PREScribing INFORMATION

PrVIBRAMYCIN* CAPSULES
doxycycline hyclate capsules USP
doxycycline 100 mg

PrVIBRA-TABS* FILM COATED TABLETS
doxycycline hyclate tablets USP
doxycycline 100 mg

Antibiotic

PFIZER CANADA INC.
17 300 Trans-Canada Highway
Kirkland, Quebec H9J 2M5

DATE OF REVISION
September 6, 2013

Submission Control # 166401

*Pfizer Canada Inc.
NAME OF DRUGS

Pr VIBRAMYCIN* CAPSULES
doxycycline hyclate capsules USP
doxycycline 100 mg

Pr VIBRA-TABS* FILM COATED TABLETS
doxycycline hyclate tablets USP
doxycycline 100 mg

THERAPEUTIC CLASSIFICATION

Antibiotic

ACTION

Doxycycline hyclate is a broad-spectrum antibiotic and is active against a wide range of Gram-negative and Gram-positive organisms. Doxycycline exerts its bacteriostatic effect by the inhibition of protein synthesis.

INDICATIONS AND CLINICAL USE

VIBRAMYCIN/VIBRA-TABS (doxycycline hyclate) may be indicated for the treatment of:

Pneumonia: Single and multilobe pneumonia and bronchopneumonia due to susceptible strains of Streptococcus pneumoniae and other Streptococcus spp., Staphylococcus spp., H. influenzae and Klebsiella pneumoniae.
Other Respiratory Tract Infections: Pharyngitis, tonsillitis, sinusitis, otitis media, bronchitis caused by susceptible strains of β-hemolytic Streptococcus, Staphylococcus spp., Streptococcus pneumoniae and H. influenzae.


In adult patients with urethritis, cervicitis and vaginitis with a positive test for Chlamydia trachomatis and/or Ureaplasma urealyticum, clinical resolution and absence of detectable organisms have only been observed at completion of ORAL therapy with VIBRAMYCIN/VIBRA-TABS. Relapses or reinfection can occur. In these cases, limited data suggest that some patients may derive clinical benefit from an alternative therapy. The effect on long term morbidity has not been established.

Skin and Soft Tissue Infections: Impetigo, furunculosis, cellulitis, abscess, wound infections, paronychia, caused by susceptible strains of Staphylococcus aureus and epidermidis, Streptococcus spp., E. coli, Klebsiella spp. and Enterobacter aerogenes.

Gastro-intestinal Infections: Caused by susceptible strains of Shigella spp., Salmonella spp. and E. coli.
Up to 44 percent of strains of *Streptococcus pyogenes* and 74 percent of *Streptococcus faecalis* have been found to be resistant to tetracycline drugs.

Appropriate culture and susceptibility studies should be carried out prior to initiation of therapy with **VIBRAMYCIN/VIBRA-TABS** and if clinically indicated during treatment. Consideration may be given to the initiation of therapy before obtaining results of these tests, however modification of such treatment may be required once the results become available.

**CONTRAINDICATIONS**

**VIBRAMYCIN/VIBRA-TABS** (doxycycline hyclate) is contraindicated in individuals who have shown hypersensitivity to **VIBRAMYCIN/VIBRA-TABS** (doxycycline hyclate), and to any of its inert ingredients or to any other tetracycline, and in patients with myasthenia gravis.

**WARNINGS**

General

**VIBRAMYCIN/VIBRA-TABS** (doxycycline hyclate) like other tetracyclines, may form a stable calcium complex in any bone-forming tissue, though *in vitro* it binds calcium less strongly than other tetracyclines. It should be anticipated that the use of **VIBRAMYCIN/VIBRA-TABS** during tooth development (last trimester of pregnancy, during lactation, neonatal period and early childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Though more commonly associated with long term use of tetracyclines, this effect has also been known to occur after short courses. Enamel hypoplasia has also been reported.

**VIBRAMYCIN/VIBRA-TABS** should, therefore, not be used in these age groups unless other drugs are unlikely to be effective or are contraindicated.
Carcinogenesis and Mutagenesis
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).

Gastrointestinal
Instances of esophageal lesions (esophagitis and ulcerations), sometimes severe, have been reported in patients receiving doxycycline. The patients must be instructed to take VIBRAMICIN/VIBRA-TABS with a full glass of water, to keep in orthostatic position after the administration and not to go to bed within 1-2 hours after the intake. If symptoms such as dysphagia and retrosternal pain occur, VIBRAMYCIN/VIBRA-TABS should be discontinued and an esophageic lesion must be investigated (see PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION and INFORMATION FOR THE PATIENT).
VIBRAMICIN/VIBRA-TABS should not be prescribed to patients with obstructive esophageic pathology, such as stenosis and achalasia.

Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including VIBRAMYCIN/VIBRA-TABS. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea, or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.
Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of Clostridium difficile. C. difficile produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against Clostridium difficile. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against Clostridium difficile. Surgical evaluation should be instituted as clinically indicated, as surgical intervention may be required in certain severe cases. (see ADVERSE REACTIONS)

Skin
Photosensitivity reaction 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 VIBRAMYCIN/VIBRA-TABS, and treatment should be discontinued at the first evidence of skin erythema (see PRECAUTIONS, ADVERSE REACTIONS and INFORMATION FOR THE PATIENT). The use of sunscreen or sunblock prior to sun or UV light exposure should be considered in patients taking VIBRAMYCIN/VIBRA-TABS.

Hypersensitivity
Hypersensitivity adverse drug reactions that included, but not limited to anaphylactic reaction, angionedema, dyspnea, tachycardia, hypotension, pericarditis, urticaria, rash, erythema multiforme, Stevens-Johnson and toxic epidermal necrolysis have been reported with VIBRAMYCIN/VIBRA-TABS use. Some of these reactions were serious. If an allergic reaction occurs, administration of VIBRAMYCIN/VIBRA-TABS should be discontinued and appropriate therapy should be initiated.
**VIBRAMYCIN/VIBRA-TABS** has been associated with the development of autoimmune adverse drug reactions including exacerbation of systemic lupus erythematosus, rash, peripheral edema, arthralgia, myalgia, serum sickness. If patients with autoimmune reactions are suspected, administration of **VIBRAMYCIN/VIBRA-TABS** should be discontinued and liver function tests, ANA, CBC, and other appropriate tests should be performed to evaluate the patients.

**Renal**
The anti-anabolic action of tetracyclines may cause an increase in BUN. Studies to date indicate that this anti-anabolic effect does not occur with the use of doxycycline in patients with impaired renal function.

**Usage in Pregnancy**
**VIBRAMYCIN/VIBRA-TABS** should not be administered to pregnant women, unless in the judgment of the physician the potential benefit to the mother outweighs the risk to the fetus (see above **WARNINGS** section about use during tooth development).

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.

**Usage During Lactation**
Tetracyclines are excreted in the milk of lactating women. Accordingly the use of **VIBRAMYCIN/VIBRA-TABS** is not recommended in women while they are breast feeding (see above **WARNINGS** section about use during tooth development).
Use in Newborns, Infants and Children

The use of VIBRAMYCIN/VIBRA-TABS in children under 8 years is not recommended because safe conditions for its use have not been established (see above WARNINGS section about use during tooth development).

Doxycycline hyclate like other tetracyclines forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracycline in doses of 25 mg/kg every six hours. This reaction was shown to be reversible when the drug was discontinued.

PRECAUTIONS

In clinical studies to date, administration of VIBRAMYCIN/VIBRA-TABS (doxycycline hyclate) did not lead to increased serum levels nor to an increase in the serum half-life of doxycycline in patients with impaired renal function. Modification of VIBRAMYCIN/VIBRA-TABS dosage for these patients is not necessary. Although no evidence of increased toxicity has been observed in such patients, the potential for increased hepatic or other toxicity should be considered until further data on the metabolic fate of doxycycline under these conditions become available.

Concurrent administration of VIBRAMYCIN/VIBRA-TABS with agents known to be hepatotoxic should be avoided.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms including fungi; thus, observation of the patient is essential.

Patients should be advised that the use of doxycycline might increase the incidence of vaginal candidiasis (see ADVERSE REACTIONS and INFORMATION FOR THE PATIENT).
Fontanelle bulging in infants and benign intracranial hypertension in adults have been reported in individuals receiving full therapeutic dosages. Although the mechanism of this phenomenon is unknown the signs and symptoms have disappeared rapidly upon cessation of treatment with no sequelae (see ADVERSE REACTIONS).

Cases of esophageal injury consisting of esophagitis and esophageal ulceration have been reported in patients receiving VIBRAMYCIN/VIBRA-TABS orally. Most of these patients took medication immediately before going to bed and/or without adequate amount of fluid (see DOSAGE AND ADMINISTRATION). If this should occur, VIBRAMYCIN/VIBRA-TABS should be discontinued until healing occurs. Administration of antacids and/or cimetidine has provided relief in the treatment of such cases. TO REDUCE THE RISK OF ESOPHAGEAL INJURY, PATIENTS SHOULD BE ADVISED TO TAKE VIBRAMYCIN CAPSULES OR VIBRA-TABS FILM COATED TABLETS WITH AN ADEQUATE AMOUNT OF FLUID WHILE STANDING OR SITTING UPRIGHT. VIBRAMYCIN/VIBRA-TABS should not be given at bedtime.

In long term therapy with VIBRAMYCIN/VIBRA-TABS, periodic laboratory evaluation of organ systems, including hematopoietic, renal and hepatic studies should be performed. Liver function tests should be carried out at regular intervals on patients receiving high doses for prolonged periods of time.

Drug interactions
VIBRAMYCIN/VIBRA-TABS should be given with caution to patients receiving oral anticoagulants. Because the tetracyclines have been shown to depress plasma prothrombin activity, patients who are on anticoagulant therapy may require downward adjustment of their anticoagulant dosage.
Antacids containing aluminum, calcium or magnesium impair absorption and should not be given to patients taking VIBRAMYCIN/VIBRA-TABS.

The concurrent use of VIBRAMYCIN/VIBRA-TABS (doxycycline hyclate) with alcohol, barbiturates, phenytoin and carbamazepine (hepatic enzyme inducers) has been reported to result in a reduction of plasma half-life of doxycycline, thereby reducing the antimicrobial effectiveness of VIBRAMYCIN/VIBRA-TABS. This effect may last for several days after discontinuation of therapy with the interacting agent. Therefore, consideration should be given to re-adjustment of the daily dose of VIBRAMYCIN/VIBRA-TABS when administered concomitantly with alcohol and with drugs known to be enzyme inducers.

It has been reported that concurrent administration of ferrous sulphate (iron) lowered serum concentrations of doxycycline given orally and shortened the serum half-life after a single intravenous injection. In the event that iron and iron-containing products have to be given during treatment with VIBRAMYCIN/VIBRA-TABS, the interval between administration of each drug should be as wide as possible.

It has been reported that when subsalicylate bismuth was given simultaneously and as a multiple-dose regimen before oral VIBRAMYCIN/VIBRA-TABS there was a reduced bioavailability of doxycycline. Also peak serum concentrations of doxycycline were significantly decreased when subsalicylate bismuth was given 2 hours before oral VIBRAMYCIN/VIBRA-TABS but not when given 2 hours after oral VIBRAMYCIN/VIBRA-TABS. Therefore subsalicylate bismuth should not be taken during therapy with oral VIBRAMYCIN/VIBRA-TABS.

Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving VIBRAMYCIN/VIBRA-TABS, or any other tetracycline, in conjunction with penicillin.
There have been anecdotal reports that concurrent use of tetracyclines may render oral contraceptives less effective.

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

**Drug Laboratory Test Interactions**

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.

**ADVERSE REACTIONS**

**GASTROINTESTINAL:**

As with other broad spectrum antibiotics administered orally and parenterally, gastro-intestinal disturbances such as anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, stomatitis, proctitis and enterocolitis, may occur, but have rarely been sufficiently troublesome to warrant discontinuation of therapy with **VIBRAMYCIN/VIBRA-TABS** (doxycycline hyclate). Abdominal pain, dyspepsia (heartburn/gastritis), pseudomembranous colitis, *C. difficile* diarrhea and inflammatory lesions (with monilial overgrowth) in the anogenital region have also been reported. Due to oral doxycycline’s virtually complete absorption, side effects of the lower bowel, particularly diarrhea, have been infrequent.

Cases of esophagitis and esophageal ulcerations, sometimes severe, in patients receiving capsule and tablet form of **VIBRAMYCIN/VIBRA-TABS** (doxycycline hyclate) have been reported (see **WARNINGS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, INFORMATION FOR THE PATIENT**).

**AUTONOMIC NERVOUS SYSTEM:**

Flushing.
HYPERSENSITIVITY
Hypersensitivity reactions consisting of urticaria, angioedema, anaphylactic reaction, anaphylactoid reaction, Henoch-Schonlein Purpura, dyspnea, hypotension, pericarditis, peripheral edema, serum sickness, tachycardia and exacerbation of systemic lupus erythematosus have been reported.

SKIN:
Maculopapular and erythematous rashes, photosensitivity reaction, photo-onycholysis, erythema multiforme, Stevens-Johnson syndrome and Toxic Epidermal Necrolysis have been reported. Exfoliative dermatitis has also been reported but is uncommon (see WARNINGS, skin).

MUSCULO-SKELETAL:
Arthralgia and myalgia.

CENTRAL NERVOUS SYSTEM:
Headache, fontanelle bulging in infants and benign intracranial hypertension in adults. In relation to benign intracranial hypertension, symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported (see PRECAUTIONS).

LIVER/BILIARY:
There have been reports of hepatotoxicity (including hepatic failure, autoimmune hepatitis and cholestasis) and hepatic function abnormal. As with other tetracyclines, hepatitis, elevation of SGOT or SGPT values have been reported, the significance of which is not known.

HAEMATOLOGIC:
Hemolytic anemia, thrombocytopenia, neutropenia, eosinophilia, leukopenia.
IMMUNE SYSTEM DISORDERS:
Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

HEARING/VESTIBULAR:
Tinnitus.

INVESTIGATIONS (Renal Function Analyses)
Blood urea increased (apparently dose related) has been reported.

UROGENITAL:
Vaginal candidiasis (see PRECAUTIONS)

OTHERS:
When given over prolonged periods tetracyclines have been reported to produce brown-black microscopic discolouration of the thyroid gland. Abnormalities of thyroid function have not been shown to date (see TOXICOLOGY, Subacute Toxicity).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Specific information on symptoms or treatment of overdosage with VIBRAMYCIN/VIBRA-TABS (doxycycline hyclate) is not available. In case of overdosage, discontinue medication. Treatment, therefore, should be symptomatic and gastric lavage may be considered for overdosage with the oral preparation. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

For management of suspected drug overdose contact your regional Poison Control Centre.
DOSAGE AND ADMINISTRATION

DOSAGE

EXCEEDING THE RECOMMENDED DOSAGE MAY RESULT IN AN INCREASED INCIDENCE OF SIDE EFFECTS.

**Adults** The recommended dosage of oral VIBRAMYCIN/VIBRA-TABS for the majority of susceptible infections is a single loading dose of 200 mg on the first day of treatment followed by a maintenance dosage of 100 mg once daily at the same time each day thereafter.

In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg should be given daily throughout the treatment period.

Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. It should be noted, however, that effective antibacterial levels are usually present 24 to 36 hours following discontinuance of VIBRAMYCIN/VIBRA-TABS therapy.

When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

For treatment of uncomplicated acute gonococcal infections, the recommended dosage is 200 mg starting and 100 mg in the evening, the first day, followed by 100 mg b.i.d. for 3 days.
For treatment of uncomplicated urethral, endocervical, or vaginal infections in adults associated with *Chlamydia trachomatis* and *Ureaplasma urealyticum*: 100 mg, by mouth, twice a day for at least 10 days.

No alteration in recommended dosage schedule need be made when treating patients with impaired renal function.

**ADMINISTRATION**

**VIBRAMYCIN** Capsules and **VIBRA-TABS** Film Coated Tablets should be given with or after a meal in order to minimize the possibility of gastric upset. Antacids and iron preparations impair absorption and should not be given concomitantly to patients taking oral **VIBRAMYCIN/VIBRA-TABS**.

Patients should be advised to take **VIBRAMYCIN** Capsules and **VIBRA-TABS** Film Coated Tablets with a full glass of water, to keep in orthostatic position after the administration and not to go to bed within 1-2 hours after the intake.
CHEMISTRY

Trade name(s): VIBRAMYCIN CAPSULES, VIBRA-TABS FILM COATED TABLETS

Proper Name: doxycycline hyclate

Chemical Name: 2-Naphthacenecarboxamide, 4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,5,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-monohydrochloride, compd. with ethanol (2:1), monohydrate, \( 4S-(4\alpha,4a\alpha,5\alpha,5a\alpha,6\alpha,12\alpha) \) -or \( \alpha-6\)-deoxy-5-oxytetracycline

Structural Formula:

Molecular Formula: \( (C_{22}H_{24}N_{2}O_{8}\cdot HCl)_2 \cdot C_2 H_5 OH \cdot H_2 O \)

Molecular Weight: 1025.89

Description:
Doxycycline hyclate is a light yellow, crystalline powder essentially free of solvent odor. It is soluble in water: pH (1 %, H_2O) is between 2.0 and 3.0. It decomposes without melting at 201°C.
Composition:

**VIBRAMYCIN CAPSULES:** each blue, hard gelatin capsule contains: doxycycline hyclate equivalent to doxycycline 100 mg. Also contains microcrystalline cellulose, magnesium stearate/sodium lauryl sulfate. Capsule shell contains gelatin, sulfur dioxide, titanium dioxide and FD & C Blue #1 dye. Supplied in plastic bottles (high density polyethylene) of 50 capsules.

**VIBRA-TABS:** each orange film coated tablet contains doxycycline hyclate equivalent to doxycycline 100 mg. Also contains microcrystalline cellulose, ethylcellulose, hypromellose, magnesium stearate/sodium lauryl sulfate, propylene glycol, talc, titanium dioxide, FD & C Yellow #6, and aluminum hydroxide. Supplied in plastic bottles (high density polyethylene) of 100 tablets.

**DOSAGE FORMS**

**AVAILABILITY**

**VIBRAMYCIN CAPSULES** 100 mg are available as blue hard gelatin capsules imprinted in black with “VIBRA/PFIZER 095” containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 50.

**VIBRA-TABS FILM COATED TABLETS** 100 mg are available as orange film coated tablets containing doxycycline hyclate equivalent to 100 mg of doxycycline, supplied in bottles of 100.

**STORAGE**

**VIBRAMYCIN CAPSULES** (doxycycline hyclate) 100 mg and **VIBRA-TABS** (doxycycline hyclate) 100 mg. Store at a temperature 15-30°C; protect from light. Dispense in a light-resistant container.
Doxycycline is a broad spectrum antibiotic and has been shown to be active in vitro against the following Gram-negative, Gram-positive and other micro-organisms:

- *Staphylococcus aureus*
- *Staphylococcus epidermidis (albus)*
- *Streptococcus pyogenes*
- *Streptococcus faecalis*
- *Streptococcus pneumoniae*
- *Streptococcus viridans*
- *Listeria monocytogenes*
- *Klebsiella pneumoniae*
- *Salmonella typhi*
- *Salmonella typhimurium*
- *Salmonella enteriditis*
- *Shigella sonnei*
- *Shigella flexneri*

Corynebacterium diphtheriae
- *Bacillus anthracis*
- *Bacillus subtilis*
- *Neisseria gonorrhoeae*
- *Neisseria catarrhalis*
- *Escherichia coli*
- *Enterobacter aerogenes*
- *Pseudomonas aeruginosa*
- *Haemophilus influenzae*
- *Serratia spp.*
- *Brucella spp.*
- *Proteus spp.*
- *Pasteurella spp.*
- *Mycoplasma pneumoniae*
- *Chlamydia trachomatis*
- *Ureaplasma urealyticum*
The drugs in the tetracycline class have closely similar antimicrobial spectra, and cross-resistance among them is common.

**SUSCEPTIBILITY TESTING**

The Kirby-Bauer method of disc susceptibility testing (using the 30 μg doxycycline disc) and dilution susceptibility should be interpreted according to the criteria in **TABLE 1**.

**TABLE 1**

**SUSCEPTIBILITY TEST**

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>ZONE DIAMETER (30 μ doxycycline disc) mm</th>
<th>M.I.C. mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible</td>
<td>≥ 16</td>
<td>≤ 4</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13-15</td>
<td>8</td>
</tr>
<tr>
<td>Resistant</td>
<td>≤ 12</td>
<td>≥16</td>
</tr>
</tbody>
</table>

**PHARMACOLOGY**

Serum levels of doxycycline administered orally follow a similar pattern to those obtained with equivalent dosages administered intravenously as shown in **TABLE 2**. Peak serum levels were slightly higher and occurred earlier following intravenous administration than for oral administration (see **TABLE 2**).
TABLE 2
Serum levels (mg/L) after oral and I.V. infusion over 60 minutes (0.5 mg/mL) of a total daily dose of 200 mg of doxycycline hyclate on the first day (100 mg every 12 hours) and a dose of 100 mg on the second and third day of administration (22 Male Volunteers/Group).

<table>
<thead>
<tr>
<th>Time (hr:min)</th>
<th>Mean Serum Level I.V.</th>
<th>Mean Serum Level Capsules</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>0:05</td>
<td>2.455</td>
<td>0.000</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>1:00</td>
<td>1.608</td>
<td>1.206</td>
<td>&lt; .01</td>
</tr>
<tr>
<td>2:00</td>
<td>1.551</td>
<td>1.643</td>
<td></td>
</tr>
<tr>
<td>3:00</td>
<td>1.421</td>
<td>1.482</td>
<td></td>
</tr>
<tr>
<td>16:00</td>
<td>1.131</td>
<td>1.124</td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td>0.800</td>
<td>0.815</td>
<td></td>
</tr>
<tr>
<td>13:00</td>
<td>2.397</td>
<td>1.107</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>15:00</td>
<td>2.130</td>
<td>2.000</td>
<td></td>
</tr>
<tr>
<td>24:00</td>
<td>1.468</td>
<td>1.663</td>
<td>.088</td>
</tr>
<tr>
<td>35:00</td>
<td>1.734</td>
<td>1.725</td>
<td></td>
</tr>
<tr>
<td>48:00</td>
<td>1.159</td>
<td>1.078</td>
<td></td>
</tr>
<tr>
<td>48:05</td>
<td>3.658</td>
<td>1.124</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>49:00</td>
<td>2.945</td>
<td>2.147</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>50:00</td>
<td>2.848</td>
<td>2.406</td>
<td>.056</td>
</tr>
<tr>
<td>51:00</td>
<td>2.760</td>
<td>2.436</td>
<td></td>
</tr>
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<td>54:00</td>
<td>2.150</td>
<td>1.989</td>
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</tr>
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<td>59:00</td>
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<td>1.516</td>
<td></td>
</tr>
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<td>72:00</td>
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<td>0.945</td>
<td></td>
</tr>
<tr>
<td>83:00</td>
<td>0.700</td>
<td>0.709</td>
<td></td>
</tr>
<tr>
<td>96:00</td>
<td>0.426</td>
<td>0.399</td>
<td></td>
</tr>
<tr>
<td>107:00</td>
<td>0.247</td>
<td>0.234</td>
<td></td>
</tr>
</tbody>
</table>

Where no p is stated, p>.10

____ time of dosing

Doxycycline was rapidly and almost completely absorbed following oral administration. The absorption of doxycycline was not significantly influenced by ingestion of food or milk (see TABLE 3).
TABLE 3
Effect of Food or Milk on Absorption of a Single Oral Dose of Doxycycline 100 mg as Hyclate (5 Male Volunteers/Group).

<table>
<thead>
<tr>
<th>Hours</th>
<th>Breakfast</th>
<th>Fasting</th>
<th>6 oz. milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>0.966</td>
<td>1.004</td>
<td>1.081</td>
</tr>
<tr>
<td>2</td>
<td>1.188</td>
<td>1.377</td>
<td>1.325</td>
</tr>
<tr>
<td>3</td>
<td>1.269</td>
<td>1.296</td>
<td>1.244</td>
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<tr>
<td>5</td>
<td>1.036</td>
<td>1.133</td>
<td>1.046</td>
</tr>
<tr>
<td>8</td>
<td>0.973</td>
<td>0.936</td>
<td>0.885</td>
</tr>
<tr>
<td>12</td>
<td>0.738</td>
<td>0.801</td>
<td>0.686</td>
</tr>
<tr>
<td>24</td>
<td>0.498</td>
<td>0.528</td>
<td>0.475</td>
</tr>
</tbody>
</table>

Doxycycline is approximately 93% protein bound. The serum half-life of doxycycline is 18 hours. Doxycycline is excreted in the urine (approximately 35-40% of the administered dose) and in the bile. The volume of distribution is approximately 0.7 L/kg. Hemodialysis does not alter the serum half-life.

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10 mL/min.). The serum half-life of doxycycline is not increased, nor does it accumulate in the blood of patients with impaired renal function.
Doxycycline Hyclate

a) Acute Toxicity

The acute oral and parenteral toxicity of doxycycline in mice, rats and dogs are as follows:

<table>
<thead>
<tr>
<th></th>
<th>LD$_{50}$ (95% Confidence Limits) mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORAL</td>
</tr>
<tr>
<td>Mice</td>
<td>1,900 (1696-2128)</td>
</tr>
<tr>
<td>Rats</td>
<td>&gt;2,000</td>
</tr>
<tr>
<td>Dogs</td>
<td>&gt; 500</td>
</tr>
</tbody>
</table>

The intraperitoneal LD$_{50}$'s of doxycycline in weanling and newborn rats are 262 (222-309) and 300 (275-327) mg/kg, respectively.

b) Subacute Toxicity

One to 2 1/2-month subacute toxicity studies were conducted in rats, hamsters, dogs and monkeys. Doxycycline induced a yellow fluorescence (under ultraviolet light) of bone, teeth, kidney and/or liver, in all animal species tested. In rats, doxycycline produced no toxic effects in doses of up to 500 mg/kg/day for 30 days. In hamsters, doxycycline in dosages of 500 or 250 mg/kg/day produced weight loss and early death, but the 50 mg/kg level (for 30 days) was nontoxic. In dogs, doxycycline in dosages of 250 mg/kg/day for one month produced discoloration of the thyroid gland with the presence of intracytoplasmic granules in follicular acini and occasional amorphous body formation within follicular colloid.

Certain biochemical, functional and histological changes of the liver occurred in the dogs (but not in the rats, hamsters, or monkeys) receiving doxycycline for 30 days at dosage levels of 250 and 50 mg/kg/day, but not at the 25 mg/kg/day level. The biochemical changes in the blood were elevations of alkaline phosphatase, SGPT
and/or BSP retention. Histologic changes were confined to bile ductular proliferation and hepatocellular intracytoplasmic inclusion bodies and Kupffer cells swollen with PAS-positive granular material. These changes in the dog were reversible upon drug withdrawal.

Monkeys which received doxycycline at dosages of 25 and 50 mg/kg/day for 1 1/2 to 2 1/2 months showed mild yellow ultraviolet fluorescence of liver, kidney and bone, and the presence of small amounts of intracytoplasmic granular material in the thyroid gland.

c) Chronic Toxicity

In an 18-month chronic toxicity study, rats were fed diets containing doxycycline at levels to provide daily drug intake of 500, 250, 50 and 0 mg/kg. Slight depression of weight gains in some rats receiving the 500 mg/kg/day dose occurred during the middle third of the study. The usual yellow ultraviolet fluorescence of bone, teeth and/or kidneys was seen in rats receiving all levels of doxycycline for 6, 12 or 18 months. Dark to light brown discoloration of the thyroid gland was also noted in rats receiving doxycycline for 12 months at levels of 500 and 250 mg/kg/day, and at 18 months at all levels. The only other change noted was depletion of hepatic glycogen in four rats receiving the highest dose level for 12 months.

Beagle dogs received doxycycline at levels of 10 and 100 mg/kg, six days per week. Moderate to marked elevations of alkaline phosphatase and SGPT (occasionally SGOT) were observed in animals receiving doxycycline, 100 mg/kg/day. One of two dogs receiving doxycycline, 100 mg/kg/day, displayed mild bile ductular proliferation and hepatocellular inclusion bodies after 5 months (biopsy sample) and 12 months (necropsy sample). Administration of doxycycline for 5 and 12 months at a level of 100 mg/kg/day and for 12 months at a level of 10 mg/kg caused black and brownish discoloration of the thyroid gland, respectively, with intracytoplasmic granules. Other changes included vasodilatation and focal areas of necrosis of the mucosa of the
pyloric and fundic stomach of dogs, and yellow ultraviolet fluorescence of teeth and bones of animals at 100 mg/kg/day dose levels of doxycycline.

Additional groups of 4 beagles each received doxycycline in dosages of 5, 1 and 0 mg/kg/day for 6 months. The only abnormal findings were slight elevations of SGPT values in 3 dogs at the 5 mg/kg level at 180 days.

In a one year chronic toxicity study, groups of four rhesus monkeys each received doxycycline in oral doses of 0, 5, 25 and 50 mg/kg/day, respectively. Oral dosage of 100 mg/kg produced severe gastrointestinal symptoms, e.g., vomiting and diarrhea. In one out of 4 monkeys receiving the 50 mg/kg/day dose, occasional anorexia and diarrhea were observed during the first six months.

Significant pathologic changes noted in monkeys sacrificed after receiving doxycycline for 1 year at dose levels of 50 mg/kg/day were: 1) grossly, very light brown discoloration of the thyroid gland in one of the four monkeys, and 2) microscopically, brownish intracytoplasmic inclusions in the acinar cells of thyroid follicles of three out of four monkeys. Bone and dentin exhibited slight to moderate ultraviolet fluorescence.

Two monkeys, in another study, receiving the 25 mg/kg/day dosage, were sacrificed after 6 and 8 months on test, respectively. Significant gross and histopathologic findings were slight yellow ultraviolet fluorescence of the endosteum and periosteum of bone, and microscopic appearance of small amounts of granular intracytoplasmic material in the acinar cells of thyroid follicles.

The highlights of the chronic toxicity studies can be summarized as follows:

1) Discoloration of the thyroid gland, with deposition of intracytoplasmic granules in the acinar cells of the follicle. Thyroid function, however, did not seem to be affected. This phenomenon appears to be a result of the interaction of the antibiotic with the active iodinating system of the gland.
2) Yellow staining of bones and teeth, which is thought to be due to formation of a
tetracycline-calcium-phosphate complex.

Otherwise doxycycline was well tolerated by the rat and monkey at doses up to and
including 500 and 50 mg/kg/day for 18 and 12 months, respectively. In dogs,
however, repeated daily oral administration of large doses of doxycycline resulted in
certain hepatic functional and histopathologic changes which are reversible after drug
withdrawal. No adverse hepatic effects were noted in the hamster (1 month), rats (18
months) or monkeys (12 months) for doses up to and including 500, 500 and 50
mg/kg/day, respectively. In view of this and in view of the lack of notable toxicity in
our wide human clinical program, it is our opinion that this is a species specific
phenomenon, for the dog only.

d) Reproduction and Teratogenic Studies
Doxycycline has no teratologic effects in rats, rabbits or monkeys.

Breeding rats received doxycycline by gavage in doses of 50 and 250 mg/kg/day prior
to and throughout two consecutive litters. There was no evidence that doxycycline
interfered with the reproductive process in rats.

Pregnant female white New Zealand rabbits received doxycycline orally in doses of 8
and 40 mg/kg/day, respectively, from day 8 to day 16 of pregnancy. Spina bifida and
partial anencephaly in one pup each in the control and the 8 mg/kg group,
respectively, are believed to be spontaneous and drug-induced.

In teratogenic studies using a limited number of monkeys, doxycycline, in doses
ranging from 1 to 50 mg/kg/day, did not produce any teratologic effects.

Doxycycline Monohydrate
With bulk doxycycline monohydrate administered in a 10% aqueous suspension, the oral
\(LD_{50}\) for albino male mice was greater than 5000 mg/kg.
Doxycycline Hyclate with Ascorbic Acid

Studies in mice and rats showed the LD$_{50}$ of VIBRAMYCIN I.V. to be 75 mg/kg in mice and 88 mg/kg in rats of doxycycline (using a preparation of doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid as a sterile powder).

No signs of drug toxicity were seen in dogs receiving 20 to 21 daily doses of VIBRAMYCIN I.V. at a dose level of 5 mg/kg when administered as a 0.5% solution at a rate of 1 mg/kg/min. Dogs receiving 14, 16 or 17 daily intravenous doses of 10 mg VIBRAMYCIN I.V. per kg of bodyweight, or 4 daily 60 minute infusions of 300 mg VIBRAMYCIN I.V., or 300 mg degraded VIBRAMYCIN I.V. evidenced serum alkaline phosphatase and serum glutamic pyruvic transaminase elevations. No morphological basis for these enzyme elevations was established although moderate bile ductular proliferation was seen in 1 of 2 dogs receiving 4 daily intravenous infusions of degraded VIBRAMYCIN I.V.

In 8 dogs receiving daily intravenous doses of 10 mg VIBRAMYCIN I.V./kg/day (0.5% solution), 5 of 24 vessels used for injections evidenced degrees of thrombosis with recanalization.

Thrombosis in 3 of 6 sites occurred in 2 dogs receiving infusions of degraded VIBRAMYCIN I.V. (30 mg/kg-0.5% solution). Injection site thrombosis did not occur in 6 dogs (18 sites) receiving daily doses of 5 mg VIBRAMYCIN I.V./kg bodyweight administered as a 0.5% solution at a rate of 1 mg/kg/min (approximately 1 mL/min).

Studies to date indicate that the maximum tolerated intravenous daily dose of VIBRAMYCIN (doxycycline) I.V. in dogs for 21 consecutive days is 5 mg/kg/day when administered as a 0.5% solution at a rate of 1 mg/kg/min.
BIBLIOGRAPHY

VIBRAMYCIN/VIBRA-TABS - GENERAL


Clinical Research Reports, Medical Division, Pfizer Co. Ltd. Montreal


**VIBRAMYCIN/VIBRA-TABS IN GONORRHEA**


**VIBRAMYCIN/VIBRA-TABS IN CHLAMYDIA TRACHOMATIS AND UREAPLASMA UREALYTICUM INFECTIONS**


INFORMATION FOR THE PATIENT

Please read this leaflet carefully before you use this medication. This leaflet provides some useful information for you on VIBRAMYCIN (doxycycline hyclate capsules) and VIBRA-TABS (doxycycline hyclate film-coated tablets). If you have any questions about this medication or your condition, please ask your doctor or pharmacist.

REMEMBER: This medication is for YOU. Never give it to others. It may harm them even if their symptoms are the same as yours.

What is VIBRAMYCIN/VIBRA-TABS?

The name of this medication is VIBRAMYCIN/VIBRA-TABS. Each tablet contains 100 mg of the active ingredient doxycycline hyclate. Each tablet also contains the inactive ingredients microcrystalline cellulose, ethylcellulose, hypromellose, magnesium stearate/sodium lauryl sulfate, propylene glycol, talc, titanium dioxide, FD & C Yellow #6, and aluminum hydroxide. Each capsule contains 100 mg of the active ingredient doxycycline hyclate. Each capsule also contains the inactive ingredients microcrystalline cellulose, magnesium stearate/sodium lauryl sulfate. Capsule shell contains gelatin, sulfur dioxide, titanium dioxide and FD & C Blue #1 dye.

VIBRA-TABS tablets are flat, orange, and round-shaped.
VIBRAMYCIN capsules are blue and capsule-shaped.

What is VIBRAMYCIN/VIBRA-TABS used for?

VIBRAMYCIN/VIBRA-TABS may be prescribed by your doctor to treat bacterial infections.

When should VIBRAMYCIN/VIBRA-TABS not be used?

Do not take VIBRAMYCIN/VIBRA-TABS if:
• You are allergic to VIBRAMYCIN/VIBRA-TABS, other tetracyclines, or to any of the inactive ingredients listed at the beginning of this leaflet,
• you have myasthenia gravis (a chronic autoimmune neuromuscular disease which cause muscle weakness)
Before taking VIBRAMYCIN/VIBRA-TABS

You should tell your doctor if:

- you are pregnant, or planning to become pregnant
- you are breastfeeding your child. VIBRAMYCIN/VIBRA-TABS is not recommended in women who are breastfeeding. Tetracycline is excreted in human breastmilk.
- VIBRAMYCIN/VIBRA-TABS is prescribed for a child, and your child is under 8 years old. VIBRAMYCIN/VIBRA-TABS is not recommended for children under 8 years of age.
- you have or have had any other health problems especially:
  - you have difficulty swallowing, or medical conditions such as the narrowing or obstruction of your esophagus (passage from your mouth to stomach)
  - you are taking any other medicines, including medicines you buy without a prescription from a pharmacy, supermarket, or health food store.

Taking VIBRAMYCIN/VIBRA-TABS with other medicines

- VIBRAMYCIN and VIBRA-TABS should not be taken with alcohol, barbiturates, phenytoin, carbamazepine and methoxyflurane*
  *Methoxyflurane is not marketed in Canada

Some medicines and VIBRAMYCIN/VIBRA-TABS may interfere with each other and your doctor may wish to change dosage or directions for the following medications or may recommend other medications:

- oral anticoagulants
- penicillin
- bismuth subsalicylate
- antacids containing aluminum, calcium or magnesium reduce VIBRAMYCIN/VIBRA-TABS absorption and should not be given to patients taking VIBRAMYCIN/VIBRA-TABS
- iron-containing products should be taken at a different time than VIBRAMYCIN/VIBRA-TABS
- use of VIBRAMYCIN/VIBRA-TABS may reduce the effectiveness of oral contraceptives
How should you take VIBRAMYCIN/VIBRA-TABS?

Antibacterial drugs including VIBRAMYCIN/VIBRA-TABS should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by VIBRAMYCIN/VIBRA-TABS or other antibacterial drugs in the future.

Follow your doctor’s instructions carefully about how much VIBRAMYCIN/VIBRA-TABS to take and when to take it.

VIBRAMYCIN/VIBRA-TABS should be swallowed, preferably with food.

When should you take VIBRAMYCIN/VIBRA-TABS?

VIBRAMYCIN/VIBRA-TABS should be taken with or after a meal. This should be swallowed with a full glass of water to avoid potential irritation or ulceration of the esophagus (passage from mouth to stomach). Remain in an upright position for a time and do not go to bed right away (at least 1-2 hours), to avoid direct irritation of the esophagus.

What should you do if you forget to take your medication?

If you should forget to take your tablet or your capsule at the usual time, take it as soon as you remember unless it is time to take the next one. Continue with the remaining doses as before. Do not take more than one dose at a time.

What if you take too many tablets or capsules?

Do not take more tablets or capsules than your doctor has told you to.

If you take too many tablets or capsules by accident, call your doctor, pharmacist, local poison control centre or hospital emergency department immediately, even if there are no symptoms.
While taking VIBRAMYCIN/VIBRA-TABS

- Follow your doctor’s instructions carefully,
- Stop taking VIBRAMYCIN/VIBRA-TABS immediately if you become pregnant and consult your doctor.
- Tell your doctor and pharmacist that you are taking VIBRAMYCIN/VIBRA-TABS if you are about to start taking any new medicines.
- Do not stop taking your medicine until your doctor tells you to, even if you are feeling better.
- Do not use VIBRAMYCIN/VIBRA-TABS to treat any other medical complaints unless your doctor tells you to.

Are there any side effects with VIBRAMYCIN/VIBRA-TABS?

VIBRAMYCIN/VIBRA-TABS may cause side effects. If they occur, they are likely to be minor and temporary. However, some may be serious and need medical attention. VIBRAMYCIN/VIBRA-TABS may cause side effects such as nausea, vomiting, diarrhea, loss of appetite, abdominal pain, pain or difficulty in swallowing, tooth discolouration and rash.

Use of VIBRAMYCIN/VIBRA-TABS may increase the incidence of vaginal candidiasis (infection) and benign intracranial hypertension (high blood pressure in the brain).

Sensitivity to sunlight and development of a sunburn reaction have occurred with some individuals taking tetracyclines. If you plan to be exposed to direct sunlight, preventative use of a sunscreen or other physical measures are recommended. Avoid excessive sunlight or artificial ultraviolet exposure. Discontinue use if phototoxicity develops (e.g. skin eruption...).

Tell your doctor or pharmacist right away if you suffer from any of the following side effects while taking this medication:
- if you develop diarrhea, watery diarrhea, bloody stools, with or without stomach cramps and fever, contact your doctor as soon as possible.

Tell your doctor or pharmacist right away, and stop taking VIBRAMYCIN/VIBRA-TABS, if you suffer any of the following side effects while taking this medication
• You develop a hypersensitivity (allergic) reaction which may include symptoms such as difficulty in breathing, fast heartbeat, dizziness, itching, rash, and skin blistering.
• You develop symptoms such as swelling of the hands and feet, muscle and joint pain, and rash, as these may be signs of an auto-immune reaction.

Check with your doctor or pharmacist right away if you have any problems while taking VIBRAMYCIN/VIBRA-TABS, even if you do not think the problems are connected with the medicine or are not listed in this leaflet.

**How to store VIBRAMYCIN/VIBRA-TABS**

Store at room temperature 15°C to 30°C.

You should not use your medication after the expiration date printed on the carton and label.

*Keep all medications out of the reach of children. This medication could harm them.*