69-1940-00-3

# VIBRAMYCIN®
**doxycycline hyclate for injection**

# INTRAVENOUS
**FOR INTRAVENOUS USE ONLY**

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

## DESCRIPTION

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

## 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.

Following a single 100 mg dose administered in a concentration of 0.4 mg/mL in a one-hour infusion, normal adult volunteers average a peak of 2.5 mcg/mL, while 200 mg of a concentration of 0.4 mg/mL administered over two hours averaged a peak of 3.6 mcg/mL. Excretion of doxycycline by the kidney is about 40 percent/72 hours in individuals with normal function (creatinine clearance about 75 mL/min.). This percentage excretion may fall as low as 1-5 percent/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 this serum half-life of doxycycline.

### 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.

Resistance

Cross resistance with other tetracyclines is common.

Antimicrobial Activity

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 for VIBRAMYCIN.

**Gram-Negative Bacteria**

*Acinetobacter* species
*Bartonella bacilliformis*
*Brucella* species
*Klebsiella* species
*Klebsiella granulomatis*
*Campylobacter fetus*
*Enterobacter aerogenes*
*Escherichia coli*
*Francisella tularensis*
*Haemophilus ducreyi*
*Haemophilus influenzae*
*Neisseria gonorrhoeae*
*Shigella* species
*Vibrio cholerae*
*Yersinia pestis*

**Gram-Positive Bacteria**

*Bacillus anthracis*
*Listeria monocytogenes*
*Streptococcus pneumoniae*

**Anaerobic Bacteria**

*Clostridium* species
*Fusobacterium fusiforme*
*Propionibacterium acnes*

**Other Bacteria**

*Nocardiae* and other aerobic *Actinomyces* species
*Borrelia recurrentis*
*Chlamydophila psittaci*
*Chlamydia trachomatis*
*Mycoplasma pneumoniae*
Rickettsiae
*Treponema pallidum*
*Treponema pallidum subspecies pertenue*
*Ureaplasma urealyticum*

**Parasites**

*Balantidium coli*

*Entamoeba* species
*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 Testing Methods**
When available, the clinical microbiology laboratory should provide cumulative reports of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

**Dilution Techniques**
Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized test method[1,2,4] (broth or agar). The MIC values should be interpreted according to criteria provided in Table 1.

**Diffusion Techniques**
Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[1,3,4] This procedure uses paper disks impregnated with 30-µg doxycycline to test the susceptibility of microorganisms to doxycycline. The disk diffusion interpretive criteria are provided in Table 1.

**Anaerobic Techniques**
For anaerobic bacteria, the susceptibility to doxycycline can be determined by a standardized test method[5]. The MIC values obtained should be interpreted according to the criteria provided in Table 1.

**Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline**

| **Bacteria[a]** | **Minimal Inhibitory Concentration (mcg/mL)** | | | **Zone Diameter (mm)** | | | **Agar Dilution (mcg/mL)** | | |
|---|---|---|---|---|---|---|---|---|---|
| | **S** | **I** | **R** | **S** | **I** | **R** | **S** | **I** | **R** |
| *Acinetobacter* spp. | | | | | | | | | |
| Doxycycline | ≤4 | 8 | ≥16 | ≥13 | 10–12 | ≤9 | - | - | - |
| Tetracycline | ≤4 | 8 | ≥16 | ≥15 | 12–14 | ≤11 | - | - | - |
| Anaerobes | | | | | | | | | |
| Tetracycline | - | - | - | - | - | - | ≤4 | 8 | ≥16 |
| *Bacillus anthracis*[b] | | | | | | | | | |

| Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Bacteria[a]** | **Minimal Inhibitory Concentration (mcg/mL)** | | | **Zone Diameter (mm)** | | | **Agar Dilution (mcg/mL)** | | |
| | **S** | **I** | **R** | **S** | **I** | **R** | **S** | **I** | **R** |
| Doxycycline | ≤1 | - | - | - | - | - | - | - | - |
| Tetracycline | ≤1 | - | - | - | - | - | - | - | - |
| *Brucella* species[b] | | | | | | | | | |
| Doxycycline | ≤1 | - | - | - | - | - | - | - | - |
| Tetracycline | ≤1 | - | - | - | - | - | - | - | - |
| *Enterobacteriaceae* | | | | | | | | | |
| Doxycycline | ≤4 | 8 | ≥16 | ≥14 | 11–13 | ≤10 | - | - | - |
| Tetracycline | ≤4 | 8 | ≥16 | ≥15 | 12–14 | ≤11 | - | - | - |
| *Franciscella tularensis*[b] | | | | | | | | | |
| Doxycycline | ≤4 | - | - | - | - | - | - | - | - |
| Tetracycline | ≤4 | - | - | - | - | - | - | - | - |
| *Haemophilus influenzae* | | | | | | | | | |
| Tetracycline | ≤2 | 4 | ≥8 | ≥29 | 26–28 | ≤25 | - | - | - |
| *Mycoplasma pneumoniae*[b] | | | | | | | | | |
| Tetracycline | - | - | - | - | - | - | ≤2 | - | - |
| *Nocardiae* and other aerobic *Actinomyces* species[b] | | | | | | | | | |
| Doxycycline | ≤1 | 2-4 | ≥8 | - | - | - | - | - | - |
| *Neisseria gonorrhoeae*[c] | | | | | | | | | |
| Tetracycline | - | - | - | ≥38 | 31–37 | ≤30 | ≤0.25 | 0.5-1 | ≥2 |
| *Streptococcus pneumoniae* | | | | | | | | | |
| Doxycycline | ≤0.25 | 0.5 | ≥1 | ≥28 | 25–27 | ≤24 | - | - | - |
| Tetracycline | ≤1 | 2 | ≥4 | ≥28 | 25–27 | ≤24 | - | - | - |
| *Vibrio cholerae* | | | | | | | | | |
| Doxycycline | ≤4 | 8 | ≥16 | - | - | - | - | - | - |
| Tetracycline | ≤4 | 8 | ≥16 | - | - | - | - | - | - |
| *Yersinia pestis* | | | | | | | | | |
| Doxycycline | ≤4 | 8 | ≥16 | - | - | - | - | - | - |
| Tetracycline | ≤4 | 8 | ≥16 | - | - | - | - | - | - |
| *Ureaplasma urealyticum* | | | | | | | | | |
| Tetracycline | - | - | - | - | - | - | ≤1 | - | ≥2 |

[a] Organisms susceptible to tetracycline are also considered susceptible to doxycycline. However, some

| Table 1: Susceptibility Test Interpretive Criteria for Doxycycline and Tetracycline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Bacteria[a]** | **Minimal Inhibitory Concentration (mcg/mL)** | | | **Zone Diameter (mm)** | | | **Agar Dilution (mcg/mL)** | | |
| | **S** | **I** | **R** | **S** | **I** | **R** | **S** | **I** | **R** |
| organisms that are intermediate or resistant to tetracycline may be susceptible to doxycycline.<br>[b] The current absence of resistance isolates precludes defining any results other than "Susceptible". If isolates yielding MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.<br>[c] Gonococci with 30 mcg tetracycline disk zone diameters of <19 mm usually indicate a plasmid-mediated tetracycline resistant *Neisseria gonorrhoeae* isolate. Resistance in these strains should be confirmed by a dilution test (MIC ≥16 mcg/mL). | | | | | | | | | |

A report of Susceptible (S) indicates that the antimicrobial drug is likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentration usually achievable at the site of infection. A report of *Intermediate* (I) indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug product is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of *Resistan*t (R) indicates that the antimicrobial drug is not likely to inhibit growth of the microorganism if the antimicrobial drug reaches the concentrations usually achievable at the infection site; other therapy should be selected.

**Quality Control**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of the supplies and reagents used in the assay, and the techniques of the individuals performing the test[1,2,3,4,5,6,7]. Standard doxycycline and tetracycline powders should provide the following range of MIC values noted in Table 2. For the diffusion technique using the 30 mcg doxycycline disk the criteria noted in Table 2 should be achieved.

| Table 2: Acceptable Quality Control Ranges for Susceptibility Testing for Doxycycline and Tetracycline | | | |
|---|---|---|---|
| **QC Strain** | **Minimal Inhibitory Concentration (mcg/mL)** | **Zone Diameter (mm)** | **Agar Dilution (mcg/mL)** |
| *Enterococcus faecalis ATCC 29212* | | | |
| Doxycycline | 2-8 | - | - |
| Tetracycline | 8-32 | - | - |
| *Escherichia coli ATCC 25922* | | | |
| Doxycycline | 0.5–2 | 18-24 | - |
| Tetracycline | 0.5-2 | 18-25 | - |
| *Eggerthella lenta ATCC 43055* | | | |
| Doxycycline | 2-16 | - | - |
| *Haemophilus influenzae ATCC 49247* | | | |
| Tetracycline | 4-32 | 14-22 | - |
| *Neisseria gonorrhoeae ATCC 49226* | | | |
| Tetracycline | - | 30-42 | 0.25-1 |
| *Staphylococcus aureus ATCC 25923* | | | |
| Doxycycline | - | 23-29 | - |
| Tetracycline | - | 24-30 | - |
| *Staphylococcus aureus ATCC 29213* | | | |
| Doxycycline | 0.12-0.5 | - | - |
| Tetracycline | 0.12-1 | - | - |
| *Streptococcus pneumoniae ATCC 49619* | | | |
| Doxycycline | 0.015–0.12 | 25-34 | - |
| Tetracycline | 0.06–0.5 | 27-31 | - |
| *Bacteroides fragilis ATCC 25285* | | | |
| Tetracycline | - | - | 0.12–0.5 |
| *Bacteroides thetaiotaomicron ATCC 29741* | | | |
| Doxycycline | 2–8 | - | - |
| Tetracycline | - | - | 8–32 |
| *Mycoplasma pneumoniae ATCC 29342* | | | |
| Tetracycline | 0.06-0.5 | - | 0.06-0.5 |
| *Ureaplasma urealyticum ATCC 33175* | | | |
| Tetracycline | - | - | ≥8 |

## INDICATIONS

To reduce the development of drug-resistant bacteria and maintain effectiveness of Vibramycin and other antibacterial drugs, Vibramycin 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 or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Doxycycline is indicated in infections caused by the following microorganisms:

Rickettsiae (Rocky Mountain spotted fever, typhus fever, and the typhus group, Q fever, rickettsialpox and tick fevers).
*Mycoplasma pneumoniae* (PPLO, Eaton Agent).
Agents of psittacosis and ornithosis.
Agents of lymphogranuloma venereum and granuloma inguinale.
The spirochetal agent of relapsing fever (*Borrelia recurrentis*).

The following gram-negative microorganisms:

*Haemophilus ducreyi* (chancroid),
*Yersinia pestis*
*Francisella tularensis*,
*Bartonella bacilliformis*,
*Bacteroides* species,
*Vibrio cholerae* and
*Campylobacte fetus*,
*Brucella* species (in conjunction with streptomycin).

Because many strains of the following groups of microorganisms have been shown to be resistant to tetracyclines, 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*,
*Shigella* species,
*Acinetobacter* species,
*Haemophilus influenzae* (respiratory infections),
*Klebsiella* species (respiratory and urinary infections).

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

Streptococcus species:

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 for streptococcal disease unless the organism has been demonstrated to be sensitive.

For upper respiratory infections due to group A beta-hemolytic streptococci, penicillin is the usual drug of choice, including prophylaxis of rheumatic fever.

*Streptococcus pneumoniae*,
*Staphylococcus aureus*, respiratory skin and soft tissue infections. Tetracyclines are not the drugs of choice in the treatment of any type of staphylococcal infections.

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 infections due to:

*Neisseria gonorrhoeae* and *N. meningitidis*,
*Treponema pallidum* and *Treponema pallidum* subspecies *pertenue* (syphilis and yaws),
*Listeria monocytogenes*,
*Clostridium* species,
*Fusobacterium fusiforme* (Vincent's infection),
*Actinomyces* species.

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

Doxycycline is indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

## 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. Use doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies.

*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Vibramycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following the use of antibacterial drugs. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing use of antibacterial drugs not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Severe skin reactions, such as exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in patients receiving doxycycline. (See ADVERSE REACTIONS.) If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

Intracranial hypertension (IH, pseudotumor cerebri) has been associated with the use of tetracyclines including Vibramycin. Clinical manifestations of IH include headache, blurred vision, diplopia, and vision loss; papilledema can be found on fundoscopy. Women of childbearing age who are overweight or have a history of IH are at greater risk for developing tetracycline associated IH. Concomitant use of isotretinoin and Vibramycin should be avoided because isotretinoin is also known to cause pseudotumor cerebri.

Although IH typically resolves after discontinuation of treatment, the possibility for permanent visual loss exists. If visual disturbance occurs during treatment, prompt ophthalmologic evaluation is warranted. Since intracranial pressure can remain elevated for weeks after drug cessation patients should be monitored until they stabilize.

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.

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.

## PRECAUTIONS

### General

As with other antibacterial drugs, use of Vibramycin may result in overgrowth of nonsusceptible organisms, including fungi. If superinfection occurs, Vibramycin should be discontinued and appropriate therapy instituted.

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

Prescribing Vibramycin in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

All infections due to group A beta-hemolytic streptococci should be treated for at least 10 days.

### Information For Patients

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

Patients should be counseled that antibacterial drugs, including Vibramycin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Vibramycin is prescribed to treat a bacterial infection, patients should be told that 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 or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial drugs, which usually ends when the antibacterials are discontinued. Sometimes after starting treatment with antibacterial drugs, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the

antibacterial drug. If this occurs, patients should contact their physician as soon as possible.

**Laboratory Tests**
In venereal diseases 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 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 tetracycline in conjunction with penicillin.

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.

**Usage in Pregnancy**
(See WARNINGS about use during tooth development.)

Vibramycin Intravenous has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, it is essential for the welfare of the patient.

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 in Children**
The use of Vibramycin Intravenous in children under 8 years is not recommended because safe conditions for its use have not been established. Because of the effects of drugs of the tetracycline-class on tooth development and growth, use doxycycline in pediatric patients 8 years of age or less only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g., anthrax, Rocky Mountain spotted fever), particularly when there are no alternative therapies. (See WARNINGS and DOSAGE AND ADMINISTRATION.)

As with other tetracyclines, doxycycline 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 6 hours. This reaction was shown to be reversible when the drug was discontinued.

Tetracyclines are present in the milk of lactating women who are taking a drug in this class.

## ADVERSE REACTIONS

Gastrointestinal: anorexia, nausea, vomiting, diarrhea, glossitis, dysphagia, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, and pancreatitis. Hepatotoxicity has been reported rarely. These reactions have been caused by both the oral and parenteral administration of tetracyclines. Superficial discoloration of the adult permanent dentition, reversible upon drug discontinuation and professional dental cleaning has been reported. Permanent tooth discoloration and enamel hypoplasia may occur with drugs of the tetracycline class when used during tooth development. (See WARNINGS.)

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.)

Immune: Hypersensitivity reactions including urticaria, angioneurotic edema, anaphylaxis, anaphylactoid purpura, pericarditis, exacerbation of systemic lupus erythematosus, and drug reaction with eosinophilia and systemic symptoms (DRESS).

Other: Bulging fontanels in infants and intracranial hypertension in adults. (See WARNINGS.)

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

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

## DOSAGE AND ADMINISTRATION

Note: Rapid administration is to be avoided. Parenteral therapy is indicated only when oral therapy is not indicated. Oral therapy should be instituted as soon as possible. If intravenous therapy is given over prolonged periods of time, thrombophlebitis may result.

The usual dosage and frequency of administration of Vibramycin I.V. (100-200 mg/day) differs from that of the other tetracyclines (1-2 g/day). Exceeding the recommended dosage may result in an increased incidence of side effects.

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

Adults:

The usual dosage of Vibramycin I.V. is 200 mg on the first day of treatment administered in one or two infusions. Subsequent daily dosage is 100 to 200 mg depending upon the severity of infection, with 200 mg administered in one or two infusions.

In the treatment of primary and secondary syphilis, the recommended dosage is 300 mg daily for at least 10 days.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 100 mg of doxycycline, twice a day. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

Pediatric Patients:

For all pediatric patients weighing less than 45 kg with severe or life-threatening infections (e.g., anthrax, Rocky Mountain spotted fever), the recommended dosage is 2.2 mg/kg of body weight administered every 12 hours. Children weighing 45 kg or more should receive the adult dose. (See WARNINGS and PRECAUTIONS.)

For pediatric patients with less severe disease (greater than 8 years of age and weighing less than 45 kg), the recommended dosage schedule is 4.4 mg/kg of body weight divided into two doses on the first day of treatment, followed by a maintenance dose of 2.2 mg/kg of body weight (given as a single daily dose or divided into twice daily doses). For pediatric patients weighing over 45 kg, the usual adult dose should be used.

In the treatment of inhalational anthrax (post-exposure) the recommended dose is 2.2 mg/kg of body weight, twice a day in children weighing less than 45 kg. Parenteral therapy is only indicated when oral therapy is not indicated and should not be continued over a prolonged period of time. Oral therapy should be instituted as soon as possible. Therapy must continue for a total of 60 days.

General: The duration of infusion may vary with the dose (100 to 200 mg per day), but is usually one to four hours. A recommended minimum infusion time for 100 mg of a 0.5 mg/mL solution is one hour. Therapy should be continued for at least 24-48 hours after symptoms and fever have subsided. The therapeutic antibacterial serum activity will usually persist for 24 hours following recommended dosage.

Intravenous solutions should not be injected intramuscularly or subcutaneously. Caution should be taken to avoid the inadvertent introduction of the intravenous solution into the adjacent soft tissue.

## PREPARATION OF SOLUTION

To prepare a solution containing 10 mg/mL, the contents of the vial should be reconstituted with 10 mL (for the 100 mg/vial container) or 20 mL (for the 200 mg/vial container) of Sterile Water for Injection or any of the ten intravenous infusion solutions listed below. Each 100 mg of Vibramycin (i.e., withdraw entire solution from the 100 mg vial) is further diluted with 100 mL to 1000 mL of the intravenous solutions listed below. Each 200 mg of Vibramycin (i.e., withdraw entire solution from the 200 mg vial) is further diluted with 200 mL to 2000 mL of the following intravenous solutions:

1. Sodium Chloride Injection, USP
2. 5% Dextrose Injection, USP
3. Ringer's Injection, USP
4. Invert Sugar, 10% in Water
5. Lactated Ringer's Injection, USP
6. Dextrose 5% in Lactated Ringer's
7. Normosol-M® in D5-W (Abbott)
8. Normosol-R® in D5-W (Abbott)
9. Plasma-Lyte® 56 in 5% Dextrose (Travenol)
10. Plasma-Lyte® 148 in 5% Dextrose (Travenol)

This will result in desired concentrations of 0.1 to 1.0 mg/mL. Concentrations lower than 0.1 mg/mL or higher than 1.0 mg/mL are not recommended.

**Stability**

Vibramycin IV is stable for 48 hours in solution when diluted with Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, to concentrations between 1.0 mg/mL and 0.1 mg/mL and stored at 25°C. Vibramycin IV in these solutions is stable under fluorescent light for 48 hours, but must be protected from direct sunlight during storage and infusion. Reconstituted solutions (1.0 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

Vibramycin IV, when diluted with Ringer's Injection, USP, or Invert Sugar, 10% in Water, or Normosol-M® in D5-W (Abbott), or Normosol-R® in D5-W (Abbott), or Plasma-Lyte® 56 in 5% Dextrose (Travenol), or Plasma-Lyte® 148 in 5% Dextrose (Travenol) to a concentration between 1.0 mg/mL and 0.1 mg/mL, must be completely infused within 12 hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Reconstituted solutions (1.0 to 0.1 mg/mL) may be stored up to 72 hours prior to start of infusion if refrigerated and

protected from sunlight and artificial light. Infusion must then be completed within 12 hours. Solutions must be used within these time periods or discarded.

When diluted with Lactated Ringer's Injection, USP, or Dextrose 5% in Lactated Ringer's, infusion of the solution (ca. 1.0 mg/mL) or lower concentrations (not less than 0.1 mg/mL) must be completed within six hours after reconstitution to ensure adequate stability. During infusion, the solution must be protected from direct sunlight. Solutions must be used within this time period or discarded.

Solutions of Vibramycin (doxycycline hyclate for injection) at a concentration of 10 mg/mL in Sterile Water for Injection, when frozen immediately after reconstitution are stable for 8 weeks when stored at –20°C. If the product is warmed, care should be taken to avoid heating it after the thawing is complete. Once thawed the solution should not be refrozen.

## HOW SUPPLIED

Vibramycin (doxycycline hyclate for injection) Intravenous is available as a sterile powder in a vial containing doxycycline hyclate equivalent to 100 mg of doxycycline with 480 mg of ascorbic acid; packages of 5 (0049-0960-77), and in individually packaged vials containing doxycycline hyclate equivalent to 200 mg of doxycycline with 960 mg of ascorbic acid (0049-0980-81).

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This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.


LAB-0075-7.0
Revised: July 2017