DOXYCYCLINE CAPSULES USP
Rx only

To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline capsules and other antibacterial drugs, doxycycline capsules should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION
Doxycycline Capsules USP is a broad-spectrum antibiotic synthesized derived from oxytetracycline. Doxycycline 150 mg, 100 mg and 50 mg capsules contain Doxycycline monohydrate equivalent to 150 mg, 100 mg or 50 mg of doxycycline for oral administration. Inactive ingredients include colloidal silica, silicon dioxide, gelatin, magnesium stearate, microcrystalline cellulose, sodium starch glycolate and titanium dioxide. In addition, the 50 mg strength contains FD&C and D&C Yellow No. 6. The 100 mg strength also contains black iron oxide, red iron oxide and yellow iron oxide. The 150 mg strength includes FD&C Red and D&C Yellow No. 6. Its molecular weight is 462.46. The chemical designation of the light-yellow crystalline powder is alpha-H-d-oxo-5,6-s-ninhydrinocycline. Structural formula:

\[
\text{C}_{22}\text{H}_{24}\text{N}_{2}\text{O}_{8}\cdot\text{H}_{2}\text{O}
\]

Doxycycline Capsules USP 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.

CLINICAL PHARMACOLOGY
Tetracyclines are readily absorbable 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:

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Concentration (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>2.0</td>
<td>3.0</td>
</tr>
<tr>
<td>4.0</td>
<td>8.0</td>
</tr>
<tr>
<td>12.0</td>
<td>24.0</td>
</tr>
<tr>
<td>24.0</td>
<td>48.0</td>
</tr>
<tr>
<td>72.0</td>
<td>40.0</td>
</tr>
</tbody>
</table>

Clinical Pharmacokinetics
Excretion of doxycycline by the kidney is about 40%/72 hours in individuals who receive either 100 mg or 200 mg tablets. Hemodialysis does not alter serum half-life. Serum half-life is about 10 hours in patients with severe renal insufficiency (creatinine clearance below 10 mL/min). Doxycycline is metabolized by the liver to inactive metabolites (range 18 to 22 hours) in individuals with normal and severely impaired renal function.

Hemodialysis does not alter serum half-life.

Microbiology:
Mechanism of Action
Doxycycline inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit. Doxycycline has bacteriostatic activity against a broad range of Gram-positive and Gram-negative bacteria. Cross resistance with other tetracyclines is common.

Doxycycline has been shown to be active against most isolates of the following microorganisms, both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section of the package insert.

Gram-Negative Bacteria

<table>
<thead>
<tr>
<th>Organism</th>
<th>Minimal Inhibitory Concentration (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acinetobacter spp.</td>
<td>≥4</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≤4</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤4</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>≤4</td>
</tr>
<tr>
<td>Bacillus anthracis</td>
<td>1-2</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.5-1</td>
</tr>
<tr>
<td>Brucella abortus</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Brucella melitensis</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Brucella suis</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Francisella novicidae</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>HACEK species</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>≥8</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>≥1</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≥1</td>
</tr>
</tbody>
</table>

Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline

Bacteria * | Minimal Inhibitory Concentration (mcg/mL) | Zone Diameter (mm) | Agar Dilution (mg/mL) |
-------------|--------------------------------------------|--------------------|------------------------|
Acinetobacter spp. | ≥4 | 216 | 10-12 |
Bacillus anthracis | ≤4 | 216 | 10-12 |
B. melitensis | ≥8 | 216 | 10-12 |
Haemophilus ducreyi | ≥8 | 216 | 10-12 |
HACEK species | ≥8 | 216 | 10-12 |
Klebsiella pneumoniae | ≥8 | 216 | 10-12 |

* Organisms susceptible to tetracycline are also considered susceptible to doxycycline.

Dilution Techniques
Quantitative methods that require measurement of zone diameters also provide a more precise estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antibacterial compounds. The zone size should be determined using a standard test method.1,4 This procedure uses paper disks impregnated with 30 mcg doxycycline to test the susceptibility of bacterial strains to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

M. tuberculosis
For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method.1,4 The MIC values should be interpreted according to the criteria provided in Table 1.

INDICATIONS AND USAGE
To reduce the development of drug-resistant bacteria and maintain the effectiveness of doxycycline capsules USP and other antibacterial drugs, doxycycline capsules USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting the antibacterial drug or regimen for the treatment of each infection. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Doxycycline Capsules USP is indicated for the treatment of the following infections:


Doxycycline Capsules USP 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. Tularemia due to Francisella tularensis. Cholera caused by Vibrio cholerae. Campylobacter fetus infections caused by Campylobacter 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 Capsules USP is indicated for treatment of infections caused by the following gram-positive microorganisms, when bacteriologic testing indicates appropriate susceptibility to the drug:

Eubacterium aerogenes
Escherichia coli
Indole-positive bacilli
Nonindole-positive bacilli

Bacteriocidal aerogenes
Shigella species
Acinetobacter species
Respiratory tract infections caused by Haemophilus influenzae. Respiratory tract and urinary tract infections caused by Klebsiella species.

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

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


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 tetracyclines. Doxycycline has also been observed following repeated short-term courses. Enamel hypoplasia has also been reported with atovaquone and cisapride when used with tetracyclines in children. The use of drugs in this class during the period of human tooth formation (first trimester of pregnancy through the seventh month of pregnancy) may result in permanent staining of the tooth dentin and enamel. Use of tetracyclines in this manner is contraindicated for the treatment of infections in pregnant women when other, safer, antibacterial agents are available (see CLINICAL PHARMACOLOGY, Tetracyclines). EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN TOOTH DISCOLORATION.

Drug Interactions:
Concurrent use of tetracyclines may render oral contraceptives less effective. Contraceptive failure has been reported with tetracyclines, including doxycycline. Sperm motility is depressed by tetracyclines, and prolonged use may cause infertility in men treated with these agents. These effects are reversible when the tetracyclines are discontinued.

Drug/Laboratory Test Interactions:
False elevations of urinary catecholamine levels may occur due to interference with the reaction. These effects are reversible when the tetracyclines are discontinued.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Long-term studies in animals to evaluate the carcinogenic potential of doxycycline, tetracycline PO4, and methacycline; in minipigs by doxycycline, tetracycline, tetracycline PO4, and methacycline; in monkeys by tetracycline, minocycline, tetracycline PO4, and methacycline; and in dogs by doxycycline, oxytetracycline, and minocycline; in monkeys by minocycline.

Nongonococcal urethritis caused by C. trachomatis and U. urealyti-

Pharmacokinetics:

Information for Patients:
Informing the patient of the possibility of permanent visual loss exists. If visual disturbance occurs during therapy or at any time thereafter, the patient should be referred to an ophthalmologist for evaluation.

Pediatric Use:
Tetracyclines are excreted in human milk, however, the extent of absorption of tetracyclines, including doxycycline, by the breastfed infant is not known. The possibility of adverse reactions in nursing infants when the mother is administered tetracyclines is unknown. 11 Because of the potential for adverse reactions in nursing infants, doxycycline should not be used in women who are or may become pregnant while taking this drug. If doxycycline is used in pregnancy, the patient should be advised to discontinue the drug at the first evidence of skin erythema.

Pregnancy:
Doxycycline Capsules USP 50 mg have a bufXquate cap printed ‘‘726’’ in brown ink/white opaque body printed ‘‘726’’ in brown ink. Each capsule contains doxycycline monohydrate equivalent to 50 mg of doxycycline. They are supplied as follows:

Storage at 20° C to 25° C (68° F to 77° F). [See USP Control Room Temp.] Protect from light.

ANIMAL PHARMACOLOGY AND ANIMAL TOXICOLOGY
Hyperpigmentation of the skin has been produced by the members of this group of drugs in a variety of species, including man, when given in amounts adequate to produce the desired therapeutic effect. When the causative drug is withheld, hyperpigmentation persists, but is not increased. It can be removed by prolonged treatment with tetracyclines, but hyperpigmentation may recur whenever tetracyclines are administered. The reaction is more common with preparations containing tetracycline PO4 and methacycline; in minipigs by doxycycline, tetracycline, tetracycline PO4, and methacycline; in monkeys by minocycline. Minocycline, tetracycline PO4, methacycline, doxycycline, tetracycline base, oxytetracycline HCl and tetracycline HCl were gottifingered in rats fed a low protein diet, but not gottifingered by high radiocative iodine uptake. Administration of minocycline also produced a large goiter with (H, pseudosinon cerbri) and a marked increase in the radioiodine uptake.

REFERENCES
1. Clinical and Laboratory Standards Institute (CLSI). Performance Stan-
2. Clinical and Laboratory Standards Institute. Methods for Dilution Antimi-

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