Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibiotics, including doxycycline, and has ranged in severity from mild diarrhoea 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 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 diarrhoea following antibiotic treatment.Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Oesophagitis: instances of oesophagitis and oesophageal 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 or with inadequate amounts of fluid.

Porphyria: There have been rare reports of porphyria in patients receiving tetracyclines.

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

Beta-haemolytic streptococci infections: Infections due to Group A beta-haemolytic Streptococci should be treated for at least 10 days.

Myasthenia gravis: Due to a potential for weak neuromuscular blockade, care should be taken in administering tetracyclines to patients with myasthenia gravis.

Systemic lupus erythematous: Tetracyclines can cause exacerbation of systemic lupus erythematosus (SLE).

Methoxyflurane: Caution is advised in administering tetracyclines with methoxyflurane.

Jarisch-Herxheimer reaction: Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline treatment is started.

PREGNANCY & LACTATION

Pregnancy: Doxycycline is contra-indicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development.

Nursing mothers: Tetracylines are excreted into milk and are therefore contra-indicated in nursing mothers.

OVERDOSE AND TREATMENT

Acute overdosage with antibiotics is rare. In the event of overdosage discontinue medication. Gastric lavage plus appropriate supportive treatment is indicated.

Dialysis does not alter serum half-life and thus would not be of benefit in treating cases of overdosage.

STORAGE:

Store in a cool,dry and dark place.

Keep out of reach of children.

PRESENTATION:

Box containing 10 x 10's Capsules.

Manufactured by : Tanmed Pharma (I) Pvt Ltd.,
No.1/429, Multi Industrial Nagar,
Gerugambakkam, Chennai – 600 128.

Marketed in India by :

Senses Pharmaceuticals Pvt. Ltd.,

No.124,5th A Main Road,Yeshwanthpur Industrial Suburb,
2nd stage, Yeshwanthpur Bangalore-560 022,

Doxycycline with Lactic acid bacillus Capsules

ProDoxt

CATEGORY: Broad spectrum antibacterial agent.

DESCRIPTION:

Each hard gelatin capsule contains:

Doxycycline Hydrochloride	I.P.
Equivalent to Doxycycline	100 mg
Lactic Acid Bacillus	5 billion spores

Approved colours used in empty gelatin capsules.

INDICATIONS:

Doxycycline with Lactic Acid Bacillus capsules belongs to a group of medications called antibiotics, used to treat bacterial infections such as urinary tract infections, intestinal infections, respiratory infections, eye infections, gum infections, and sexually transmitted infections (like gonorrhoea, syphilis). Bacterial infections are caused due to the multiplication of harmful bacteria inside or on the body. Doxycycline prevents the synthesis of essential proteins which are necessary for the survival of the bacteria, thereby kills the bacteria. Lactic acid bacteria is a microorganism that helps in restoring the balance of good bacteria in the gut, which may have gotten upset due to infections or antibiotic use. Together, Doxycycline with Lactic Acid Bacillus capsules helps in treating bacterial infections. Doxycycline with Lactic Acid bacillus capsule does not work against infections caused by the virus, including cold and flu.

CLINICAL PHARMACOLOGY

Pharmacodynamics:

Doxycycline is primarily bacteriostatic and is believed to exert its antimicrobial effect by the inhibition of protein synthesis. Doxycycline is active against a wide range of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

Lactic acid bacteria is a microorganism that helps in restoring the balance of good bacteria in the gut, which may have gotten upset due to infections or antibiotic use. Together, Doxycycline with Lactic Acid Bacillus helps in treating bacterial infections.

Pharmacokinetics:

Tetracyclines are readily absorbed and are bound to plasma proteins in varying degrees. They are concentrated by the liver in the bile and excreted in the urine and faeces 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 micrograms/ml of doxycycline at 2 hours decreasing to 1.45 micrograms/ml at 24 hours. Doxycycline has a high degree of lipid solubility and a low affinity for calcium. It is highly stable in normal human serum. Doxycycline will not degrade into an epianhydro form.

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 paediatric patients (2-18 years of age) showed that allometrically-scaled clearance (CL) of doxycycline in paediatric 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 paediatric patients >8 to 18 years of age (3.27 [1.11-8.12] L/h/70 kg, N=33). For paediatric 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 paediatric 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 paediatric patients who received the oral (N=19) or IV (N=21) formulation alone.

DOSAGE:

Adults and children aged 12 years to less than 18 years: The usual dose of Doxycycline with Lactic acid Capsules for the treatment of acute infections in adults and children aged 12 years to less than 18 years is 200mg on the first day (as a single dose or divided doses), followed by a maintenance dose of 100mg/day. In the management of more severe infections, 200mg daily should be given throughout treatment.

Children aged 8 years to less than 12 years: The use of doxycycline with Lactic acid bacillus capsules for the treatment of acute infections in children aged 8 years to less than 12 years should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

In such circumstance, the doses for the treatment of acute infections are:

• For children 45 kg or less- Initial dose: 4.4 mg/kg (in single or 2 divided doses) with maintenance dose: 2.2 mg/kg (in single or 2 divided doses). In the management of more severe infections, up to 4.4 mg/kg should be given throughout treatment.

• For children, over 45 kg - Dose administered for adults should be used.

Children aged from birth to less than 8 years: Doxycycline should not be used in children aged younger than 8 years due to the risk of teeth discolouration.

Dosage recommendations in specific infections:

Acne vulgaris: 50mg daily with food or fluid for 6-12 weeks.

Sexually transmitted diseases: 100mg twice daily for 7 days is recommended in the following infections: uncomplicated gonococcal infections (except anorectal infections in men); uncomplicated urethral, endocervical or rectal infection caused by Chlamydia trachomatis; non-gonococcal urethritis caused by Ureaplasma urealyticum.

Acute epididymo-orchitis caused by Chlamydia trachomatis or Neisseria gonorrhoeae: 100mg twice daily for 10 days.

Primary and secondary syphilis: Non-pregnant penicillin-allergic patients who have primary or secondary syphilis can be treated with the following regimen: doxycycline 200 mg orally twice daily for two weeks, as an alternative to penicillin therapy.

Louse-borne and tick-borne relapsing fevers: A single dose of 100mg or 200mg according to severity.

Treatment of chloroquine-resistant falciparum malaria: 200mg daily for at least 7 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.

Prophylaxis of malaria: 100mg daily in adults and children over the age of 12 years. Prophylaxis can begin 1-2 days before travel to malarial areas. It should be continued daily during travel in the malarial areas and for 4 weeks after the traveller leaves the malarial area.

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

For the prevention of travellers' diarrhoea in adults: 200mg on the first day of travel (administered as a single dose or as 100mg every 12 hours) followed by 100mg 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: 200mg once each week throughout the stay in the area and 200mg at the completion of the trip. Data on the use of the drug prophylactically are not available beyond 21 days.

Use in the elderly: Doxycycline may be prescribed in the elderly in the usual dosages with no special precautions. No dosage adjustment is necessary in the presence of renal impairment.

Use in patients with impaired hepatic function: Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs.

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

Rocky Mountain spotted fever: *Adults:* 100 mg every 12 hours; *Children*: weighing less than 45 kg: 2.2 mg/kg body weight given twice a day. Children weighing 45 kg or more should receive the adult dose.

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

Method of administration

For oral use. The capsules should be swallowed with plenty of fluid in either the resting or standing position and well before going to bed for the night to reduce the likelihood of oesophageal irritation and ulceration.

If gastric irritation occurs, it is recommended that Doxycycline with Lactic acid bacillus Capsules be given with food or milk. Studies indicate that the absorption of doxycycline is not notably influenced by simultaneous ingestion of food or milk.

Exceeding the recommended dosage may result in an increased incidence of side effects. Therapy should be continued for 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.

CONTRAINDICATIONS:

• Hypersensitivity to the active substance, any of the tetracyclines or to any of the excipients used in the product.

• Pregnancy: Doxycycline is contra-indicated in pregnancy. It appears that the risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development.

• Nursing mothers: Tetracylines are excreted into milk and are therefore contra-indicated in nursing mothers.

SIDE EFFECTS & CAUTION :

Common: Doxycycline associated Fixed Drug Eruption (FDE), Headache, Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, angioedema, exacerbation of systemic lupus erythematosus, pericarditis, serum sickness, Henoch-Schonleinpurpura, hypotension, dyspnoea, tachycardia, peripheral oedema and urticaria), Nausea, vomiting, Photosensitivity reaction, rash including maculopapular and erythematous rashes.

Uncommon: Vaginal infection, Dyspepsia (Heartburn/gastritis).

Rare: Candida Infection, Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Jarisch-Herxheimer reaction, Brown-black microscopic discolouration of thyroid glands, Porphyria, decreased appetite, Anxiety, benign intracranial hypertension (pseudotumor cerebri)[a], fontanelle bulging, Tinnitus, Visual disturbance, Flushing, Pancreatitis, pseudomembranous colitis, *Clostridium difficile* colitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, glossitis, stomatitis, Hepatic failure, hepatitis, hepatotoxicity, jaundice, hepatic function abnormal, Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, dermatitis exfoliative, photoonycholysis, skin hyperpigmentation, Arthralgia, myalgia, blood urea increased.

Unknown: tooth discoloration.

CNS SIDE EFFECTS :

Restlessness,anxiety,irritability,nervousness and dizziness.

DRUG INTERACTION:

The absorption of doxycycline may be impaired by concurrently administered antacids containing Aluminium,Calcium,Magnesium or other drugs containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.Since bacteriostatic drugs may interfere with the bactericidal action of penicillin, it is advisable to avoid giving doxycycline in conjunction with penicillin.There have been reports of prolonged prothrombin time in patients taking warfarin and doxycycline. Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anticoagulants may be necessary.

The serum half-life of doxycycline may be shortened when patients are concurrently receiving barbiturates, carbamazepine or phenytoin. An increase in the daily dosage of Doxycycline should be considered.

Alcohol may decrease the half-life of doxycycline.

A few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline antibiotics with oral contraceptives.

Doxycycline may increase the plasma concentration of ciclosporin. Co-administration should only be undertaken with appropriate monitoring.

The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity. Concomitant use of isotretinoin or other systemic retinoids and doxycycline should be avoided. Each of these agents used alone has been associated with benign intracranial hypertension (pseudotumor cerebri).

PRECAUTIONS/WARNINGS:

Paediatric population: The use of drugs of the tetracycline class during tooth development (last half of pregnancy; infancy and childhood to the age of 8 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This adverse reaction is more common during long-term use of the drugs but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients aged younger than 8 years only when the potential benefits are expected to outweigh the risks in severe or life-threatening conditions (e.g. Rocky Mountain spotted fever), only when there are no adequate alternative therapies.

Use in patients with impaired hepatic function: Doxycycline should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic drugs. Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline.

Use in patients with renal impairment: Excretion of doxycycline by the kidney is about 40%/72 hours in individuals with normal renal function. This percentage excretion may fall to a range as low as 1-5%/72 hours in individuals with severe renal insufficiency (creatinine clearance below 10ml/min). Studies have shown no significant difference in the serum half-life of doxycycline in individuals with normal and severely impaired renal function. Haemodialysis does not alter the serum half-life of doxycycline. The anti-anabolic action of the tetracyclines may cause an increase in blood urea.

Serious skin reactions: Serious 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. If serious skin reactions occur, doxycycline should be discontinued immediately and appropriate therapy should be instituted.

Photosensitivity: 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

Photoonycholysis has also been reported in patients receiving doxycycline.

Benign intracranial hypertension: Bulging fontanelles in infants have been reported in individuals receiving tetracyclines. Benign intracranial hypertension (pseudotumor cerebri) has been associated with the use of 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 or other systemic retinoids and doxycycline should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri).

Microbiological overgrowth: The use of antibiotics may occasionally result in over-growth of non-susceptible organisms, including Candida. If a resistant organism appears, the antibiotic should be discontinued and appropriate therapy instituted.

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 diarrhoea subsequent to the administration of antibacterial agents.