

VIBRAMYCIN

Doxycycline Hydrochloride

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 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

Doxycycline is available as:

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

Description

Doxycycline film-coated tablet is a smooth, well formed, round bi-convex, white to grey film-coated tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment:

Doxycycline is indicated for treatment of the following infections:

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

Q fever, rickettsial pox 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;

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

Early (Stage 1) 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*).

Doxycycline 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.

Doxycycline 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.

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: 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.

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

Doxycycline 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

Doxycycline 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 doxycycline 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 doxycycline 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): Doxycycline 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.

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*: Doxycycline 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: Doxycycline 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:

Doxycycline 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: Doxycycline 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: Doxycycline 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 – Doxycycline 100 mg every 12 hours, plus cefoxitin 2 g IV every six 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 – Doxycycline 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.

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

Administration of adequate amounts of fluid along with tablet form 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-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., Rocky Mountain spotted fever), particularly when there are no alternative therapies.

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.

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).

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.

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment of spirochete infections.

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, phenytoin and rifampicin 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.

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC.

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
Blood and lymphatic system disorders			Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, 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	Headache		Benign intracranial hypertension (pseudotumor cerebri), fontanelle bulging
Ear and labyrinth disorders			Tinnitus
Vascular disorders			Flushing
Gastrointestinal disorders	Nausea/vomiting	Dyspepsia (heartburn/gastritis)	Pancreatitis, pseudomembranous colitis, <i>Clostridium difficile</i> colitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region,

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000
			dysphagia, abdominal pain, diarrhoea, glossitis, tooth discolouration ^a
Hepatobiliary disorders			Hepatotoxicity, hepatitis, hepatic function abnormal
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash including maculopapular and erythematous rashes		Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, dermatitis exfoliative, fixed eruption, skin hyperpigmentation ^c , photoonycholysis
Musculoskeletal and connective tissue disorders			Arthralgia, myalgia
Renal and urinary disorders			Blood urea increased

CIOMS III categories: Common ≥1/100 to <1/10 (≥1% and <10%), Uncommon ≥1/1,000 to <1/100 (≥0.1% and <1%), Rare ≥1/10,000 to <1/1,000 (≥0.01% and <0.1%).

^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 mcg/ml of doxycycline at two hours, decreasing to 1.45 mcg/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.

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, oxytetracycline).

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

Vibramycin Film-coated Tablet: Doxycycline Hydrochloride, Lactose, Carmellose Calcium, Corn Starch, Hydroxypropylcellulose, Magnesium Stearate, Hydroxypropylmethylcellulose 2910, Macrogol 6000, Titanium Oxide, Liquid Paraffin, Talc, Carnauba Wax, White Beeswax, Isopropanol and Ethanol.

6.2 Incompatibilities

Not known

6.3 Shelf-life

Please refer to carton for shelf-life.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Vibramycin Film-coated tablets: packs of 100's (blister).

6.6 Instructions for Use/Handling

Doxycycline tablets are for oral administration only.

7. MANUFACTURER

Viartis Pharmaceuticals (Dalian) Co. Ltd.,
Dalian, China

Packaged By:
Pfizer Global Supply Japan Inc.
Aichi, Japan

Date of Revision: 01 OCT 2025

VIBRAMYCIN-1025