

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

Vibranord 10 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml oral liquid contains 10 mg doxycycline hyclate

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by tetracycline sensitive aerobic and anaerobic gram-positive and gram-negative microorganisms, chlamydia, mycoplasma, spirochetes, rickettsiae and actinomycetes.

Inhalational anthrax (post-exposure) in adults and children: to reduce the incidence or progression of disease following the inhalation of *Bacillus anthracis*.

4.2 Posology and method of administration

Depends on type of infection. Exceeding the recommended dose may result in an increased incidence of undesirable effects. Therapy should be continued for at least 24 to 48 hours after symptoms and fever have subsided. When used in beta-hemolytic streptococcal infections, therapy should be continued for 10 days to prevent the development of rheumatic fever or glomerulonephritis. **Adults and children above 12 years of age:** 200 mg (20 ml) on the first day of treatment, followed by 100 mg (10 ml) per day. In the management of more severe infections 200 mg (20 ml) daily should be given throughout the treatment period. **Children aged 8-12 years:** (see section 4.4 Special Warnings and Special Precautions for Use) >50 kg: Same as for adults. <50 kg: 4 mg/kg the first day of treatment, followed by 2 mg/kg of body weight (given as a single dose or divided into two doses). For more severe infections, up to 4 mg/kg may be used; also after the first day.

Inhalational anthrax (post-exposure): Adults: 100 mg (10 ml) of doxycycline, twice a day for 60 days. Children: (weighing less than 45 kg); 2.2 mg/kg body weight, twice a day for 60 days. Children weighing 45 kg or more should receive the adult dose (see Section 4.4 Special Warnings and Special Precautions for Use: Use in Children).

Post-exposure prophylaxis is only indicated if at least one of the following conditions is met:

- Detection of inhalational anthrax in a person who has stayed in the same building.
- Detection of *B. anthracis* in environmental samples from rooms or buildings where the patient has stayed and where spreading by air could have taken place.
- When a person has stayed in an area/building where it is known that the air has been contaminated by *B. Anthracis*.

Treatment should be initiated as soon as possible following suspected or confirmed exposure to inhalational anthrax. However, when the results of antimicrobial susceptibility testing are available the choice of adequate treatment should be reviewed.

Special infections: *Chlamydial urethritis*: 200 mg (20 ml) the first day, followed by 100 mg (10 ml) daily for 7-10 days. *Chlamydial salpingitis*: 100 mg (10 ml) twice daily for 10 days. *Ureaplasma*

urealyticum (T-mycoplasma) infections: 100 mg (10 ml) twice daily for 4 weeks (partner also to be treated).

4.3 Contraindications

Hypersensitivity to tetracyclines. Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Due to the affinity of doxycycline for calcium in bone-forming tissue, teeth and dental buds doxycycline may cause permanent changes in enamel and tooth substance and reversible changes in bone-forming tissue. However, this tendency is less with doxycycline than with other tetracyclines due to the lower affinity for calcium. This effect is greatest during the last half of pregnancy and in children below the age of 12, where the medicinal product should only be used in exceptional cases and confirmed indications. The use of tetracyclines is not recommended during pregnancy.

In case of inhalational anthrax (post-exposure) the benefit/risk evaluation shows that treatment of growing children and youths, pregnant and lactating women is appropriate. However, when the results of antimicrobial susceptibility testing are available doxycycline should if possible be replaced by a medicine with a better risk profile. (See Section 4.2 Posology and method of administration and 4.6 Pregnancy and lactation). Bulging fontanels in infants and benign intracranial hypertension in adults disappeared rapidly when the drug was discontinued.

Pseudomembranous colitis has been reported with 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 doxycycline.

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.

Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving tetracycline medication in capsule and tablet forms, including doxycycline. Most of these patients took the medicine immediately before going to bed.

Caution should be exercised in case of hepatic disease. Dosage adjustment should be considered. Abnormal hepatic function has been reported in rare instances and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline. In long-term therapy, periodic laboratory evaluation of hematopoietic, renal and hepatic studies should be performed.

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

Due to the increased risk of photosensitivity, patients should be advised to avoid sunbathing during and up until 2 weeks after end of treatment. 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.

Patients with rare hereditary problems of fructose intolerance should not take this medicine as it contains sorbitol.

4.5 Interaction with other medicinal products and other forms of interaction

The concurrent use of tetracyclines and methoxyflurane has been reported to cause fatal renal toxicity. Antacids or other medicines containing two and three-valent metal ions such as iron, aluminium, magnesium, bismuth and calcium, should be taken 1 hour prior to or 2-3 hours after doxycycline administration as they form poorly soluble compounds with tetracyclines and result in decreased absorption. Administration of iron supplementation should if possible be discontinued during short term tetracycline treatment (1-2 weeks). Alcohol, barbiturates, carbamazepine and phenytoin decrease the half-life of doxycycline. There have been reports of prolonged prothrombin time in patients concomitantly taking warfarin and doxycycline. As tetracyclines have been shown to depress plasma prothrombin activity, a downward adjustment of anticoagulant dosage may be required. Since bacteriostatic activity may interfere with the bactericidal action of penicillin, it is advisable to avoid giving doxycycline in conjunction with penicillin. Concurrent use of tetracyclines may in rare instances render oral contraceptives less effective.

4.6 Pregnancy and lactation

Pregnancy: Tetracyclines have been shown to cause irreversible tooth damage and may be incorporated in foetal bone tissue. Pregnant women are more susceptible to tetracycline induced liver injury at higher doses. A few epidemiological studies of pregnant women who had taken tetracyclines during the first trimester indicated a possible increase in minor malformations (inguinal hernia and hypospadias). Other studies have not indicated an increase in malformations. Available animal studies do not indicate unambiguous teratogenicity results. Tetracyclines should not be used during pregnancy unless the benefits outweigh the potential risks to the child.

Lactation: Tetracyclines are excreted into milk. The milk:plasma ratio is 0.25-1.5. The child's teeth and skeletal development may be affected. It cannot be ruled out that the flora of the child's mouth and alimentary tract may be affected. Tetracyclines should not be used during breast-feeding.

In case of Inhalational anthrax (post-exposure) the benefit/risk evaluation shows that treatment of pregnant and lactating women is appropriate. However, when the results of antimicrobial susceptibility testing are available doxycycline should if possible be replaced by a medicine with a better risk profile. (See Section 4.2 Posology and method of administration).

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.

4.8 Undesirable effects

The frequencies of undesirable effects are defined as follows: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) including isolated cases.

<i>MedDRA system organ class</i>	Frequency	Undesirable effects
<i>Blood and lymphatic system disorders</i>	Rare	Haemolytic anaemia, thrombocytopenia, neutropenia and eosinophilia

<i>Immune system disorders</i>	Rare	Hypersensitivity reactions, including anaphylactic shock, anaphylactoid reaction, anaphylactoid purpura, hypotension, angioneurotic oedema, exacerbation of systemic lupus erythematosus, dyspnoea, serum sickness, peripheral oedema, tachycardia and urticaria.
<i>Metabolism and nutrition disorders</i>	Rare	Anorexia
<i>Nervous system disorders</i>	Uncommon	Headache
	Rare	Bulging fontanel in infants and benign intracranial hypertension in adults
<i>Ear and labyrinth disorders</i>	Rare	Tinnitus
<i>Cardiac disorders</i>	Rare	Pericarditis
<i>Vascular disorders</i>	Rare	Flushing
<i>Gastrointestinal disorders</i>	Common	Nausea
	Uncommon	Vomiting, diarrhoea and glossitis
	Rare	Abdominal pain, dysphagia, dyspepsia, enterocolitis, pseudomembranous colitis, <i>C. difficile</i> diarrhoea and inflammatory lesions (with monilial overgrowth) in the anogenital region. Oesophagitis and oesophageal ulceration have been reported in patients receiving tetracyclines as tablets or capsules
<i>Hepatobiliary disorder</i>	Rare	Abnormal liver function, hepatitis, hepatotoxicity
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Rash, including maculopapular and erythematous rashes, photosensitivity
	Rare	Erythema multiforme, exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis, photoonycholysis
<i>Musculoskeletal and</i>	Rare	Arthralgia and myalgia

<i>connective tissue disorders</i>		
<i>Investigations</i>	Rare	Increased BUN, brown-black microscopic discoloration of thyroid glands when given over a prolonged period of time.

4.9 Overdose

Discontinue medication, treat symptomatically and institute supportive measures. Dialysis is not expected to increase the secretion of doxycycline.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracycline. ATC code: J01A A02.

Classification: Broad-spectrum antibiotic. *Mechanism of action:* Bacteriostatic effect by inhibiting the protein synthesis of micro-organisms.

5.2 Pharmacokinetic properties

Absorption: Doxycycline is virtually completely absorbed after oral administration. Minor influence by the ingestion of food (milk products). 200 mg administered orally results in peak serum levels of about 3-5 µg/ml at 2-3 hours, decreasing to about 1.5 µg/ml at 24 hours. *Protein binding:* about 90%. *Metabolism:* Small degree. *Elimination:* Serum half-life: 18-22 hours, relatively uninfluenced by the renal function. Haemodialysis does not affect the serum half-life. *Excretion:* In urine and faeces in active form. Excretion by the kidneys is about 40% per 72 hours with normal renal function. Part of the enterohepatic circulation. High concentrations in the bile.

5.3 Preclinical safety data

There are no pre-clinical data of relevance to safety.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Calcium chloride hexahydrate; sorbitol 70%, liquid (crystallising); magnesium and aluminium silicate (Veegum K); povidone; glycerol; butyl parahydroxybenzoate; propyl parahydroxybenzoate; saccharin sodium; sodium metabisulphite; sodium hydroxide; simethicone emulsion; water, purified. Raspberry and apple flavouring.

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Pipet bottle: 10 ml. Bottle: 60 ml.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

NordMedica A/S
Jægersborg Alle 164
DK-2820 Gentofte
Denmark

8. MARKETING AUTHORISATION NUMBER

5266

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MT first renewal: 17.10.1967

Last renewal: 17.10.2002

10. DATE OF REVISION OF THE TEXT

16-06-2010