

**SUMMARY OF PRODUCT CHARACTERISTICS**  
Droximicin<sup>®</sup> (Doxycycline 100mg) Capsule

## **1. NAME OF THE MEDICINAL PRODUCT**

Droximicin® (Doxycycline 100mg) Capsule

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 100mg of Doxycycline.

(For a full list of excipients, see section 6.1).

## **3. PHARMACEUTICAL FORM**

Hard gelatin capsule

Hard gelatin capsule with opaque green cap and opaque green body with "100mg" printed in white ink.

## **4. Clinical particulars**

### **4.1 Therapeutic indications**

Doxycycline has been found clinically effective in the treatment of a variety of infections caused by susceptible strains of Gram-positive and Gram-negative bacteria and certain other micro-organisms.

#### **Respiratory tract infections**

Pneumonia and other lower respiratory tract infections due to susceptible strains of *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and other organisms. *Mycoplasma pneumoniae* pneumonia. Treatment of chronic bronchitis, sinusitis.

#### **Urinary tract infections**

Infections caused by susceptible strains of *Klebsiella* species, *Enterobacter* species, *Escherichia coli*, *Streptococcus faecalis* and other organisms.

#### **Sexually transmitted diseases**

Infections due to *Chlamydia trachomatis* including uncomplicated urethral, endocervical or rectal infections. Non-gonococcal urethritis caused by *Ureaplasma urealyticum* (T- mycoplasma).

Doxycycline is also indicated in chancroid, granuloma inguinale and lymphogranuloma venereum. Doxycycline is an alternative drug in the treatment of gonorrhoea and syphilis.

#### **Dermatological infections**

Acne vulgaris when antibiotic therapy is considered necessary.

Since Doxycycline is a member of the tetracycline group of antibiotics, it may be expected to be useful in the treatment of infections, which respond to other tetracyclines, such as:

##### **Ophthalmic infections**

Due to susceptible strains of gonococci, staphylococci and *Haemophilus influenzae*. Doxycycline Capsules are indicated in the treatment of trachoma, although the infectious agent is not always eliminated, as judged by immunofluorescence.

##### **Rickettsial infections**

Rocky Mountain spotted fever, typhus group, Q fever, *Coxiella endocarditis* and tick fevers.

##### **Other infections**

Psittacosis, cholera, melioidosis, leptospirosis, other infections due to susceptible strains of *Yersinia* species, *Brucella* species (in combination with Streptomycin), *Clostridium*

species, *Francisella tularensis* and chloroquine-resistant falciparum malaria.

Doxycycline Capsules are indicated for prophylaxis in the following conditions: Scrub typhus, travellers' diarrhoea (enterotoxigenic *Escherichia coli*), leptospirosis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

## **4.2 Posology and method of administration**

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 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.

### Posology

#### **Adults**

The usual dosage of Doxycycline 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 in divided doses with a twelve hour interval) followed by a maintenance dose of 100mg/day. In the management of more severe infections (particularly chronic infections of the urinary tract), 200mg daily should be given throughout the treatment period.

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 the 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.

#### **Special populations**

##### Elderly patients

Amlodipine tablets used at similar doses in elderly or younger patients is equally well tolerated. Normal dosage regimens are recommended in the elderly, but increase of the dosage should take place with care.

##### Patients with hepatic impairment

Dosage recommendations have not been established in patients with mild to moderate hepatic impairment; therefore dose selection should be cautious and should start at the lower end of the dosing range. The pharmacokinetics of amlodipine have not been studied in severe hepatic impairment. Amlodipine should be initiated at the lowest dose and titrated slowly in patients with severe hepatic impairment.

##### Patients with renal impairment

Changes in amlodipine plasma concentrations are not correlated with degree of renal impairment, therefore the normal dosage is recommended. Amlodipine is not dialysable.

#### **Paediatric population**

Not recommended.

## **Children aged 8 years to less than 12 years**

The use of doxycycline 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.

## **Elderly patients**

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

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

The anti-anabolic action of the tetracyclines may cause an increase in blood urea. Studies to date indicate that this does not occur with the use of doxycycline in patients with impaired renal function.

Haemodialysis does not alter the serum half-life of doxycycline.

## **4.3 Contraindications**

Hypersensitivity to the active substance, any of the tetracyclines or to any of the excipients listed in section 6.1

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

Nursing mothers: Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers.

Sucrose intolerance: Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrose-isomaltase insufficiency should not take doxycycline.

## **4.4 Special warnings and precautions for use**

## 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), particularly only when there are no adequate alternative therapies.

Although the risk of permanent teeth staining is rare in children aged 8 years to less than 12 years, the use of doxycycline should be carefully justified in situations where other drugs are not available, are not likely to be effective or are contraindicated.

### 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.

### 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. Studies to date indicate that this anti-anabolic effect does not occur with the use of Doxycycline in patients with impaired renal function.

### 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.

### Microbiological overgrowth

The use of antibiotics may occasionally result in overgrowth 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.

*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 should be considered in all patients who present with diarrhoea after 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.

#### 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. 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 or other systemic retinoids and doxycycline should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri).

#### Porphyria

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

#### Venereal disease

When treating venereal disease, where co-existent syphilis is suspected, proper diagnostic procedures, including dark-field examinations, should be utilised. In such cases monthly serological tests should be performed 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 erythematosus

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

Jarisch-Herxheimer reaction

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.

Methoxyflurane

Caution is advised in administering tetracyclines with methoxyflurane

#### **4.5 Interaction with other medicinal products and other forms of 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).

## Laboratory test interactions

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

Drugs that induce hepatic enzymes such as rifampicin may accelerate the decomposition of doxycycline, thereby decreasing its half-life. Sub-therapeutic doxycycline concentrations may result. Monitoring concurrent use is advised and an increase in doxycycline dose may be required.

Ergotamine; There is an increased risk of ergotism when doxycycline is co-administered with ergotamine.

Methotrexate; Doxycycline increases the risk of methotrexate toxicity; prescribe with caution to patients on methotrexate.

Quinapril contains magnesium carbonate and may interfere with the absorption of doxycycline

## 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. Studies to date indicate that this anti-anabolic effect does not occur with the use of Doxycycline in patients with impaired renal function.

## **4.6 Pregnancy and Lactation**

### **Pregnancy**

See "Contra-indications", section 4.2.

### **4.7 Effects on ability to drive and use machines**

Visual disturbances such as blurring of vision may occur during treatment with doxycycline and in such cases; patients must refrain from driving or operating machinery.



#### 4.8 Undesirable effects

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline.

<b>System Organ Class</b>	<b>Common <math>\geq 1/100</math> to <math>&lt; 1/10</math></b>	<b>Uncommon <math>\geq 1/1000</math> to <math>&lt; 1/100</math></b>	<b>Rare <math>\geq 1/10,000</math> to <math>&lt; 1/1000</math></b>	<b>Not known Cannot be estimated from the available data.</b>
Infections and infestations		Vaginal infection	Candida Infection, pseudomembranous colitis, Clostridium difficile colitis	
Blood and lymphatic system disorders			Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, exacerbation of systemic lupus erythematosus, serum sickness)		Jarisch-Herxheimer reaction <sup>b</sup>	
Congenital, familial and genetic disorders			Porphyria	
Endocrine disorders			Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders			decreased appetite	
Nervous system disorders	Headache		benign intracranial	

			hypertension (pseudotumor cerebri)*, fontanelle bulging	
Psychiatric Disorders			Anxiety	
Ear and labyrinth Disorders			Tinnitus	
Vascular disorders	Hypotension		Flushing	
Gastrointestinal disorders	Nausea/vomiting	Dyspepsia (Heartburn/gastritis)	Pancreatitis, oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, glossitis, stomatitis	tooth discolouration <sup>a</sup>
Hepatobiliary disorders			Hepatic failure, hepatitis, hepatotoxicity, jaundice, hepatic function abnormal	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash including maculopapular and erythematous rashes, Henoch-Schonlein purpura, Urticaria		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), angioedema, Toxic epidermal necrolysis, Stevens- Johnson syndrome, Erythema multiforme, Dermatitis exfoliative, photoonycholysis, skin hyperpigmentation <sup>c</sup>	

Musculoskeletal , connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders			Blood urea increased	
Cardiac Disorders	Pericarditis, Tachycardia			
Respiratory, thoracic and mediastinal disorders	Dyspnoea			
General disorders and administration site conditions	Peripheral oedema			

\* Symptoms included blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.

The following adverse reactions have been observed in patients receiving tetracyclines, including doxycycline

#### **4.9 Overdose**

Acute overdosage with antibiotics is rare. In the event of overdosage 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.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamics properties**

Pharmacotherapeutic group: tetracyclines, ATC code: J01AA02

Doxycycline is primarily a bacteriostatic antibiotic.

#### Mechanism of action

The main mechanism of action of doxycycline is on protein synthesis. Doxycycline passes directly through the lipid bilayer of the bacterial cell wall and an energy dependent active transport system pumps the drug through the inner cytoplasmic membrane. Once inside the cell doxycycline inhibits protein synthesis by binding to 30S ribosomes and prevents the addition of amino acids to the growing peptide chain. Doxycycline will impair protein synthesis in mammalian cells at very high concentrations but these cells lack the active transport system found in bacteria.

Doxycycline is clinically effective in the treatment of a variety of infections caused by a wide range of gram-negative and gram-positive bacteria, as well as certain other micro-organisms.

## **5.2 Pharmacokinetic properties**

### **Absorption**

Doxycycline is almost completely absorbed and is not subject to presystemic metabolism, the mean bioavailability being approximately 93%.

Absorption is rapid (effective concentrations are attained as from the first hour), and the peak serum concentration occurs after 2 to 4 hours.

Almost all of the product is absorbed in the upper part of the digestive tract. Absorption is not modified by administration with meals, and milk has little effect.

### **Distribution**

Tissue distribution is good and Doxycycline has a strong affinity for renal and lung tissue. The volume of distribution for doxycycline ranges from 0.9-1.8 l/kg-1.

In adults, an oral dose of 200 mg results in;

- A peak serum concentration of more than 3 µg/ml
- A residual concentration of more than 1 µg/ml after 24 hours
- A serum half-life of 16 to 22 hours.
- Protein binding varying between 82 and 93% (labile binding) intra- and extracellular diffusion is good.

With usual dosages, effective concentrations are found in the ovaries, uterine tubes, uterus, placenta, testicles, prostate, bladder, kidneys, lung tissue, skin, muscles, lymph glands, sinus secretions, maxillary sinus, nasal polyps, tonsils, liver, hepatic and gallbladder bile, gallbladder, stomach, appendix, intestine, omentum, saliva and gingival fluid. Doxycycline is transferred into breast milk.

Only small amounts are diffused into the cerebrospinal fluid.

### **Biotransformation**

No significant metabolism occurs.

### **Elimination**

Doxycycline is cleared intact by renal and biliary mechanisms

The antibiotic is concentrated in the bile. About 40% of the administered dose is eliminated in 3 days in active form in the urine and about 32% in the faeces.

Urinary concentrations are roughly 10 times higher than plasma concentrations at the same time. In the presence of impaired renal function, urinary elimination decreases, faecal elimination increases and the half-life remains unchanged. The half-life is not affected by haemodialysis.

## **5.3 Preclinical safety data**

Not applicable

## **6 PHARMACEUTICAL PARTICULARS**

## **6.1 List of excipients**

Corn starch (Dried)  
Sodium Cross Carmellose  
Lactose Monohydrate  
Magnesium Stearate  
Sodium Lauryl Sulphate

## **6.2 Incompatibilities**

Not applicable.

## **6.3 Shelf life**

48 Months

## **6.4 Special precautions for storage**

None

## **6.5 Nature and contents of container and special equipment for use, administration or implantation**

Droximixin<sup>®</sup> capsules is available in 10×10's blister pack with leaf enclosed:

## **6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements

## **7 APPLICANT/MANUFACTURER**

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