VIBRAMYCIN®
(Doxycycline)

1. NAME OF THE MEDICINAL PRODUCT

VIBRAMYCIN®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline and is available as doxycycline calcium, doxycycline hydrochloride, doxycycline monohydrate and doxycycline hyclate (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. Doxycycline will not degrade into an epianhydro form.

3. PHARMACEUTICAL FORM

VIBRAMYCIN® is available as:

Capsules containing 100 mg of doxycycline as the hyclate salt.

Film-coated tablets containing 100 mg of doxycycline as the hyclate salt.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Treatment

VIBRAMYCIN® is indicated for treatment of the following infections:

Rocky Mountain spotted fever, typhus fever and the typhus group;

Q fever, rickettsialpox and tick fevers caused by *Rickettsiae*;

Respiratory infections caused by *Mycoplasma pneumoniae*;

Psittacosis caused by *Chlamydia psittaci*;

Lymphogranuloma venereum, caused by *Chlamydia trachomatis*;

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

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

Inclusion conjunctivitis caused by *Chlamydia trachomatis* may be treated with oral doxycycline alone or with a combination of topical agents;

Acute epididymo-orchitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*;

Granuloma inguinale (donovanosis) caused by *Calymmatobacterium granulomatis*;

Early (Stage 1 and 2) Lyme disease caused by *Borrelia burgdorferi*;

Louse-borne relapsing fever caused by *Borrelia recurrentis*;

Tick-borne relapsing fever caused by *Borrelia duttonii*;

Non-gonococcal urethritis (NGU) caused by *Ureaplasma urealyticum (T-Mycoplasma*).

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

Acinetobacter species;

Bacteroides species;

Fusobacterium species;

Brucellosis caused by *Brucella* species (in conjunction with streptomycin);

Plague caused by *Yersinia pestis*;

Tularemia caused by *Francisella tularensis*;

Bartonellosis caused by *Bartonella bacilliformis*;

Campylobacter fetus.

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

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

Shigella species;

Uncomplicated gonorrhea caused by *Neisseria gonorrhoeae*;

Respiratory infections caused by *Haemophilus influenzae*;

Respiratory and urinary infections caused by *Klebsiella* species;

Escherichia coli;

Enterobacter aerogenes;

Moraxella catarrhalis.

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

Streptococcus species: A certain percentage of strains of *Streptococcus pyogenes* and *Streptococcus faecalis* have been found to be resistant to tetracycline drugs. Tetracyclines should not be used for streptococcal infections unless the organism has been demonstrated to be sensitive.

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

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

Upper respiratory tract infections caused by *Streptococcus pneumoniae*;

Respiratory, skin and soft-tissue infections caused by *Staphylococcus aureus*. Tetracyclines are not the drug of choice in the treatment of staphylococcal infections.

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

Actinomycosis caused by *Actinomyces* species;

Infections caused by *Clostridium* species;

Syphilis caused by *Treponema pallidum* and yaws caused by *Treponema pertenue*;

Listeriosis caused by *Listeria monocytogenes*;

Vincent's infection (acute necrotizing ulcerative gingivitis) caused by *Leptotrichia buccalis* (formerly, *Fusobacterium fusiform*).

Adjunctive treatment

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

In severe acne caused by *acne vulgaris*, doxycycline may be useful adjunctive therapy.

Treatment and Prophylaxis

VIBRAMYCIN® is indicated for the prophylaxis and treatment of the following infections:

Malaria caused by *Plasmodium falciparum* (in areas with chloroquine-resistant *P. falciparum*).

Leptospirosis caused by genus *Leptospira*.

Cholera caused by *Vibrio cholerae.*

Prophylaxis

VIBRAMYCIN® is indicated as prophylaxis in the following conditions:

Scrub typhus caused by *Rickettsia tsutsugamushi*;

Traveler's diarrhea caused by enterotoxigenic *Escherichia coli*.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

Dosage

It must be remembered that the usual dosage and frequency of administration of VIBRAMYCIN® differs from that of most other tetracyclines. Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued at least 24 to 48 hours after symptoms and fever have subsided. When used in streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis.

The usual dose of VIBRAMYCIN® in adults is 200 mg on the first day of treatment (administered as a single dose or as 100 mg every 12 hours) followed by a maintenance dose of 100 mg/day (administered as a single dose or as 50 mg every 12 hours). In the management of more severe infections (particularly chronic infections of the urinary tract), 200 mg daily should be given throughout the treatment period.

For children above 8 years of age: The recommended dosage schedule for children weighing 45 kg or less is 4.4 mg/kg of body weight (given as a single daily dose or divided into two doses on the first day of treatment), followed by 2.2 mg/kg of body weight (given as a single daily dose or divided into two doses), on subsequent days. For more severe infections, up to 4.4 mg/kg of body weight may be used. For children over 45 kg, the usual adult dose should be used (see section **4.4 Special Warnings and Precautions for Use:** Use in Children).

Tick- and louse-borne relapsing fevers and louse-borne typhus have been successfully treated with a single oral dose of 100 or 200 mg, according to severity. As an alternative to reduce the risk of persistence or relapse of tick-borne relapsing fever, doxycycline 100 mg every 12 hours for seven days is recommended.

Early Lyme disease (Stage 1 and 2): VIBRAMYCIN® 100 mg orally twice daily for 14-60 days, according to clinical signs, symptoms and response.

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

Acute epididymo-orchitis caused by *C. trachomatis* or *N. gonorrhoeae*: Ceftriaxone 250 mg IM or other appropriate cephalosporin in a single dose, plus doxycycline 100 mg by mouth twice daily for 10 days.

Non-gonococcal urethritis (NGU) caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg, by mouth, twice daily for seven days.

Lymphogranuloma venereum caused by *Chlamydia trachomatis*: VIBRAMYCIN® 100 mg orally twice daily for a minimum of 21 days.

Uncomplicated gonococcal infections of the cervix, rectum or urethra where gonococci remain fully sensitive: VIBRAMYCIN® 100 mg by mouth twice daily for seven days plus co-treatment with an appropriate cephalosporin or quinolone is recommended, such as the following: Cefixime 400 mg orally in a single dose or Ceftriaxone 125 mg intramuscularly (IM) in a single dose or Ciprofloxacin 500 mg orally in a single dose or Ofloxacin 400 mg orally in a single dose.

Uncomplicated gonococcal infections of the pharynx, where gonococci remain fully sensitive: VIBRAMYCIN® 100 mg by mouth twice daily for seven days, plus co-treatment with an appropriate cephalosporin or quinolone is recommended, such as the following: Ceftriaxone 125 mg IM in a single dose or Ciprofloxacin 500 mg orally in a single dose or Ofloxacin 400 mg orally in a single dose.

Primary and secondary syphilis: Non-pregnant penicillin-allergic patients who have primary or secondary syphilis can be treated with the following regimen: VIBRAMYCIN® 100 mg orally twice daily for two weeks, as an alternative to penicillin therapy.

Latent and tertiary syphilis: Non-pregnant penicillin-allergic patients who have tertiary or secondary syphilis can be treated with the following regimen: VIBRAMYCIN® 100 mg orally twice daily for two weeks, as an alternative to penicillin therapy if the duration of the infection is known to have been less than one year. Otherwise, doxycycline should be administered for four weeks.

Acute pelvic inflammatory disease (PID):

Inpatient: VIBRAMYCIN® 100 mg every 12 hours, plus cefoxitin 2 g IV every 6 hours or cefotetan 2 g IV every 12 hours for at least four days and at least 24 to 48 hours after patient improves. Then continue doxycycline 100 mg by mouth twice daily to complete 14 days total therapy.

Out-Patient: VIBRAMYCIN® 100 mg by mouth twice daily for 14 days as adjunctive therapy with Ceftriaxone 250 mg IM once or Cefoxitin 2 g IM, plus probenecid 1 g orally in a single dose concurrently once, or other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime).

Acne Vulgaris: 50-100 mg daily for up to 12 weeks.

For treatment of chloroquine-resistant falciparum malaria: 200 mg daily for at least seven days. Due to the potential severity of the infection, a rapid-acting schizonticide such as quinine should always be given in conjunction with doxycycline; quinine dosage recommendations vary in different areas.

For prophylaxis of malaria: 100 mg daily in adults; for children over 8 years of age the dose is 2 mg/kg given once daily up to the adult dose. Prophylaxis can begin 1-2 days before travel to malarious areas. It should be

continued daily during travel in the malarious areas and for four weeks after the traveler leaves the malarious area.

For the treatment and selective prophylaxis of cholera in adults: 300 mg in a single dose.

For the prevention of scrub typhus: 200 mg as a single oral dose.

For the prevention of traveler's diarrhea in adults: 200 mg on the first day of travel (administered as a single dose or as 100 mg every 12 hours) followed by 100 mg daily throughout the stay in the area. Data on the use of the drug prophylactically are not available beyond 21 days.

For the prevention of Leptospirosis: 200 mg orally on a weekly basis throughout the stay in the area and 200 mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

For the treatment of Leptospirosis: 100 mg orally twice daily for seven days.

Inhalational anthrax (post-exposure):

ADULTS: 100 mg of doxycycline, by mouth, twice a day for 60 days.

CHILDREN: weighing less than 45 kg; 2.2 mg/kg of body weight, by mouth, twice a day for 60 days. Children weighing 45 kg or more should receive the adult dose (see section **4.4 Special Warnings and Precautions for Use:** Use in Children).

Rocky Mountain spotted fever:

Doxycycline is the first line treatment for adults and children of all ages:

ADULTS: 100 mg every 12 hours.

CHILDREN: weighing less than 45 kg: 2.2 mg/kg body weight given twice a day. Children weighing 45 kg or more should receive the adult dose (see section 4.4 **Special Warnings and Precautions for Use**: Use in Children).

Patients should be treated for at least 3 days after the fever subsides and until there is evidence of clinical improvement. Minimum course of treatment is 5-7 days.[11,12]

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

Administration

Capsules and film-coated tablets: Administration of adequate amounts of fluid along with capsule and tablet forms of drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.

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

4.3. CONTRAINDICATIONS

This drug is contraindicated in persons who have shown hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Use in Children

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 six hours. This reaction was shown to be reversible when the drug was discontinued.

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 discolouration of the teeth (yellow-grey-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.[7]

General

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 section **4.8 Undesirable effects**). If severe skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.[8]

Benign intracranial hypertension (pseudotumor cerebri) has been associated with the use of tetracyclines including doxycycline. Benign intracranial hypertension (pseudotumor cerebri) is usually transient, however cases of permanent visual loss secondary to benign intracranial hypertension (pseudotumor cerebri) have been reported with tetracyclines including doxycycline. 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. Concomitant use of isotretinoin and doxycycline should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri).[3]

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including doxycycline, and has ranged in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including doxycycline, 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 antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms, including fungi. Constant observation of the patient is essential. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

Instances of esophagitis and esophageal ulcerations have been reported in patients receiving capsule and tablet forms of drugs in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed.

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.

Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

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

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines, including doxycycline. Patients likely 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.

When treating venereal disease when co-existent syphilis is suspected, proper diagnostic procedures, including dark-field examinations, should be utilized. In all such cases monthly serological tests should be made for at least four months.

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

Information for Patients

All patients taking doxycycline should be advised:

- To avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline and to discontinue therapy if phototoxicity (e.g., skin eruption, etc.) occurs. Sunscreen or sunblock should be considered.
- To drink fluids liberally along with doxycycline to reduce the risk of esophageal irritation and ulceration.
- That the absorption of tetracyclines is reduced when taking bismuth subsalicylate.
- That the use of doxycycline might increase the incidence of vaginal candidiasis.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. 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.

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

Absorption of tetracyclines is impaired by antacids containing aluminum, calcium, magnesium or other drugs containing these cations, iron-containing preparations and bismuth salts.

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

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

Concurrent use of tetracyclines may render oral contraceptives less effective.

Laboratory Test Interactions

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

4.6. FERTILITY, PREGNANCY AND LACTATION

Use in Pregnancy

Doxycycline has not been studied in pregnant patients. It should not be used in pregnant women unless, in the judgment of the physician, the potential benefit outweighs the risk (see section **4.4 Special Warnings and Precautions for Use:** Use in Children).

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.

Lactation

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 six hours. This reaction was shown to be reversible when the drug was discontinued (see section **4.4 Special Warnings and Precautions for Use:** Use in Children).

Doxycycline should be avoided in nursing mothers, as tetracyclines including doxycycline are present in the milk of lactating women who are taking a drug of this class.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effect of doxycycline on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that doxycycline may affect these abilities.

4.8. UNDESIRABLE EFFECTS

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline.

Adverse Drug Reaction Table[1,3,4,5,6,13,14]	
System Organ Class	**Adverse Drug Reactions**
Blood and lymphatic system disorders	Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction,[9,10] angioedema, exacerbation of systemic lupus erythematosus, pericarditis, serum sickness, Henoch-Schonlein purpura, hypotension, dyspnoea, tachycardia, peripheral oedema and urticaria), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Jarisch-Herxheimer reaction[b]
Endocrine disorders	Brown-black microscopic discolouration of thyroid glands
Metabolism and nutrition disorders	Decreased appetite
Nervous system disorders	Benign intracranial hypertension (pseudotumor cerebri), fontanelle bulging, headache
Ear and labyrinth disorders	Tinnitus
Vascular disorders	Flushing
Gastrointestinal disorders	Pancreatitis, pseudomembranous colitis, *Clostridium difficile* colitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, nausea/vomiting, dyspepsia (heartburn/gastritis), glossitis, tooth discolouration[a,7,10]
Hepatobiliary disorders	Hepatotoxicity, hepatitis, hepatic function abnormal
Skin and subcutaneous tissue disorders	Toxic epidermal necrolysis, Stevens-Johnson Syndrome, erythema multiforme, dermatitis exfoliative, photosensitivity reaction, skin hyperpigmentation[c], photoonycholysis, rash including maculopapular and erythematous rashes
Musculoskeletal and connective tissue disorders	Arthralgia, myalgia
Renal and urinary disorders	Blood urea increased
[a] Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline [b] in the setting of spirochete infections treated with doxycycline. [c] with chronic use of doxycycline	

4.9. OVERDOSE

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

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

Gram-Negative Bacteria

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

Bacteroides species

Bartonella bacilliformis

Brucella species

Calymmatobacterium granulomatis

Campylobacter fetus

Enterobacter aerogenes

Escherichia coli

Francisella tularensis (formerly *Pasteurella tularensis*)

Haemophilus ducreyi

Haemophilus influenzae

Klebsiella species

Moraxella catarrhalis

Neisseria gonorrhoeae

Shigella species

Vibrio cholera (formerly *Vibrio comma*)

Yersinia Pestis (formerly *Pasteurella pestis*)

Gram-Positive Bacteria

Alpha-hemolytic streptococci (viridans groups)

Enterococcus groups (*S. faecalis* and *S. faecium*)

Streptococcus pneumoniae

Streptococcus pyogenes

Other Microorganisms

Actinomyces species

Bacillus anthracis

Balantidium coli

Borrelia burgdorferi

Borrelia duttonii

Borrelia recurrentis

Chlamydia psittaci

Chlamydia trachomatis

Clostridium species

Entamoeba species

Fusobacterium species

Leptotrichia buccalis (formerly *Fusobacterium fusiforme*)

Leptospira species

Listeria monocytogenes

Mycoplasma pneumoniae

Plasmodium falciparum (asexual erythrocytic forms only)

Propionibacterium acnes

Rickettsiae

Treponema pallidum

Treponema pertenue

Ureaplasma urealyticum

5.2. PHARMACOKINETIC PROPERTIES

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degree. They are concentrated by the liver in the bile, and excreted in the urine and feces at high concentrations and in a biologically active form. Doxycycline is virtually completely absorbed after oral administration. Studies reported to date indicate that the absorption of doxycycline, unlike certain other tetracyclines, is not notably influenced by the ingestion of food or milk.

Following a 200 mg dose, normal adult volunteers averaged peak serum levels of 2.6 µg/ml of doxycycline at two hours, decreasing to 1.45 µg/ml at 24 hours. 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). Studies 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.

Children and Adolescents (2 to 18 years of age)

Population pharmacokinetic analysis of sparse concentration-time data of doxycycline following standard of care intravenous (IV) and oral dosing in 44 pediatric patients (2-18 years of age) showed that allometrically-scaled clearance (CL) of doxycycline in pediatric patients ≥2 to ≤8 years of age (median [range] 3.58 [2.27-10.82] L/h/70 kg, N=11) did not differ significantly from pediatric patients >8 to 18 years of age (3.27 [1.11-8.12] L/h/70 kg, N=33). For pediatric patients weighing ≤45 kg, body weight normalized doxycycline CL in those ≥2 to ≤8 years of age (median [range] 0.071 [0.041-0.202] L/kg/h, N=10) did not differ significantly from those >8 to 18 years of age (0.081 [0.035-0.126] L/kg/h, N=8). In pediatric patients weighing >45 kg, no clinically significant differences in body weight normalized doxycycline CL were observed between those ≥2 to ≤8 years (0.050 L/kg/h, N=1) and those >8 to 18 years of age (0.044 [0.014-0.121] L/kg/h, N=25). No clinically significant difference in CL between oral and IV dosing was observed in the small cohort of pediatric patients who received the oral (N=19) or IV (N=21) formulation alone.[15]

5.3. PRECLINICAL SAFETY DATA

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, oxytetracyline).

Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Tablets: Microcystalline Cellulose. Magnesium Stearate, Sodium Lauryl Sulphate, Methyl Alcohol, Isopropyl Alcohol, Ethyl Cellulose, Hydroxy Propyl Methyl Cellulose, Propylene Glycol, Titanium Dioxide, Talc, FD&C Yellow No. 6

Capsules: Corn Starch, Lactose, Alginic Acid, Magnesium Stearate, Sodium Lauryl Sulphate

6.2. INCOMPATIBILITIES

Not available

6.3. SHELF LIFE

Please see pack for expiry of product.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store in a dry place at room temperature.
Avoid exposure to heat and sunlight.

6.5. NATURE AND CONTENTS OF CONTAINER

VIBRAMYCIN® 100 mg capsules are available in the pack of 120s.
VIBRAMYCIN® 100 mg tablets are available in the pack of 30s.

Vibramycin/LPD/PK-06
According to CDS V 12 dated: June 15, 2020; Supersedes CDS V 11 dated: February 16, 2018

Marketed By
Pfizer Pakistan Limited

*Please visit our website **www.pfizerpro.com.pk** for latest version of Product leaflet.*

7. REFERENCES

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2. Report of CIOMS Working Groups III and V, Guidelines for Preparing Core Clinical-Safety Information on Drugs, Second Edition.
3. 2 5 Clinical Overview: To support updates to section 4.4 and section 4.8 of the doxycycline Core Data Sheets with addition of text regarding benign intracranial hypertension, August 2015.
4. 2 5 Clinical Overview: To support adverse drug reaction frequency and category updates to

doxycycline Core Data Sheets, August 2015.

5. 2.5 Clinical Overview: To support the addition of adverse drug reaction Pancreatitis to section 4.8 Undesirable Effects of the Core Data Sheets, December 2015.

6. 2.5 Clinical Overview: To support updates to the adverse drug reaction frequency and category tables of the Core Data Sheets (addition of pancreatitis), December 2015.

7. 2.5 Clinical Overview: To Support the Revision of the Warning about Tooth Discolouration among Children in Section 4.4, Special Warnings and Special Precautions for Use and the Addition of Adverse Drug Reaction Tooth Discolouration to Section 4.8, Undesirable Effects of the Core Data Sheets, October 2016.

8. 2.5 Clinical Overview: To Support the Addition of Warning Statement on Severe Cutaneous Adverse Reaction (SCAR) To Section 4.4, Special Warnings and Precautions for Use of the Core Data Sheets, October 2016.

9. 2.5 Clinical Overview: To Support Update to Anaphylactic Information Under Section 4.8, Undesirable Effects, of the Core Data Sheets, October 2016.

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11. US Department of Health and Human Services. Centers for Disease Control and Prevention, Tickborne diseases of the United States. A reference manual for healthcare providers. 4th edition. 2017. Available at: https://www.cdc.gov/lyme/resources/TickborneDiseases.pdf

12. 2.5 Clinical Overview: To Support the Update to Section 4.2 Posology and Method of Administration of the Core Data Sheets, October 2017.

13. 2.5 Clinical Overview: To Support the Addition of Jarisch-Herxheimer reaction and Skin hyperpigmentation to Section 4.8, Undesirable effects of the Core Data Sheets, February 2018.

14. 2.5 Clinical Overview: Doxycycline Adverse Drug Reaction Frequency Justification Document, February 2018.

15. 2.5 Clinical Overview: To Support Updates to Section 5.2 Pharmacokinetic Properties of the Doxycycline Core Data Sheets, May 2020.