VIBRAMYCIN®

Doxycycline monohydrate

100 mg Tablets

Reference Market: Switzerland

SUMMARY OF PRODUCT CHARACTERISTICS

Vibramycin® Tabs

Composition

Active substances

Doxycycline as doxycyline monohydrate.

Excipients:

Anhydrous colloidal silicon dioxide, microcrystalline cellulose and carmellose sodium, magnesium stearate, quinoline yellow aluminium lake (E 104), indigo carmine aluminium lake (E 132).

Each 100 mg tablet contains 1.67 mg sodium.

Each 200 mg tablet contains 3.34 mg sodium.

Pharmaceutical form and active ingredient quantity per unit

Tablet with 100 mg: 1 tablet contains 100 mg doxycycline as doxycycline monohydrate.
Light green round tablet engraved with «VN» on one side and a breaker score on the other side; may be dotted with a darker green; scored.

Tablet with 200 mg: 1 tablet contains 200 mg doxycycline as doxycycline monohydrate.
Light green oblong tablet engraved with code «VB 200» and scored on both sides; may be dotted with a darker green; scored.

Indications/Applications

Clinical indications, if the pathogen is included in the antimicrobial activity spectrum of doxycycline.

Respiratory tract infections

Pneumonias: lobar and bronchial pneumonias, caused by pathogens sensitive to doxycycline.

Other infections of the ENT region

Pharyngitis, tonsillitis, otitis media, bronchitis, and sinusitis.
For infections of the upper respiratory tract with beta-haemolytic streptococci of group A penicillin is usually the antibiotic of choice, including for prophylaxis of rheumatic fever.

Infections of the urinary tract and genital organs

Pyelonephritis, cystitis, urethritis, non-specific urethritis (non-gonococcal urethritis, lymphogranuloma venereum). In gonococcal infections Vibramycin Tabs is indicated as concomitant treatment for suspected or proven coinfection caused by *Chlamydia trachomatis*.

Gastrointestinal infections
See «Antimicrobial spectrum *in vitro*».

Vibramycin Tabs is indicated for the treatment and selective prophylaxis of cholera.

Skin and soft tissue infections
Impetigo, furunculosis, phlegmon, abscesses, infected traumatic and operative wounds, paronychia. In the treatment of infections of the soft tissues with Vibramycin Tabs, the necessary surgical measures should simultaneously be undertaken.

Ophthalmological infections
Vibramycin Tabs is indicated in trachoma, even though the causative agent is not always eradicated - as immunofluorescence examinations show.
Inclusion body conjunctivitis (swimming pool conjunctivitis) can be treated with Vibramycin Tabs alone, or in combination with topical medicines.

Borrelioses, Lyme disease
Lyme disease (stage 1 and 2), i.e. skin manifestations with transient joint manifestations and transient and neurological manifestations limited to the face.

Epidemic relapsing fever and louse-borne typhus fever

Vibramycin Tabs is indicated for the treatment of epidemic relapsing fever (caused by *Borrelia recurrentis*) and of louse-borne typhus fever (caused by *Rickettsia prowazekii*).

Leptospirosis
Vibramycin Tabs is indicated for the prophylaxis and treatment of leptospirosis.

Other infections

Ornithosis, prostatitis, granuloma inguinale (caused by *Calymmatobacterium granulomatis*), syphilis, yaws, chancroid (ulcus molle) and Vincent's infection (angina). Malaria due to chloroquine-resistant *Plasmodium falciparum*.

In *acute intestinal amebiasis* Vibramycin Tabs can be a useful supplement to amebicides.

Prophylaxis
In the case of an enhanced risk of infection, Vibramycin Tabs is indicated for prophylaxis against both scrub typhus (caused by *Rickettsia tsutsugamushi*), traveller's diarrhea (enterotoxic *E.coli* strains) and leptospirosis as well as malaria in regions with chloroquine-resistant *Plasmodium falciparum* strains.

Official recommendations for an appropriate use of antibiotics should be taken into consideration.

Specially the recommendations to prevent the increase of antibiotic resistance.

Dosage/Administration

Usual dosage

The usual dosage and frequency of administration of Vibramycin Tabs are different from those of the other tetracyclines. Exceeding the recommended dose may result in an increased incidence of side effects. When used in streptococcal infections, therapy should be continued for at least 10 days to prevent the development of rheumatic fever or glomerulonephritis.

Adults

The usual dose of Vibramycin Tabs in adults is 200 mg on the first day, administered as a single dose, and 100 mg on each subsequent day. In more severe infections (particularly, chronic infections of the urinary tract) a daily dose of 200 mg daily should be given throughout the entire treatment period.

Special dosage instructions

Acute epididymo-orchitis caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*: ceftriaxone or other appropriate cephalosporin (for dosage instructions see corresponding comprehensive information for professionals of these drug products) to treat gonococcal infection; additionally doxycycline 100 mg orally twice daily, for at least 10 days to treat *C. trachomatis* infection.

Non-gonococcal urethritis caused by *Chlamydia trachomatis* or *Ureaplasma urealyticum*: 100 mg orally twice daily, for at least 7 days.

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

Uncomplicated urethral, endocervical, rectal or pharyngeal infections caused by *Chlamydia trachomatis*: doxycycline 100 mg orally twice daily for 7 days.

Suspected *Chlamydia trachomatis* infection concomitant to a gonococcal infection (the gonococcal infection has to be treated by e.g. cephalosporins or fluorchinolones. Dosage recommendation see corresponding comprehensive information for professionals of these drug products): doxycycline 100 mg orally twice daily, for 7 days.

Primary and secondary syphilis: non-pregnant, penicillin-allergic patients with primary or secondary syphilis can be treated according to 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 with tertiary or secondary syphilis can be treated according to 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 1 year. Otherwise, doxycycline should be administered for 4 weeks.

Adnexitis (pelvic inflammatory disease, «PID»): Hospitalized patients: 100 mg doxycycline i.v. every 12 hours plus cefoxitin 2 g i.v. every 6 hours for at least 4 days, and at least 24 to 48 hours after patient improves. Then continue with 200 mg oral doxycycline per day – divided into 2 doses - for a total duration of therapy of 10–14 days.
Out-patient: doxycycline 100 mg orally twice daily for 14 days as adjunctive therapy with a suitable

cephalosporin (e.g. ceftriaxone, cefoxitin or cefotaxime; for dosage instructions of these cephalosporins refer to corresponding comprehensive information for professionals).

Lyme disease stage 1 and 2: doxycycline 100 mg orally twice daily for 10-60 days, according to clinical signs and symptoms, and response.

Malaria (chloroquine-resistant *Plasmodium falciparum* strains): 200 mg daily for at least 7 days. Due to the potential severity of the infection, a rapid-acting schizontocide, e.g. quinine, should always be given in conjunction with Vibramycin Tabs; quinine dosage recommendations vary in different areas.

Malarial prophylaxis in areas with chloroquine-resistant *Plasmodium falciparum* strains: 100 mg daily in adults. For children over 12 years of age, the dose is 2 mg/kg given once daily (up to the adult dose at maximum).
Prophylaxis can begin 1-2 days before travel to malaria areas. It should be continued daily during travelling in the malaria areas and for 4 weeks after leaving the malaria area.

Epidemic relapsing fever and louse-borne typhus fever have been successfully treated orally with a single dose of 100 or 200 mg, according to severity of the infection. As an alternative to reduce the risk of persistence or relapse of tick-borne relapsing fever, 100 mg doxycycline every 12 hours for 7 days is recommended.

Scrub typhus prophylaxis: 200 mg orally as a single oral dose.

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

Traveller's diarrhea prophylaxis: 200 mg on first day of travelling in a single dose, followed by 100 mg/day throughout the entire stay in the danger zone. Data on the prophylactic use of the drug is not available beyond 21 days.

Prophylaxis of leptospirosis: 200 mg Vibramycin Tabs orally per week throughout the entire stay in the hazard zone. At the end of the stay, a further 200 mg of Vibramycin Tabs. Data on the use of the prophylactic use of the drug is not available beyond 21 days.

For the treatment of leptospirosis: 100 mg orally twice daily for 7 days.

Children and adolescents
Children above 12 years
Children of more than 12 years of age weighing 50 kg or less receive 4 mg/kg of body weight as a single dose on the first day and 2 mg/kg of body weight as a single dose on subsequent days. For more severe infections 4 mg/kg/day may be administered throughout the entire period of treatment.
For Children with a body weight over 50 kg the usual adult doses should be used.

Children below 12 years
Concerning use in children below 12 years, see «Warnings and precautions».

Mode of administration
Vibramycin Tabs should be taken sitting or standing together with adequate amount of fluid, at least one hour before a meal and at least one hour before going to bed (see «Warnings and precautions»).

Vibramycin Tabs tablets can be taken as such with an adequate amount of fluid or suspended in about 50 ml of water and swallowed.
If Vibramycin Tabs tablets are taken dissolved, at least 100 ml water should be drunk afterwards.

Administration of adequate amounts of fluid along with drugs in the tetracycline class is recommended to reduce the risk of oesophageal irritation and ulceration.
If serious gastric irritation occurs under recommended manner of ingestion, it is recommended that doxycycline is given with food or a glass of milk; whereby however the absorption of doxycycline is insignificantly reduced (see «Pharmacokinetics/Absorption»).

Contraindications

Vibramycin Tabs is contraindicated in patients with known hypersensitivity to doxycycline, any of the inert ingredients or to any of the tetracyclines.
Vibramycin Tabs is also contraindicated in patients with severe disturbance of liver function.

Warnings and precautions

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

Odontogenesis

The use of antibiotics of the tetracycline class during odontogenesis (second half of pregnancy, infant and childhood up to 12 years) may cause permanent yellow-grey-brown discolouration of the teeth. This adverse reaction is more common during long-term use but has also been observed following repeated short-term courses. Enamel hypoplasia has also been reported.

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 «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) (see «Interactions»).

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 following to the administration of antibacterial agents. In the advent of a pseudomembranous colitis, hypoperistaltic drugs are contraindicated.

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.

With severe diarrhea peristalsis inhibitors are contraindicated.

The use of antibiotics may occasionally result in overgrowth of non-susceptible organisms (mycoses, pseudomembrane colitis). Constant surveillance of the patient is essential. If a resistant organism appears the antibiotic should be discontinued and appropriate therapy instituted.

Photosensitivity has been observed in some individuals taking tetracyclines, including doxycycline. This reaction which is triggered by sunlight or ultraviolet radiation is manifest by excessive sunburn, rarely with nail involvement (nail loosening and discolouration). Patients likely to be exposed to direct sunlight or UV-radiation, should be advised that this reaction can occur with tetracycline drugs, and treatment should be discontinued at the first evidence of skin erythema.

Instances of oesophagitis and oesophagea ulcerations have been reported in patients receiving tablet forms in the tetracycline class, including doxycycline. Most of these patients took medications immediately before going to bed. The existing theoretical risk, in particular for bedridden patients or those with dysphagia, can be reduced still further by suspending the Vibramycin Tabs tablets in about 50 ml of water or another suitable liquid.

The anti-anabolic effect of tetracyclines may cause an increase of blood urea nitrogen. Studies to date indicate that this anti-anabolic effect does not occur with the use of Vibramycin Tabs in patients with

impaired renal function.

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

In patients with mild to moderate disturbance of liver function or co-administration of hepatotoxic drugs, doxycycline should be used with precaution.

When treating venereal disease and when coexisting syphilis is suspected, proper diagnostic procedures should be undertaken, including dark field examinations. In all such cases serological tests should be made 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.

Infections with beta-haemolytic streptococci of group A must be treated for at least 10 days.

In case of co-administration of doxycycline and methotrexate the serum concentration of methotrexate should be carefully monitored (see «Interactions»).

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.

Excipients of particular interest
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e. it is almost «sodium-free».

Interactions

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.

Doxycycline may intensify the effect of sulfonylureas.

Since bacteriostatic drugs may interfere with the bactericidal drugs, it is advisable as a rule to avoid giving doxycycline in conjunction with bactericidal drugs (for exceptions see «Dosage/Administration»).

Absorption of tetracyclines is impaired by the simultaneous taking of antacids containing aluminium, calcium, magnesium or other drugs containing these cations, iron-containing preparations, and bismuth salts. This also applies for medical active coal and cholestyramine. Therefore Vibramycin Tabs should be taken either 2 hours before or 4 hours after the intake of these preparations.

The antibiotic rifampicin, inducing substances from the class of barbiturates and other anticonvulsive drugs such as carbamazepine, diphenylhydantoin and primidone as well as chronic alcohol abuse may accelerate doxycycline's metabolization due to an enzyme induction in the liver so that no effective doxycycline concentrations are achieved with usual doses.

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

Concomitant administration of doxycycline and methotrexate may add to the toxicity of methotrexate.

Concurrent use of tetracyclines may render oral contraceptives less effective.

Co-administration of doxycycline and cyclosporine A may increase the toxic effects of the immunosuppressive drug.

Co-administration of theophylline and tetracyclines may increase the incidence of adverse reactions in the gastrointestinal tract.

Concomitant use of isotretinoin and doxycycline should be avoided since both drugs may rarely cause benign intracranial hypertension (pseudotumor cerebri).

Pregnancy/Lactation

Pregnancy

Doxycycline has not been studied in pregnant women. However, there is clear evidence of risks to the human fetus. Doxycycline should not be used in pregnant women unless it is clearly necessary (see «Warnings and precautions / Use in Children and Odontogenesis»).

During tetracycline use, there is an increased risk of hepatic impairment in pregnant women.

Lactation

Tetracyclines diffuse into the mother's milk**.** Doxycycline reaches in the breast milk, 30-40% of mother's plasma concentration and should therefore not be administered to nursing mothers (see «Warnings and precautions / Use in children and Odontogenesis»). If the administration of Vibramycin Tabs is necessary, breastfeeding should not take place.

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 directly affect these abilities. However, very rarely undesirable effects (refer to respective section) may occur during a therapy with doxycycline that partly impair these abilities severely (e.g. anaphylactic reactions, intracranial hypertension, diplopia and others*)*.

Undesirable effects

The following undesirable effects have been observed in patients receiving tetracyclines, including doxycycline and are listed below according to the standard system organ class of MedDRA. Adverse event frequencies correspond to the following incidence rates:

«Very common» (≥1/10), «common» (≥1/100, <1/10), «uncommon» (≥1/1‘000, <1/100), «rare» (≥1/10‘000, <1/1‘000) and «very rare» (<1/10’000).

Infections and infestations

Rare: The use of antibiotics may result in overgrowth of non-susceptible organisms (mycoses, pseudomembrane colitis). Constant surveillance of the patient is absolutely essential. If a resistant organism occurs, the antibiotic should be discontinued, and appropriate therapy instituted.

Blood and lymphatic system disorders

Uncommon: Blood-clotting disorder and haematuria.
Rare: Haemolytic anemia, thrombocytopenia, neutropenia, and eosinophilia, lymphocytopenia, lymphadenopathy, atypical lymphocytes, and toxic granulations of granulocytes.

Immune system disorders

Common: Hypersensitivity reactions, including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, Henoch-Schonlein purpura, hypotension, pericarditis, angioedema, generalized exanthema, exacerbation of systemic lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.

Rare: Drug rash with eosinophilia and systemic symptoms (DRESS), Jarisch-Herxheimer reaction (in the setting of spirochete infections treated with doxycycline).

There is complete cross-sensitivity within the tetracycline group.

Endocrine disorders

Rare: When given over long periods tetracyclines have been reported to produce brown-black, microscopic discolourations of the thyroid glands. No abnormities of thyroid function studies are known to occur.

Nervous system disorders

Common: Headache.

Rare: Fontanelle bulging in infants and benign intracranial hypertension (pseudotumor cerebri) in adults. Symptoms such as headache, vertigo, fatigue, diplopia may be first signs of benign intracranial hypertension. Paraesthesia, tachycardia, unrest and states of anxiety. Rarely, disorder or loss of smell and taste sensation were described, which were reversible in a few cases, and even only partly.

Very rare: Convulsions.

Ear and labyrinth disorders

Rare: Tinnitus.

Vascular disorders

Rare: Flushing.

Gastrointestinal disorders

Common: Nausea, vomiting.

Uncommon: Dyspepsia, stomatitis and pharyngitis, sore throat, individual cases of black hairy tongue.

Rare: Pancreatitis, abdominal pain, diarrhea, glossitis, reversible and superficial discolouration of permanent teeth, dysphagia, decreased appetite, changed taste, enterocolitis, pseudomembranous colitis, C. difficile colitis and inflammatory lesions in the anogenital region which are often caused by overgrowth of Candida strains. These reactions have been caused by both the oral and parenteral administration of tetracyclines.

Oesophagitis and oesophageal ulcers have been reported in patients receiving tablet forms of tetracyclines, including doxycycline (see «Warnings and precautions»).

Hepatobiliary disorders

Rare: Hepatic function abnormal, hepatitis, hepatotoxicity.

Skin and subcutaneous tissue disorders

Common: Photosensitivity reaction (see «Warnings and precautions»), rash, including maculopapular and erythematous rashes.

Uncommon: Pruritus.

Rare: Dermatitis exfoliative, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photo-onycholysis, skin hyperpigmentation, fixed drug eruption.

Musculoskeletal and connective tissue disorders

Rare: Arthralgia, myalgia.

Renal and urinary disorders

Rare: Blood urea increased (see «Warnings and precautions»). In association with doxycycline use, individual cases of renal damage e.g. interstitial nephritis, acute renal failure, and anuria were reported.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after marketing authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions according to their local country requirements.

Overdose

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures. The remainders may be bound to unabsorbable chelates by administration of antacids or calcium and magnesium salts. Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

Doxycycline has no acute toxicity when given as a single oral administration in multiple therapeutic doses. However, overdosage bears the risk of pancreatitis.

Properties/Effects

ATC code

J01 AA02

Doxycycline which belongs to the class of tetracyclines, acts bacteriostatically, probably by inhibition of protein synthesis. Doxycycline is active against Gram-positive and Gram-negative pathogens. The antimicrobial *in vitro* spectrum of all tetracyclines is almost identical (see following table).

Pharmacodynamics

Antimicrobial spectrum in vitro

Figures in brackets refer to sites/organs where the organism is pathogen, see references 1-6.

Mainly sensitive pathogens (MIC values ≤4 mg/l)

	*MIC values (mg/l); *MIC$_{90}$ (mg/l)* *** mean values or range*	*References*
Gram-positive bacterial pathogens		
Staphylococcus aureus	0.1*	(1), (2)
Streptococcus pneumoniae (Diplococcus pneum.)	0.19-3.1**	(2)
Gram-negative bacterial pathogens		

Acinetobacter sp. calcoaceticus	3.2*	(2)
Actinomyces sp.	1.0*	(5)
Bacillus anthracis	0.12-5.0**	(5)
Bacteroides sp.	0.25->8**	
Borrelia burgdorferi	≤0.25-2**	
Borrelia recurrentis	1-10**	
Borrelia duttonii	1-10**	
Moraxella catarrhalis	0.25*	(2)
Brucella sp. (with concomitant administration of streptomycin)	0.5-2.0**	
Campylobacter fetus (Vibrio fetus)	1.56*	
Chlamydia psittaci	0.03	
Chlamydia trachomatis	≤0.5*	
Clostridium sp.	0.1-6.2**	(5)
Francisella tularensis	2-10**	
Haemophilus influenzae	0.5*	(2)
Klebsiella pneumoniae	1->10**	
Leptotrichia sp. (Fusobacterium sp.)	0.1-25 **	(5)
Listeria monocytogenes	0.25-1.0 **	(5)
Neisseria gonorrhoeae	1.4*	(2)
Neisseria meningitidis	<1.0*	(5)
Rickettsiae sp.	1-10**	(6)
Vibrio cholerae (Vibrio comma)	1.4*	
Yersinia pestis	2-10**	
Other bacterial pathogens		
Mycoplasma pneumoniae	1.6	
Ureaplasma urealyticum	0.05-0.2**	

Partly sensitive and mainly moderate sensitive bacterial pathogens (MIC values >4-<16 mg/l)

	*MIC values (mg/l); *MIC$_{90}$ (mg/l)* *** mean values or range*	*References*
Gram-positive bacterial pathogens		
Streptococcus pyogenes	0.19-50**	(2), (3), (4)
Streptococcus faecalis	<0.19-≥125**	(2), (3)
Gram-negative bacterial pathogens		
Enterobacter aerogenes (Aerobacter aerogenes)	6.3-50**	(2)
Escherichia coli	5->10**	(2)
Klebsiella sp.	1->300**	(2)
Shigella sp.	5->10**	(2)

Pathogens which are clinically sensitive or moderately sensitive but cannot be cultivated, or only so with difficulty

	*MIC values (mg/l); *MIC$_{90}$ (mg/l)* *** mean values or range*	References
Leptospiren		
Treponema pallidum, Treponema pertenue		(5) (5)

Plasmodium falciparum (chloroquinin-resistant strains)		

Resistant bacterial pathogens (MIC values ≥16 mg/l)
Proteus sp., *Pseudomonas* sp., many *Klebsiella* / *Enterobacter* sp., *Providenzia* sp.

Laboratory results of the dilution test or of the standardized disk diffusion test should be interpreted according the following criteria

	Susceptible	*Moderately susceptible*	*Resistant*
Dilution test:			
Inhibition concentrations	≤4 µg/ml	8 µg/ml	≥16 µg/ml
Diffusion test (disk with 30 µg doxycycline):			
Diameter of inhibition zone	≥16 mm	13-15 mm	≤12 mm

Moderately susceptible strains are susceptible with higher antibiotic dosages or in tissue and fluids where the drugs are physiologically concentrated.

The susceptibility of the organisms should be tested to doxycycline. *In vitro* tests showed that Doxycyclin is effective against certain organisms that are resistant to other tetracyclines.

Resistance

Although tetracyclines are also active *in vitro* against some strains of Acinetobacter, Bacteroides, Enterobacter aerogenes, Escherichia coli and Klebsiella, a large percentage of strains of these organisms are resistant to the drugs. Nearly all strains of Proteus, Serratia and Pseudomonas aeruginosa are resistant to tetracyclines.

Although tetracyclines are also active *in vitro* and *in vivo* against some strains of staphylococci and streptococci, tetracycline resistance has been reported in these organisms with increasing frequency.

Clinical efficacy

No information provided.

Pharmacokinetic properties

Absorption

After oral administration doxycycline is almost completely absorbed. Studies reported to date indicate that the absorption of doxycycline may be reduced up to 20% by food or milk. Following a 200 mg single dose of doxycycline, normal volunteers averaged peak serum levels of 2.6 µg/ml at 2 hours decreasing to 1.45 µg/ml at 24 hours.

Distribution

About 90% of the doxycycline is bound to plasma proteins. Doxycycline possesses a high lipid solubility and a low affinity for calcium. The distribution volume is 0.75 l/kg.

Tetracyclines penetrate most body tissues (including sinus mucosa) and fluids including pleural fluid, bronchial secretions, sputum, saliva, ascitic fluid, synovial fluid, aqueous and vitreous humor, and prostatic and seminal fluids.

Doxycycline is also distributed into bile, where the concentration may be 5-15 times higher than the plasma concentration.

Tetracyclines are stored in the reticuloendothelial cells of the liver, spleen and bone marrow, and in bone and the dentine and enamel of unerupted teeth.

The cerebrospinal fluid concentration comes up to only 10-30% of the plasma concentration.

Tetracyclines diffuse through placental barrier.

Doxycycline is excreted into breast milk and reaches in the breast milk 30-40% of mother's plasma concentration.

Metabolism

Doxycycline is not metabolised. After elimination from the gallbladder it is inactivated by chelate formation in the intestine.

Elimination

The half-life of doxycycline is around 16 hours after single dose and around 23 hours after multiple doses. Doxycycline is concentrated in the liver to be excreted, by way of bile, into the intestine, from where it can be reabsorbed (enterohepatic circulation). Doxycycline passes through the liver to be concentrated in the gallbladder.

Doxycycline is excreted in the urine and the faeces in high concentrations (Q_0=0.7) and in a biologically active form. Within 48 hours of a single dose administration the proportion of the dose recovered as unchanged doxycycline is approximately 20% in urine and 30% in the faeces.

Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function (creatinine clearance about 75 ml/min.)

kinetics in specific patient groups

Hepatic impairment

Pharmacokinetic data in patients with impaired liver function are not available.

Renal impairment

In patients with severe impairment of renal function (creatinine-clearance <10 ml/min), renal excretion may drop from 40%/72 hours to 1-5%/72 hours of the administered amount of doxycycline.

Serum elimination half-life is similar in patients with normal and those with severely impaired renal function. According to existing studies, doxycycline does not accumulate at the usual dosage in patients with impaired renal function. Therefore, usual dosage of doxycycline may be used in patients with impaired renal function.

Dialysis

Haemodialysis and peritoneal dialysis do not alter the serum half-life of doxycycline.

Elderly patients

Pharmacokinetic data in elderly patients are not available.

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.

Use of doxycycline is only recommended in children older than 12 years of age.

Preclinical data

Genotoxicity
Mutagenicity studies with doxycycline have not been conducted; positive results in *in vitro* mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracyline).

Carcinogenicity
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).

Reproductive toxicity
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.
Orally administered doxycycline 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.

Other information

Effects on diagnostic methods
Tests for urinary glucose
Tetracyclines have caused false-positive results in urine glucose determinations using the copper sulphate method (Benedict's reagent). This effect may have been caused by ascorbic acid which is included in parenteral preparations of tetracyclines.
Tetracyclines also caused false-negative results in urine glucose determinations using glucose oxidase reagent.

Other Laboratory Tests

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

Shelf life

Do not use Vibramycin after the expiry date which is stated on the pack after EXP:. The expiry date refers to the last day of that month.

Special precautions for storage

Do not store above 30°C. Vibramycin tabs should be protected from light and humidity.

Keep out of reach of children.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Presentations

Vibramycin Tabs, 100 mg tablets (scored): 8, 10 and 25.

Vibramycin Tabs, 200 mg tablets (scored): 8.

Not all pack sizes maybe marketed.

MARKETING AUTHORIZATION HOLDER

PFIZER AG,

SCHÄRENMOOSSTRASSE 99, 8052 ZÜRICH

SWITZERLAND.

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STATUS OF INFORMATION

February 2024

THIS IS A MEDICAMENT

- Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the Pharmacist who sold the medicament.
- The doctor and the Pharmacist are experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.

Keep all medicaments out of reach and sight of children

Council of Arab Health Ministers
Union of Arabic Pharmacists