, contact dermatitis, exfoliative dermatitis.

**Special Senses:** mydriasis, conjunctivitis, photophobia, tinnitus, eye pain, deafness, ear pain, eye hemorrhage, catarract, dry eyes.

**Urogenital:** cystitis, nocturia, urinary frequency, breast enlargement, urinary incontinence, abnormal ejaculation, genital edema and anorgasmia.

**POST-MARKETING EXPERIENCE:****Cardiovascular**

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage, transient ischemic attack and hypertension, have been reported post-marketing in temporal association with the use of VIAGRA. Most, but not all, of these patients had preexisting cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of VIAGRA without sexual activity. Others were reported to have occurred hours to days after the use of VIAGRA and sexual activity. It is not possible to determine whether these events are related directly to VIAGRA, to sexual activity, to the patient's underlying cardio-

vascular disease, to a combination of these factors, or to other factors (see **WARNINGS** for further important cardiovascular information).

**Other events**

Other events reported post-marketing to have been observed in temporal association with VIAGRA and not listed in the pre-marketing adverse reactions section above include:

**Nervous:** seizure and anxiety.

**Urogenital:** prolonged erection, priapism (see **WARNINGS**) and hematuria.

**Ocular:** diplopia, temporary vision loss/decreased vision, ocular redness or bloodshot appearance, ocular burning, ocular swelling/pressure, increased intraocular pressure, retinal vascular disease or bleeding, vitreous detachment/traction and paramacular edema.

**OVERDOSAGE**

In studies with healthy volunteers of single doses up to 800 mg, adverse events were similar to those seen at lower doses but incidence rates were increased.

In cases of overdose, standard supportive measures should be adopted as required. Renal dialysis is not expected to accelerate clearance as sildenafil is highly bound to plasma proteins and it is not eliminated in the urine.

**DOSAGE AND ADMINISTRATION**

For most patients, the recommended dose is 50 mg taken, as needed, approximately 1 hour before sexual activity. However, VIAGRA may be taken anywhere from 4 hours to 0.5 hour before sexual activity. Based on effectiveness and toleration, the dose may be increased to a maximum recommended dose of 100 mg or decreased to 25 mg. The maximum recommended dosing frequency is once per day.

The following factors are associated with increased plasma levels of sildenafil: age >65 (40% increase in AUC), hepatic impairment (e.g., cirrhosis, 80%), severe renal impairment (creatinine clearance <30 mL/min, 100%), and concomitant use of potent cytochrome P450 3A4 inhibitors [ketoconazole, itraconazole, erythromycin (182%), saquinavir (210%)]. Since higher plasma levels may increase both the efficacy and incidence of adverse events, a starting dose of 25 mg should be considered in these patients.

Ritonavir greatly increased the systemic level of sildenafil in a study of healthy, non-HIV infected volunteers (11-fold increase in AUC, see **Drug Interactions**). Based on these pharmacokinetic data, it is recommended not to exceed a maximum single dose of 25 mg of VIAGRA in a 48 hour period.

VIAGRA was shown to potentiate the hypotensive effects of nitrates and its administration in patients who use nitric oxide donors or nitrates in any form is therefore contraindicated.

**HOW SUPPLIED**

VIAGRA® (sildenafil citrate) is supplied as blue, film-coated, rounded-diamond-shaped tablets containing sildenafil citrate equivalent to the nominally indicated amount of sildenafil as follows:

(See table below)

**Recommended Storage:** Store at controlled room temperature, 15° to 30°C (59° to 86°F)

**Rx only**

©1999 PFIZER INC

Distributed by

Pfizer Labs

Division of Pfizer Inc, NY, NY 10107

69-5485-00-5

Revised June 1999

Shown in Product Identification Guide, page 331

**VIBRAMYCIN® Calcium**

[vī-brā'mis-n]

doxycycline calcium

oral suspension

SYRUP

**VIBRAMYCIN® Hyclate**

[vī-brā'mis-n]

doxycycline hyclate

CAPSULES

**VIBRAMYCIN® Monohydrate**

[vī-brā'mis-n]

doxycycline monohydrate

for ORAL SUSPENSION

**VIBRA-TABS®**

[vī-brā'mis-n]

doxycycline hyclate

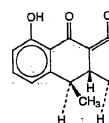
FILM COATED TABLETS

**DESCRIPTION**

Vibramycin is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Monohydrate (doxycycline monohydrate); Vibramycin Hyclate and Vibra-Tabs (doxycycline hydrochloride hemihydrate), and Vibramycin Calcium (doxycycline calcium) for oral administration.

[See chemical structure at top of next column]

The structural formula of doxycycline monohydrate is with a molecular formula of C<sub>22</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>·H<sub>2</sub>O and a molecular weight of 462.46. The chemical designation for doxycycline is 4-(Dimethylamino)-1, 4, 4a, 5, 5a, 6, 11, 12a-octahydro-3, 5, 10, 12, 12a-pentahydroxy-6-methyl-1, 11-dioxo-3-naphthacene-carboxamide monohydrate. The molecular



formula for doxycycline hemihydrate is (C<sub>22</sub>H<sub>24</sub>N<sub>2</sub>O<sub>7</sub>)·H<sub>2</sub>O. Molecular weight is 1025.89. It is a white powder. Doxycycline while doxycycline monohydrate.

Doxycycline has a high d affinity for calcium binding man serum. Doxycycline do form.

Inert ingredients in the s butylparaben; calcium chloride acid; magnesium ylene glycol; propylparal emulsion; sodium hydrox solution; water.

Inert ingredients in the s atin capsules (which may gredients); magnesium s sodium lauryl sulfate.

Inert ingredients for the s crocristalline cellulose; Red 28; simethicone em Inert ingredients for the s; hydroxypropyl met microcristalline cellulose sulfate; talc; titanium di

**CLINICAL PHARMAC**

Tetracyclines are readily proteins in varying deg liver in the bile, and exc concentrations and in a l

is virtually completely. Following a 200 mg dose peak serum levels of 2.6 decreasing to 1.45 mcg/ cycline by the kidney is

with normal function ( min.). This percentage e hours in individuals wit nine clearance below 10

significant difference i (range 18-22 hours) in fully impaired renal f Hemodialysis does not Results of animal studi the placenta and are fo

**Microbiology**

The tetracyclines are thought to exert their a of protein synthesis. T. cline, have a similar against a wide range o organisms. Cross-resist cines is common.

**Gram-Negative Bacteri**

*Neisseria gonorrhoeae*  
*Calymmatobacterium g*  
*Haemophilus ducreyi*  
*Haemophilus influenza*  
*Yersinia pestis* (formerl)  
*Francisella tularensis* (

*Vibrio cholera* (formerl)  
*Bartonella bacilliformis*  
*Brucella* species  
Because many strains i

ative microorganisms l tetracyclines, culture a mended.

*Escherichia coli*  
*Klebsiella* species  
*Enterobacter aerogenes*  
*Shigella* species  
*Acinetobacter* species (i species)

*Bacteroides* species  
**Gram-Positive Bacteria**  
Because many strains i

tive microorganisms h racycline, culture an mended. Up to 44 perc

enes and 74 percent c found to be resistant t cycline should not be i

the organism has been *Streptococcus pyogenes*  
*Streptococcus pneumor*  
*Enterococcus* group (S

*cus faecium*)  
Alpha-hemolytic strept Other Microorganisms  
*Rickettsia*  
*Chlamydia psittaci*  
*Chlamydia trachomati*

of these factors, or to  
urther important cardi-

ing to have been ob-  
VIAGRA and not listed  
ions section above in-

riapism (see **WARN.**

loss/decreased vision,  
ice, ocular burning, oc-  
raocular pressure, ret-  
rous detachment/trac-

of single doses up to  
to those seen at lower  
used.  
rative measures should  
s is not expected to ac-  
ghly below to plasma  
be urine.

dose is 50 mg taken, as  
sexual activity. How-  
re from 4 hours to 0.5  
effectiveness and tol-  
to a maximum recom-  
l to 25 mg. The maxi-  
is once per day.

with increased plasma  
ease in AUC, hepatic  
ere renal impairment  
10%), and concomitant  
hibitors (ketonazole,  
saquinavir (210%)).  
ease both the efficacy  
tardng dose of 25 mg  
s.

mic level of sildenafil  
ed volunteers (11-fold  
ons.) Based on these  
nded not to exceed a  
AGRA in a 48 hour pe-

ae hypotensive effects  
patients who use nitric  
form is therefore

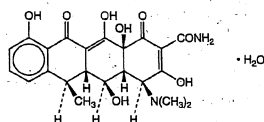
plied as blue, film-  
tablets containing  
nominally indicated

ntrolled room temper-

Revised June 1999  
Guide, page 331

R

iotic synthetically de-  
lible as Vibramycin  
ate); Vibramycin Hy-  
drochloride hemi-  
cain Calcium (doxy-  
colum)  
monohydrate is with  
 $H_2O$  and a molecular  
ation for doxycycline  
4, 6, 11, 12a-octahy-  
methyl-1, 11-dioxo-2-  
ate. The molecular



formula for doxycycline hydrochloride hemihydrate is  $(C_{22}H_{26}N_2O_7 \cdot HCl) \cdot C_2H_4O \cdot H_2O$  and the molecular weight is 1025.89. Doxycycline is a light-yellow crystalline powder. Doxycycline hyclate is soluble in water, while doxycycline monohydrate is very slightly soluble in water.

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 epianhydride form.

Inert ingredients in the syrup formulation are: apple flavor; butylparaben; calcium chloride; carmine; glycerin; hydrochloric acid; magnesium aluminum silicate; povidone; propylene glycol; propylparaben; raspberry flavor; simethicone emulsion; sodium hydroxide; sodium metabisulfite; sorbitol solution; water.

Inert ingredients in the capsule formulations are: hard gelatin capsules (which may contain Blue 1 and other inert ingredients); magnesium stearate; microcrystalline cellulose; sodium lauryl sulfate.

Inert ingredients for the oral suspension formulation are: carboxymethylcellulose sodium; Blue 1; methylparaben; microcrystalline cellulose; propylparaben; raspberry flavor; Red 28; simethicone emulsion; sucrose.

Inert ingredients for the tablet formulation are: ethylcellulose; hydroxypropyl methylcellulose; magnesium stearate; microcrystalline cellulose; propylene glycol; sodium lauryl sulfate; talc; titanium dioxide; Yellow 6 Lake.

#### CLINICAL PHARMACOLOGY

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

Hemodialysis does not alter serum half-life.

Results of animal studies indicate that tetracyclines cross the placenta and are found in fetal tissues.

#### 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.

#### Gram-Negative Bacteria

*Neisseria gonorrhoeae*  
*Calymmatobacterium granulomatis*  
*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 tetracycline, 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, tetracycline should not be used for streptococcal disease 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**  
*Rickettsia*  
*Chlamydia psittaci*  
*Chlamydia trachomatis*

*Mycoplasma pneumoniae*  
*Ureaplasma urealyticum*  
*Borrelia recurrentis*  
*Treponema pallidum*  
*Treponema pertenue*  
*Clostridium* species  
*Fusobacterium fusiforme*  
*Actinomyces* species  
*Bacillus anthracis*  
*Propionibacterium acnes*  
*Entamoeba* species  
*Balanitidum coli*  
*Plasmodium falciparum*

Doxycycline has been found to be active against the asexual erythrocytic forms of *Plasmodium falciparum* but not against the gametocytes of *P. falciparum*. The precise mechanism of action of the drug is not known.

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

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

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

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Intermediate" suggests that the organism would be susceptible if a high dosage is used or if the infection is confined to tissues and fluids in which high antimicrobial levels are attained. A report of "Resistant" indicates that achievable concentrations are unlikely to be inhibitory, and other therapy should be selected. Standardized procedures require the use of laboratory control organisms. The 30-mcg tetracycline-class disk or the 30-mcg doxycycline disk should give the following zone diameters:

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

**Dilution techniques:** Use a standardized dilution method<sup>2</sup> (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)
<i>E. coli</i> ATCC 25922	1.0-4.0
<i>S. aureus</i> ATCC 29213	0.25-1.0
<i>E. faecalis</i> ATCC 29212	8-32
<i>P. aeruginosa</i> ATCC 27853	8-32

#### INDICATIONS AND USAGE

##### Treatment:

Doxycycline is indicated for the treatment of the following infections:

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

Respiratory tract infections caused by *Mycoplasma pneumoniae*.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*.

Psittacosis (ornithosis) caused by *Chlamydia psittaci*.

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

Inclusion conjunctivitis caused by *Chlamydia trachomatis*.

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

Nongonococcal urethritis caused by *Ureaplasma urealyticum*.

Relapsing fever due to *Borrelia recurrentis*.

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

Chancroid caused by *Haemophilus ducreyi*.

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

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

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

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

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

Bartonellosis due to *Bartonella bacilliformis*.

Granuloma inguinale caused by *Calymmatobacterium granulomatis*.

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

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

*Escherichia coli*.

*Enterobacter aerogenes* (formerly *Aerobacter aerogenes*).

*Shigella* species.

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

Respiratory tract infections caused by *Haemophilus influenzae*.

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

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

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

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

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*.

Spillitis caused by *Treponema pallidum*.

Yaws caused by *Treponema pertenue*.

Listeriosis due to *Listeria monocytogenes*.

Anthrax due to *Bacillus anthracis*.

Vincent's infection caused by *Fusobacterium fusiforme*.

Actinomycosis caused by *Actinomyces israelii*.

Infections caused by *Clostridium* species.

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

In severe acne, doxycycline may be useful adjunctive therapy.

#### Prophylaxis:

Doxycycline is indicated for the prophylaxis of malaria due to *Plasmodium falciparum* in short-term travelers (<4 months) to areas with chloroquine and/or pyrimethamine-sulfadoxine resistant strains. See DOSAGE AND ADMINISTRATION section and Information for Patients subsection of the PRECAUTIONS section.

#### 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 fibula growth rate has been observed in premature given oral tetracycline in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the drug was discontinued.

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

Vibramycin Syrup contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The over-all prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in non-asthmatic people.

#### PRECAUTIONS

##### General

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

*Continued on next page*

Consult 2000 PDR® supplements and future editions for revisions



## Vibramycin/Vibra-Tabs—Cont.

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.

Doxycycline offers substantial but not complete suppression of the asexual blood stages of *Plasmodium* strains.

Doxycycline does not suppress *P. falciparum*'s sexual blood stage gametocytes. Subjects completing this prophylactic regimen may still transmit the infection to mosquitoes outside endemic areas.

### Information for Patients

Patients taking doxycycline for malaria prophylaxis should be advised:

—that no present-day antimalarial agent, including doxycycline, guarantees protection against malaria.

—to avoid being bitten by mosquitoes by using personal protective measures that help avoid contact with mosquitoes, especially from dusk to dawn (e.g., staying in well-screened areas, using mosquito nets, covering the body with clothing, and using an effective insect repellent.)

—that doxycycline prophylaxis:

—should begin 1–2 days before travel to the malarious area,

—should be continued daily while in the malarious area and after leaving the malarious area,

—should be continued for 4 further weeks to avoid development of malaria after returning from an endemic area,

—should not exceed 4 months.

All patients taking doxycycline should be advised:

—to avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs. Sunscreen or sunblock should be considered. (See WARNINGS.)

—to drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration. (See ADVERSE REACTIONS.)

—that the absorption of tetracyclines is reduced when taken with foods, especially those which contain calcium. However, the absorption of doxycycline is not markedly influenced by simultaneous ingestion of food or milk. (See DRUG INTERACTIONS.)

—that the absorption of tetracyclines is reduced when taking bismuth subsalicylate. (See DRUG INTERACTIONS.)

—that the use of doxycycline might increase the incidence of vaginal candidiasis.

### Laboratory Tests

In venereal disease, when co-existent syphilis is suspected, dark field examinations should be done before treatment is started and the blood serology repeated monthly for at least 4 months.

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

### Drug Interactions

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

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

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

Absorption of tetracyclines is impaired by bismuth subsalicylate.

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

The concurrent use of tetracycline and Penthrane (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 carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the 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 Category

Teratogenic effects: Category "D" — (See WARNINGS).

Nonteratogenic effects: (See WARNINGS).

### Labor and Delivery

The effect of tetracyclines on labor and delivery is unknown.

### Nursing Mothers

Tetracyclines are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to dis-

continue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See WARNINGS.)

### Pediatric Use

See WARNINGS and DOSAGE AND ADMINISTRATION.

### ADVERSE REACTIONS

Due to oral doxycycline's virtually complete absorption, side effects of 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. Hepatotoxicity has been reported rarely. 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 the 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, serum sickness, pericarditis, and exacerbation of systemic lupus erythematosus. Blood: Hemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia have been reported.

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 studies are known to occur.

### OVERDOSAGE

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

### DOSAGE AND ADMINISTRATION

THE USUAL DOSAGE AND FREQUENCY OF ADMINISTRATION OF DOXYCYCLINE DIFFERS FROM THAT OF THE OTHER TETRACYCLINES. EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS. Adults: The usual dose of oral doxycycline is 200 mg on the first day of treatment (administered 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day. The maintenance dose may be administered as a single dose or as 50 mg every 12 hours.

In the management of more severe infections (particularly chronic infections of the urinary tract), 100 mg every 12 hours is recommended.

For children above eight years of age: The recommended dosage schedule for children 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 children over 100 lb the usual adult dose should be used.

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

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

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

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

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

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. The dose may be administered with food, including milk or carbonated beverage, as required.

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

Nongonococcal urethritis (NGU) caused by *C. trachomatis* or *U. urealyticum*: 100 mg by mouth twice a day for 7 days. Syphilis—early: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 2 weeks.

Syphilis of more than one year's duration: Patients who are allergic to penicillin should be treated with doxycycline 100 mg by mouth twice a day for 4 weeks.

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

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

For prophylaxis of malaria: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis should begin 1–2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveler leaves the malarious area.

### HOW SUPPLIED

Vibramycin Hyclate (doxycycline hyclate) is available in capsules containing doxycycline hyclate equivalent to:

50 mg doxycycline

bottles of 50 (NDC 0069-0940-50),

unit-dose pack of 100 (10 × 10's) (NDC 0069-0940-41).

The capsules are white and light blue and are imprinted with "VIBRA" on one half and "PFIZER 094" on the other half.

100 mg doxycycline

bottles of 50 (NDC 0069-0950-50) and 500 (NDC 0069-0950-73),

unit-dose pack of 100 (10 × 10's) (NDC 0069-0950-41).

The capsules are light blue and are imprinted with "VIBRA" on one half and "PFIZER 095" on the other half.

Vibra-Tabs (doxycycline hyclate) is available in salmon colored film-coated tablets containing doxycycline hyclate equivalent to:

100 mg doxycycline

bottles of 50 (NDC 0069-0990-50) and 500 (NDC 0069-0990-73),

The tablets are imprinted on one side with "VIBRA-TABS" and "PFIZER 099" on the other side.

Vibramycin Calcium Syrup (doxycycline calcium oral suspension) is available as a raspberry-apple flavored oral suspension. Each teaspoonful (5 mL) contains doxycycline calcium equivalent to 50 mg of doxycycline: bottles of 1 oz (30 mL) (NDC 0069-0971-51), and 1 pint (473 mL) (NDC 0069-0971-93).

Vibramycin Monohydrate (doxycycline monohydrate) for Oral Suspension is available as a raspberry-flavored, dry powder for oral suspension. When reconstituted, each teaspoonful (5 mL) contains doxycycline monohydrate equivalent to 25 mg of doxycycline: 2 oz (60 mL) bottles (NDC 0069-0970-65).

All products are to be stored below 86°F (30°C) and dispensed in tight, light-resistant containers (USP). The unit dose packs should also be stored in a dry place.

### 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<sub>4</sub>, and methacycline; in minipigs by doxycycline, minocycline, tetracycline PO<sub>4</sub>, and methacycline; in dogs by doxycycline and minocycline; in monkeys by minocycline.

Minocycline, tetracycline PO<sub>4</sub>, methacycline, doxycycline, tetracycline base, oxytetracycline HCl, and tetracycline HCl were given to 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 radioactive iodine 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.

Revised April 1993

### VIBRAMYCIN® Hyclate

[vī'bra-mī'sin]

doxycycline hyclate for injection

### INTRAVENOUS

For Intravenous Use Only

### DESCRIPTION

Vibramycin (doxycycline hyclate for injection) Intravenous is a broad-spectrum antibiotic synthetically derived from oxytetracycline, and is available as Vibramycin Hyclate (doxycycline hydrochloride hemihydrate). The chemical designation of this light-yellow crystalline powder is alpha-6-deoxy-5-oxytetracycline. Doxycycline has a high degree of lipid solubility and a low affinity for calcium binding. It is highly stable in normal human serum.

### ACTIONS

Doxycycline is primarily bacteriostatic and thought to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of gram-positive and gram-negative organisms.

The drugs in the tetracycline antimicrobial spectra are common. Microorganisms doxycycline (likely to resp minimum inhibitory conce 4.0 mcg/mL. Microorganism (harboring partial resi mcg/mL and resistant (no the M.I.C. is greater than Susceptibility plate testin disc susceptibility testing should give a zone of at le doxycycline-susceptible be may be used to determin Kirby-Bauer method of di 30 mcg tetracycline disc mm when tested against a strain.

Tetracyclines are readily proteins in varying degree liver in the bile, and excre concentrations and in a b Following a single 100 m treatment average a peak concentration of 0.4 mg/m excreted a peak of 3.6 mcg Excretion of doxycycline cent/72 hours in individiv nee clearance about 75 tion may fall as low as 1- with severe renal insuffic 10 mL/min.). Studies hav in serum half-life of doxyc dividuals with normal an Hemodialysis does not al cine.

### INDICATIONS

Doxycycline is indicated in the following infections:

Rickettsiae (Rocky Mountain spotted fever) and the typhus group (fevers).

*Mycoplasma pneumoniae* Agents of psittacosis Agents of lymphogranulosa inguinale.

The spirochetal agent *Leptospira interrogans*.

The following gram-negative

*Haemophilus ducreyi*

*Pasteurella pestis* and

*Bartonella bacilliformis*

*Bacteroides* species,

*Vibrio comma* and *Vibrio*

*Brucella* species (in α

Because many strains of

ganisms have been s

cines, culture and suc

Doxycycline is indicated

by the following gram-n

terologic testing indicat

drug:

*Escherichia coli*,

*Enterobacter aerogenes*

*Shigella* species,

*Mima* species and *Ha*

*Haemophilus influenza*

*Klebsiella* species (res

Doxycycline is indicated

by the following gram-p

riologic testing indicate

drug:

*Streptococcus* species:

Up to 44 percent of st

percent of *Streptococ*

sistant to tetracycline

should not be used for

ganism has been demon

For upper respiratory i

lytic streptococci, penic

cluding prophylaxis of r

*Diplococcus pneumoniae*

*Staphylococcus aureus*

infections. Tetracyclir

treatment of any typ

When penicillin is conti

native drug in the treat

*Neisseria gonorrhoeae*

*Treponema pallidum*

is and yaws);

*Listeria monocytogenes*

*Clostridium* species,

*Bacillus anthracis*,

*Fusobacterium fusiforme*

*Actinomyces* species.

In acute intestinal ame

adjunct to amebicides.

Doxycycline is indicate

though the infectious

judged by immunofluor