SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Doxat 100 mg Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg of doxycycline as doxycycline hyclate.

Excipient(s) with known effect: 174 mg of lactose per film-coated tablet.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Yellow, oblong film-coated tablets scored on both sides.

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*. Treatment of chronic bronchitis, sinusitis.

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

Skin infections Acne vulgaris, when antibiotic therapy is considered necessary.

Since Doxat is a member of the tetracycline series 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. Trachoma, although the infectious agent, as judged by immunofluorescence, is not always eliminated. Inclusion conjunctivitis may be treated with oral Doxat alone or in combination with topical agents.

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

Other infections Psittacosis, brucellosis (in combination with streptomycin), cholera, bubonic plague, louse and tick-borne relapsing fever, tularaemia glanders, melioidosis, chloroquine-resistant falciparum malaria and acute intestinal amoebiasis (as an adjunct to amoebicides).

Doxat is an alternative drug in the treatment of leptospirosis, gas gangrene and tetanus.

Doxat is indicated for prophylaxis in the following conditions: Scrub typhus, travellers' diarrhoea (enterotoxigenic *Escherichia coli),* leptospirosis and malaria. Prophylaxis of malaria should be used in accordance to current guidelines, as resistance is an ever changing problem.

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

4.2 Posology and method of administration

Posology

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

Children aged 8 years to less than 12 years (see section 4.4)
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 (section 4.4 and 4.8).

Dosage recommendations in specific infections:

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

Sexually transmitted diseases 100 mg 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 gonorrhoea 100 mg 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 and tick-borne relapsing fevers A single dose of 100 or 200 mg according to severity.

Treatment of chloroquine-resistant falciparum malaria 200 mg 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 Doxat; quinine dosage recommendations vary in different areas.

Prophylaxis of malaria 100 mg 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 current advice on geographical resistance patterns and appropriate chemoprophylaxis, current guidelines or the Malaria Reference Laboratory should be consulted, details of which can be found in the British National Formulary (BNF).

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

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

Use in the elderly Doxat 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 See section 4.4.

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 see section 4.4.

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 (see section 4.4 paediatric population).

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

The film-coated tablets are for oral administration only.

Doxat should be administered with plenty of fluid. This should be done in the sitting or standing position and well before retiring at night to reduce the risk of oesophageal irritation and ulceration. If gastric irritation occurs, it is recommended that Doxat 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.

4.3 Contraindications

Hypersensitivity to doxycycline or to any of the tetracyclines or to any of the excipients listed in section 6.1.

Pregnancy Doxat is contraindicated 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 (see section 4.4 regarding use during tooth development).

Nursing mothers Tetracyclines are excreted into milk and are therefore contraindicated in nursing mothers (see section 4.4 regarding use during tooth development).

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), 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.

Use in patients with impaired hepatic function Doxat 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 10 ml/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 (see section 4.8). 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 (see section 4.8). 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 (see section 4.8).

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) (see section 4.5).

Microbiological overgrowth The use of antibiotics may occasionally result in the 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 antibacterial agents, including doxycycline, and may range 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 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 diarrhoea following antibiotic use. 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 disease, 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 erythematosus Tetracyclines can cause exacerbation of SLE.

Methoxyflurane Caution is advised in administering tetracyclines with methoxyflurane. See section 4.5.

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 This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 Doxat 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 Doxat 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 cyclosporin. 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. See section 4.4.

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) (see section 4.4).

Laboratory test interactions

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

4.6 Fertility, pregnancy and lactation

See section 4.3.

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. There is no evidence to suggest that doxycycline may affect these abilities.

4.8 Undesirable effects

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

System Organ Class	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Rare ≥ 1/10,000 to < 1/1,000**	**Not known Cannot be estimated from the available data**
Infections and infestations		Vaginal infection	Candida infection	
Blood and lymphatic system disorders			Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hypersensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, angioedema, exacerbation of systemic lupus erythematosus, pericarditis, serum sickness, Henoch-Schonlein purpura, hypotension, dyspnoea, tachycardia,		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Jarisch-Herxheimer reaction[b] (see section 4.4)	

	peripheral oedema, and urticaria)			
Endocrine disorders			Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders			Porphyria, decreased appetite	
Nervous system disorders	Headache		Anxiety, benign intracranial hypertension (pseudotumor cerebri)*, fontanelle bulging	
Ear and labyrinth disorders			Tinnitus	
Vascular disorders			Flushing	
Gastrointestinal disorders	Nausea/vomiting	Dyspepsia (Heartburn/gastritis)	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	Tooth discolouration[a]
Hepatobiliary disorders			Hepatic failure, hepatitis, hepatotoxicity, jaundice, hepatic function abnormal	
Skin and subcutaneous tissue disorders	Photosensitivity reaction, rash including maculopapular		Toxic epidermal necrolysis, Stevens-Johnson syndrome,	

	and erythematous rashes		erythema multiforme, dermatitis exfoliative, photoonycholysis, skin hyperpigmentation[c]	
Musculoskeletal, connective tissue and bone disorders			Arthralgia, myalgia	
Renal and urinary disorders			Blood urea increased	

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

[a] Reversible and superficial discolouration of permanent teeth has been reported with the use of doxycycline, but frequency cannot be estimated from available data.

[b] in the setting of spirochete infections treated with doxycycline.

[c] with chronic use of doxycycline.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Medicines Authority, Post-Licensing Directorate, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwan SĠN 3000, E-mail: postlicensing.medicinesauthority@gov.mt or via the Malta ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal.

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Tetracyclines, ATC Code: J01 AA02.

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.

5.2 Pharmacokinetic properties

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.

5.3 Preclinical safety data

None stated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose, lactose, sodium starch glycolate, povidone, polyethylene glycol 6000, colloidal silicon dioxide, magnesium stearate.
Film-coating: hydroxypropylmethyl cellulose, polyethylene glycol 400, titanium dioxide and riboflavine.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Three years.

6.4 Special precautions for storage

Store below 25ºC. Protect from light and humidity.

6.5 Nature and contents of container

Doxat 100 mg film-coated tablets are packed in Aluminium/PVC/PVDC blisters of 1x10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Delorbis Pharmaceuticals Ltd.,
17 Athinon Street, Ergates Industrial Area, 2643 Ergates,
P.O. Box 28629, 2081 Lefkosia,
Cyprus, European Union

8. MARKETING AUTHORISATION NUMBER(S)

Cyprus:
Doxat 100 mg film-coated tablets: 014668

Malta:
Doxat 100 mg film-coated tablets: MA115/00701

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

28-11-2006/01-11-2011

10. DATE OF REVISION OF THE TEXT

January 2021