VIBRAMYCIN®

Doxycycline monohydrate

100 mg Tablets

Reference Market: Switzerland

SUMMARY OF PRODUCT CHARACTERISTICS

Vibramycin® Tabs

Composition

Active ingredient: doxycycline as d. monohydrate.

Excipients: Colloidal silicon dioxide, microcrystalline cellulose and carboxymethylcellulose sodium, magnesium stearate, Color.: E104, E132, E173.

Pharmaceutical form and active ingredient quantity per unit

1 scored tablet Vibramycin Tabs 100 mg contains: doxycycline 100 mg (as D.monohydrate).

1 scored tablet Vibramycin Tabs 200 mg contains: doxycycline 200 mg (as D.monohydrate).

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-hemolytic streptococci of group A penicillin is usually the antibiotic of choice, even 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 proved coinfection caused by *Chlamydia trachomatis*.

Gastro-intestinal infections

(see Antimicrobial spectrum *in vitro*).

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

Infections of the skin and soft tissues

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 bodies conjunctivitis (swimming pool conjunctivitis) can be treated with Vibramycin Tabs orally 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 chloroquinine-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

It should be borne in mind that 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.

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 over 50 kg the usual adult doses should be used.

Children below 12 years

Concerning use in children, see «Warnings and precautions».

Special dosage instructions

Acute epididymo-orchitis caused by *C. trachomatis* or *N. gonorrhoeae*: Ceftriaxone or other appropriate cephalosporin (for dosage directions see the corresponding medical information) to treat Gonococcal infection plus doxycycline 100 mg orally twice daily for at least 10 days to treat *C. trachomatis* infection.

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

Suspected *Chlamydia trachomatis* infection concomitant to a gonococcal infection (Gonococcal infection has to be treated by e.g. cephalosporin or fluorchinolone. Dosage recommendation see in the corresponding medical information): Doxycycline 100 mg orally twice daily for seven days.

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 diseases (pelvic inflammatory disease «PID»):

Hospitalized patients: 100 mg doxycycline i.v. every 12 hours plus cefoxitin 2 g i.v. every six hours for at least 4 days and at least 24 to 48 hours after patient improves. Then continue with 200 mg doxycycline per day in 2 oral doses to complete 10 - 14 days of total therapy.

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 directions of these cephalosporins refer to respective medical information).

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

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

Malarial prophylaxis in areas with chloroquinine-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.

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.

Epidemic relapsing fever and Louse-borne typhus fever have been successfully treated orally with a single dose of 100 mg 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, doxycycline 100 mg every 12 hours for seven 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 1st day of travel in a single dose, followed by 100 mg/day throughout the entire stay in the danger zone. Data on the use of the drug prophylactically are not available beyond 21 days.

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

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

Correct manner of ingestion

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»).

Administration of adequate amounts of fluid along with drugs in the tetracycline class is recommended to reduce the risk of esophageal irritation and ulceration.

If serious gastric irritation occurs under recommended manner of ingestion, it is recommended that doxycycline be given with food or a glass of milk; whereby however the absorption of doxycycline is insignificantly reduced (see «Pharmacokinetic properties/Absorption»).

Contraindications

Vibramycin Tabs is contraindicated in patients with known hypersensitivity to doxycycline, any of its inert ingredients or to any of the tetracyclines.

Vibramycin Tabs is 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 six 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 subsequent 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 esophagitis and esophageal 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 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-hemolytic 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 has to be 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.

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 (exceptions please see in «Dosage/Administration»).

Absorption of tetracyclines is impaired by the simultaneous taking of antacids containing aluminum, 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 effect 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

(see also «Warnings and precautions/Odontogenesis»)

Doxycycline has not been studied in pregnant patients. However, there is clear evidence of risks to the human fetus. Doxycycline should not be used in pregnant women unless, it is absolutely 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, nursing should not be undertaken.

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 directly 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 events are ranked using the following convention:

Very common (≥1/10), common (<1/10, ≥1/100), uncommon (<1/100, ≥1/1000), rare (<1/1000, ≥1/10’000) 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 essential. If a resistant organism appears the antibiotic should be discontinued and appropriate therapy instituted.

Blood and lymphatic system disorders

Uncommon: Haematuria and blood-clotting disorder.

Rare: Hemolytic 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 a 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. Paresthesias, tachycardias, unrest and states of anxiety. Rarely, disorder or loss of smell and taste sensation were described, which were reversible on in a few cases and also only partly.

Very rare: Convulsions.

Ear and labyrinth disorders

Rare: Tinnitus.

Vascular disorder

Rare: Flushing.

Gastrointestinal disorders

Common: Nausea/vomiting.

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

Rare: Pancreatitis, abdominal pain, diarrhoea, 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.

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.

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

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

Antimicrobial spectrum in vitro

(Figures between brackets refer to sites where the organism is pathogen. See notes 1-6)

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

	*MIC values (mg/l); *MIC$_{90}$ (mg/l)* ***mean values or range*	*References*
Grampositive bacterial pathogens		
Staphylococcus aureus	0.1*	(1), (2)
Streptococcus pneumoniae (Diplococcus pneum.)	0.19 - 3.1**	(2)
Gramnegative 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*
Grampositive bacterial pathogens		
Streptococcus pyogenes	0.19 - 50**	(2), (3), (4)
Streptococcus faecalis	<0.19 - ≥125**	(2), (3)
Gramnegative 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*
Dilutiontest:			
Inhibition concentrations	≤4 µg/ml	8 µg/ml	≥16 µg/ml
Diffusion test (disc with 30µg doxycycline):			
diameter of the zones of inhibition	≥16 mm	13 - 15 mm	≤12 mm

Moderately susceptible strains are susceptible with higher antibiotic dosages or in body sites 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 resistent 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.

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 two 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 plasmaconcentration.

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 plasmaconcentration.

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 dose. 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 feces 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 feces.

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

Pharmacokinetics in special patient groups

Renal insufficiency

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

Serum elimination half-lifes are 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

Hemodialysis and peritonealdialysis does not alter the serum half-life of doxycycline.

Hepatic dysfunction

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

Elderly patients

Pharmacokinetic data in elderly patients are not available.

Pediatric patients

Pharmacokinetic data in children are not available. Doxycycline is only recommended for children

older than 12 years.

Preclinical 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).

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.

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.

Further information

Interference with diagnostic methods

Tests for urinary glucose

Although tetracyclines have reportedly caused false-positive results in urine glucose determinations using the cupric sulfate method (Benedict's reagent, Clinitest®), this effect may have been caused by ascorbic acid which is included in parenteral preparations of tetracyclines. Tetracyclines also reportedly cause false-negative results in urine glucose determinations using glucose oxidase reagent (e.g., Clinistix®, Tes-Tape®).

Other Laboratory Tests

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

Stability

The drug should only be used until the date marked by «EXP» on the package.

Special storage conditions

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
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37530 Pocé-sur-Cisse
France

Status of information

July 2018

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