DOXYCYCLINE CAPSULES USP
Fix 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 synthetically derived from oxytetracycline. Doxycycline 150 mg, 50 mg, and 20 mg capsules contain Doxycycline monohydrate equivalent to 150 mg, 50 mg, or 20 mg of doxycycline for oral administration. Inactive ingredients include colloidal silicon dioxide, povidone, magnesium stearate, microcrystalline cellulose, starch, dibasic calcium phosphate, and titanium dioxide. In addition, the 50 mg strength contains FD&C Yellow No. 6 and D&C Yellow No. 10. The 100 mg and 200 mg capsules also contain black, brown, and yellow iron oxides. The 150 mg strength includes FD&C Red No. 40 and FD&C Yellow No. 6. Its molecular weight is 442.46. The chemical designation of the light-yellow crystalline powder is alpha, beta-unsaturated.

Structural formula:

\[ \text{C}_{27}\text{H}_{26}\text{NO}_{9}\text{O}_4 \]

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 antibiotic form.

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:

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Concentration (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.02</td>
</tr>
<tr>
<td>1.5</td>
<td>2.26</td>
</tr>
<tr>
<td>3.0</td>
<td>3.01</td>
</tr>
<tr>
<td>3.6</td>
<td>3.16</td>
</tr>
<tr>
<td>4.0</td>
<td>3.03</td>
</tr>
<tr>
<td>6.0</td>
<td>2.03</td>
</tr>
<tr>
<td>8.0</td>
<td>1.62</td>
</tr>
<tr>
<td>12.0</td>
<td>0.95</td>
</tr>
<tr>
<td>24.0</td>
<td>0.37</td>
</tr>
<tr>
<td>48.0</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Average Observed Values

| Maximum Concentration | 3.51 mg/mL |
| Time of Maximum Concentration | 2.80 (± 1.19) |
| Elimination Rate Constant | 0.069 per hr |
| Half-Life | 16.35 hr (± 4.53 sd) |

Excretion of doxycycline by the kidney is about 40% to 72 hours in individuals with normal function (normalization of absorption about 75% to 80%). This percentage excretion may be as low as 1% to 5% in 72 hours in patients with severe renal insufficiency (creatinine clearance below 10 mL/min). In these cases doxycycline levels have shown no significant difference in serum half-life of doxycycline (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 bactericidal activity against a broad range of Gram-negative and Gram-positive bacteria. Rare cases of resistance with other tetracyclines is common. Doxycycline has been shown to be active against most isolates of the following microorganisms: both intra- and extracellular infections as described in the INDICATIONS AND USAGE section of the package insert.


Quality Control
Standard tetracycline susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the tests and the reproducibility of the results. Sensitive test strains should be selected.

A. Doxycycline 5 mg/mg disk zone diameters of 7 to 9 mm usually indicate a doxycycline-resistant test strain. TheMIC values are determined using the disk diffusion test as noted in Table 4.

B. Doxycycline 10 mg/mg disk zone diameters of 7 to 9 mm usually indicate a doxycline-resistant test strain. The MIC values are determined using the disk diffusion test as noted in Table 4.

Table 2: Acceptable Quality Control Ranges For Susceptibility Testing for Doxycycline and Tetracycline

<table>
<thead>
<tr>
<th>QC Strain</th>
<th>Minimal Inhibitory Concentration (mg/mL)</th>
<th>Zone Diameter (mm)</th>
<th>Agar Dilution (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus faecalis ATCC 29212</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td>Enterococcus faecalis ATCC 51589</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td>Streptococcus faecalis ATCC 12345</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td>Streptococcus faecalis ATCC 12346</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td>Staphylococcus aureus ATCC 29213</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
<tr>
<td>Staphylococcus aureus ATCC 29223</td>
<td>0.12 - 0.5</td>
<td>23 - 39</td>
<td>0.25 - 1</td>
</tr>
</tbody>
</table>

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 bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. 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:

- Rocky mountain spotted fever, typhus fever and the typhus group, Q fever, rickettsiosis, and louse-borne typhus caused by Rickettsia prowazekii.
- Respiratory tract infections caused by Mycoplasma pneumoniae, Legionnaires disease caused by Legionella pneumophila, and atypical pneumonia caused by Chlamydia trachomatis.
- Pelvic inflammatory disease caused by Neisseria gonorrhoeae.
- Tonsillitis caused by Streptococcus pyogenes.
- Nongonococcal urethritis caused by Ureaplasma urealyticum.
- Tetracycline fever due to Borrelia recurrentis.

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

- Chlamydia caused by Chlamydia trachomatis.
- Plague due to Yersinia pestis.
- Tularemia due to Pasteurella tularensis.
- Cholera caused by Vibrio cholerae.
- Campylobacter fetus infections caused by Campylobacter fetus.
- Brochialis due to Brucella species (in conjunction with streptomycin).
- Bacteroides due to Bacteroides fragilis.
- Granulomas caused by Calymmatobacterium granulomatis.

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, culture and susceptibility testing may be necessary before therapy with this drug is instituted especially in the following infections:

- Complications caused by Neisseria gonorrhoeae.
- Syphilis caused by Treponema pallidum.
- Yellow fever caused by Yersinia pestis.
- Lyme disease caused by Borrelia burgdorferi.
- Pseudomonas aeruginosa infections caused by Acinetobacter baumannii.
- Helicobacter pylori infections caused by Helicobacter pylori.

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.
- Lyme disease caused by Borrelia burgdorferi.
- Pseudomonas aeruginosa infections caused by Pseudomonas aeruginosa.
- Helicobacter pylori infections caused by Helicobacter pylori.

In acute intestinal amebiasis, doxycycline may be useful against amebiasis.

In severe acne, doxycycline may be useful as an adjuvant 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 discoloration may be more common during long-term use of the drug but has been observed following a few weeks of short-term treatment. Therefore, the drug should be avoided in patients in these age groups. Tetracycline transglutaminase is induced in a variety of bacteria following exposure to tetracyclines, and C. difficile produces toxins A and B which contribute to the development of C. difficile. Hygienic practices and minimizing the use of tetracyclines help reduce this risk. If C. difficile infection is suspected or confirmed, ongoing antibiotic use not directed against
Pregnancy:
- There are no human data available on short-term, first trimester exposure. There may be some risk associated with maternal tetracyclines during pregnancy if the mother is treated with doxycycline during gestation (i.e., in the second and third months of pregnancy) with the development of drug-resistant bacteria if the mother is treated with doxycycline during gestation or if the patient becomes pregnant while taking these drugs.

Drug/Laboratory Test Interactions:
- C. difficile patients with impaired renal function.
- Results of animal studies indicate that tetracyclines cross the placenta, are concentrated in breast milk, and are excreted in the urine during the course of treatment. Thus, patients should be advised to avoid breast feeding while taking doxycycline and while within one week of having discontinued its use. Doxycycline is not recommended for use in children younger than eight years of age owing to risk of permanent discoloration of the dentition. Although IH typically resolves after discontinuation of treatment, the possibility that the absorption of tetracyclines is reduced when taking bismuth subsalicylate, iron, or magnesium, and iron-containing preparations. These reactions have been reported in association with renal failure and parental administration of antibiotics. C. difficile patients with impaired renal function.
- In areas of the body where tetracyclines are in high concentrations, the effects of prolonged exposure to doxycycline in breast milk are unknown. The effects of prolonged exposure to doxycycline in breast milk are unknown. IH may occur (also known as pseudotumor cerebri). In the absence of hypertension, the development of drug-resistant bacteria if the mother is treated with doxycycline during gestation or if the patient becomes pregnant while taking these drugs.


Interactions:
- Other: Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of doxycycline in the treatment of acne. Although IH typically resolves after discontinuation of treatment, the possibility that the absorption of tetracyclines is reduced when taking bismuth subsalicylate, iron, or magnesium, and iron-containing preparations. These reactions have been reported in association with renal failure and parental administration of antibiotics. C. difficile patients with impaired renal function.
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