PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOXYCYL 100, capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of DOXYCYL 100 contains 100 mg doxycycline as doxycycline hyclate.

Contains sugar: Lactose monohydrate 109,353 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules

A yellow granular powder encapsulated within a no.3 capsule with a clear body and blue transparent cap.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by susceptible strains.

Upper and lower respiratory tract:

Sinusitis, pharyngitis, pneumonia (*Legionella* and *Mycoplasma*) and psittacosis.

Genito-urinary tract:

Non-specific urethritis (only if the strain is sensitive), lymphogranuloma venereum, chancroid and granuloma inguinale, gonorrhoea, gonococcal salpingitis, epididymitis, acute epididymo-orchitis, endocervical infections and syphilis (in cases of penicillin allergy).

Ophthalmic:

Trachoma and inclusion conjunctivitis.

Intestinal:

Cholera, Whipple's disease and tropical sprue.

Malaria:

For short-term prophylaxis of malaria due to *Plasmodium falciparum* in short-term travellers (< 4 months) going to areas where a high level of chloroquine resistance and/or pyrimethamine-sulfadoxine resistant strains have been reported and the traveller cannot tolerate mefloquine or other medicine for the prophylaxis of malaria.

Miscellaneous:

Rickettsial infections, brucellosis, tularemia, actinomycosis, Lyme disease, yaws, relapsing fever and Leptospirosis during the early infective phase.

4.2 Posology and method of administration

Posology

Adults

200 mg (2 capsules) during the first 24 hours as a single dose, followed by 100 mg (1 capsule)

daily during the following days.

CHILDREN *(< 50 kg)*

4 mg per kg body mass during the first 24 hours, and thereafter 2 mg per kg body mass daily during the following days.

Should only be used for children under 8 years of age on very strong indications and the effect of tetracyclines on teeth and bones should be considered.

In severe infections the initial dosage is maintained throughout the course of treatment.

Medication should be carried out for at least 24 to 48 hours after fever and other symptoms have disappeared.

For short-term malaria prophylaxis

ADULTS AND TEENAGERS

100 mg (1 capsule) daily

Contraindicated in children under 8 years.

To be started one or two days before departure to the area where malaria may occur, and continue taking the medicine every day throughout travel, and for four weeks after the last possible exposure to infection.

Trachoma

100 mg (1 capsule) daily for 40 days.

Nonspecific urethritis

100 mg (1 capsule) every 12 hours for 7 days.

Method of administration

For oral administration

DOXYCYL 100 is administered once daily and may be taken one hour before or two hours after meals. It should be taken with adequate liquid to avoid lodging of capsules in the distal oesophagus, as this may result in local corrosive irritation and ulceration.

4.3 Contraindications

- Hypersensitivity to doxycycline or any of the excipients listed in section 6.1.
- DOXYCYL 100 should not be used in pregnancy, as it crosses the placenta and is deposited in foetal bones and teeth. Pregnant women and the developing foetus are particularly susceptible to severe doxycycline-induced liver damage.
- When administered to women during the latter half of pregnancy, to nursing mothers, or during childhood up to the age of 12 years, permanent discoloration of the child's teeth may occur, as well as impaired bone growth. (see section 4.6).
- DOXYCYL 100 should not be given to patients with a known allergy to tetracyclines, since cross sensitivity may occur.
- Should be avoided in patients with systemic lupus erythematosus.
- DOXYCYL 100 should not be given to patients receiving antacid therapy, milk or calcium containing foods.
- Potentially hepatotoxic medication should not be given with DOXYCYL 100.

- The administration of DOXYCYL 100 is contraindicated in patients with porphyria.

4.4 Special warnings and precautions for use

Paediatric population

The use of medicines of the tetracycline class during tooth development (last half of pregnancy; infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow-grey-brown) (see section 4.3). This adverse reaction is more common during long-term use of the medicines but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. Use doxycycline in paediatric patients aged younger than 12 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.

The risk of permanent teeth staining is rare in children aged 8 years to less than 12 years, the use of doxycycline (e.g. DOXYCYL 100) should be carefully justified in situations where other medicines 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 (e.g. DOXYCYL 100). Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline medicines and treatment should be discontinued at the first evidence of skin erythema. Photoonycholysis has also been reported in patients receiving DOXYCYL 100 (see section 4.8).

Use in patients with impaired hepatic function

Do not use concomitantly with hepatotoxic medicines. Care must be taken when liver function is impaired. Abnormal hepatic function has been reported rarely and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline (e.g. DOXYCYL 100).

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 (e.g., DOXYCYL 100) (see section 4.8). If serious skin reactions occur, DOXYCYL 100 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 medicines, including doxycycline (e.g., DOXYCYL 100), 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 medicines.

Clostridium difficile associated diarrhoea (CDAD) has been reported with use of nearly all antibiotics, including doxycycline (e.g., DOXYCYL 100), and has ranged in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines 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 medicines.

Oesophagitis

Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving capsule and tablet forms of medicines in the tetracycline class, including doxycycline (e.g., DOXYCYL 100). 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 (e.g., DOXYCYL 100). 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 medicine cessation patients should be monitored until they stabilise. Concomitant use of isotretinoin or other systemic retinoids and DOXYCYL 100 should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri). (See section 4.5).

Venereal disease

When treating venereal disease, where co-existent syphilis is suspected, proper diagnostic procedures, including darkfield 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.

DOXYCYL 100 may interfere with some diagnostic tests including determination of urinary catecholamines or glucose.

Elderly patients

Special care should be taken in frail or elderly patients as they are susceptible to the hepatotoxic and anti-anabolic effects of DOXYCYL 100.

Myasthenia gravis

Due to a potential for weak neuromuscular blockade, care is advisable in patients with symptoms of myasthenia gravis as this may be aggravated in patients with this problem.

Jarisch-Herxheimer reaction

Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline (e.g., DOXYCYL 100) 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 (e.g., DOXYCYL 100) with methoxyflurane (see section 4.5).

Cross-sensitisation between tetracyclines are common.

It is recommended not to take DOXYCYL 100 and penicillin concomitantly, especially when a rapid bactericidal action is necessary, because of the possible antagonism of the action.

Excipients

DOXYCYL 100 contains sugar (lactose monohydrate). Patients with the rare hereditary problems of galactose intolerance total lactase deficiency, glucose-galactose malabsorption should not take DOXYCYL 100.

WHEN USED FOR MALARIA PROPHYLAXIS:

Because no form of prophylaxis is fully effective, the prevention of mosquito bites should be the mainstay of malaria prophylaxis. The following preventative measures to prevent mosquito bites should be taken:

- Endemic areas should preferably be visited during the dry season or when rainfall is low.
- High risk persons should avoid malaria areas altogether. These include:
  - babies and young children less than 5 years old
  - pregnant women
  - immunocompromised individuals such as those on long - term steroids, cancer patients, those on chemotherapy, AIDS patients and those who had their spleens removed.
- Not going outside between dusk and dawn, when mosquitos are most active.
- Applying insect repellent to exposed skin and clothing.
- Wearing long sleeves and trousers at night.
- Using mosquito nets, screens, coils or pads.

Should flu-like symptoms appear, the patient must inform the doctor that he/she has been to a malaria area.

Paediatric population

DOXYCYL 100 is not indicated for treating commonly occurring infections in children under 12 years of age (see section 4.3). For malaria prophylaxis, DOXYCYL 100 is contraindicated in children under 8 years of age.

4.5 Interaction with other medicines and other forms of interaction

The absorption of DOXYCYL 100 is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium and zinc, and therefore concomitant administration of DOXYCYL 100 with antacids, sucralfate, iron preparations, some foods such as milk and dairy

products, or other preparations containing such cations may result in subtherapeutic serum concentrations of DOXYCYL 100. Sodium bicarbonate and colestipol are reported to reduce DOXYCYL 100 absorption.

Doses of anticoagulants may need to be reduced if given concomitantly with DOXYCYL 100.

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 DOXYCYL 100 should be considered.

Alcohol may decrease the half-life of doxycycline as contained in DOXYCYL 100.

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

The concomitant use of tetracyclines (e.g., DOXYCYL 100) and methoxyflurane has been reported to result in fatal renal toxicity. See section 4.4.

Concomitant use of isotretinoin or other systemic retinoids and DOXYCYL 100 should be avoided. Each of these medicines 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 (see section 4.4).

Medicines 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 concomitant use is advised and an increase in DOXYCYL 100 dose may be required.

The nephrotoxic effects of DOXYCYL 100 may be exacerbated by diuretics.

DOXYCYL 100 may produce increased concentrations of lithium and digoxin.

It has been reported that DOXYCYL 100 increases the toxic effects of ergot alkaloids and methotrexate.

Penicillin should not be given concomitantly with DOXYCYL 100 as antagonism in action may occur, especially when a rapid bactericidal action is necessary.

DOXYCYL 100 may diminish the effectiveness of oral contraceptives. Alternative methods of contraception are advisable in women receiving DOXYCYL 100 therapy.

Quinapril contains magnesium carbonate and may interfere with the absorption of doxycycline (e.g. DOXYCYL 100).

4.6 Fertility, pregnancy and lactation

DOXYCYL 100 should not be used in pregnancy, as it crosses the placenta and is deposited in foetal bones and teeth. Pregnant women and the developing foetus are particularly susceptible to

severe doxycycline-induced liver damage.

When administered to women during the latter half of pregnancy, to nursing mothers, or during childhood up to the age of 12 years, permanent discoloration of the child's teeth may occur, as well as impaired bone growth. (See section 4.3).

Fertility

Data on fertility is not currently available.

Breastfeeding

DOXYCYL 100 is contraindicated in nursing mothers (see section 4.3).

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

Tabulated list of adverse reactions

MedDRA System Organ Class	**Frequent**	**Less frequent**	**Not known Cannot be estimated from the available data.**

Infections and infestations		Vaginal infection, candida Infection e.g. oral candidiasis results in soreness, redness and thrush in the mouth, which may extend into the trachea and bronchi, vaginal candidiasis, vulvovaginitis and pruritis ani, Pseudomembranous colitis, Clostridium difficile colitis	
Blood and lymphatic system disorders		Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hyper-sensitivity (including anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, exacerbation	Jarisch Herxheimer reaction[b] (see section 4.4)	

	of systemic lupus erythematosus, asthma, serum sickness)		
Congenital, familial and genetic disorders		Porphyria	
Endocrine disorders		Brown-black microscopic discolouration of thyroid glands	
Metabolism and nutrition disorders		Decreased appetite	Vitamin deficiency
Nervous system disorders	Headache	Benign intracranial hypertension (pseudotumor cerebri)*, fontanelle bulging	
Psychiatric disorders		Anxiety	
Ear and labyrinth disorders		Tinnitus	
Vascular disorders	Hypotension	Flushing	
Gastrointestinal	Nausea/ vomiting	Dyspepsia	Tooth discolouration[a]

disorders		(heartburn/ gastritis), pancreatitis, oesophageal ulcer, oesophagitis, enterocolitis, fulminating enteritis (due to resistant staphylococci), inflammatory lesions (with monilial overgrowth) in the anogenital region, dysphagia, abdominal pain, diarrhoea, glossitis, stomatitis, dry mouth, tongue discoloration	
Hepato-biliary disorders		Hepatic failure, hepatitis, hepatotoxicity, jaundice, abnormal hepatic function	
Skin and Sub-cutaneous	Photosensitivity reaction, rash	Drug Reaction with Eosinophilia and	

tissue disorders	including maculopapular and erythematous rashes, Henoch- Schonlein purpura, urticaria, angioneurotic oedema, angioedema	Systemic Symptoms (DRESS), Toxic epidermal necrolysis, Stevens- Johnson syndrome, Erythema multiforme, exfoliative dermatitis, photoonycholysis, skin hyperpigmentation[c]	
Musculoskeletal, connective tissue and bone disorders		Arthralgia, myalgia	
Renal and urinary disorders		Increased blood urea[d]	
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.

[a] DOXYCYL 100 is deposited in deciduous and permanent teeth causing discolouration and enamel hypoplasia. Milk teeth are affected if given to children 3 months to six years, and permanent teeth if given to children up to 12 years (frequency cannot be estimated from available data).

[b] in the setting of spirochete infections treated with DOXYCYL 100.

[c] with chronic use of DOXYCYL 100.

[d] Usual therapeutic doses given to patients with renal disease increase the severity of ureamia with increased excretion of nitrogen and losses of sodium, accompanied by acidosis and hyperphosphataemia. These effects are related to the dose and severity of renal impairment and are due to the anti-anabolic effects of DOXYCYL 100.

The use of expired DOXYCYL 100 may lead to the Fanconi-type syndrome which is characterised by polyuria and polydipsia with nausea, vomiting, proteinuria, glucosuria, acidosis, amino-aciduria, hypophosphataemia, hypocalcaemia, hypokalaemia and hyperuricaemia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

Reporting can also be done directly to Adcock Ingram Limited at:

Adcock Ingram Limited:

E-mail: Adcock.aereports@adcock.com

Tel: 011 635 0134

4.9 Overdose

In the event of sensitivity reactions, treatment should be withdrawn. Symptoms should be treated symptomatically.

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 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: tetracyclines, ATC code: J01AA02

Doxycycline is a bacteriostatic antibiotic and inhibits bacterial protein synthesis by binding to the 30S ribosomal subunit with subsequent misreading of information for protein synthesis. It is bacteriostatic against strains of a wide range of gram-positive and gram-negative organisms.

It is effective *in-vitro* against the following organisms (*in-vitro* activity does not necessarily imply *in-vivo* efficacy):

Vibrio cholerae, Ureaplasma urealyticum, Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia psittaci, Borrelia recurrensis, Calymmatobacterium granulomatis, Borrelia burgdorferi, penicillin-sensitive *Neisseria gonorrhoeae* and *Rickettsiae.*

Doxycycline is also effective against the following organisms *in-vitro*:

Clostridium tetani, Listeria monocytogenes, Haemophilus ducreyi, Campylobacter jejuni, Leptospira, Actinomyces israelli, Bacillus anthracis, Pasteurella multocida, Streptobacillus moniliformis, Erysipelothrix rhusiopathiae, Francisella tularensis, Treponema pertenue* and *Plasmodium falciparum.*

* *in-vitro* sensitivity tests must be performed.

Resistant pathogens

Many strains of the following are resistant:

Staphylococci, Enterococci, Proteus vulgaris, fungi and *yeasts [*except *Actinomyces],* *Pseudomonas aeruginosa* [all strains], *E. coli, Shigella, Streptococcus.*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Brilliant blue (C.I. 42090)

Erythrosine (C.I. 45430)

Gelatin

Lactose monohydrate

Magnesium stearate

Purified talc

Starch maize

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C in airtight containers.

Protect from light.

6.5 Nature and contents of container

6 capsules are packed in a clear polyvinylchloride film sealed with silver, aluminium foil backing. One or more blister strips are packed into an outer cardboard carton together with a leaflet.

30 or 100 capsules are packed in a white polypropylene securitainer and sealed with a white low density polyethylene snap-on cap together with a leaflet.

100 capsules are packed in a white high density polyethylene container and sealed with a white polypropylene cap, together with a white silica gel capsule and a leaflet.

500 capsules are packed in a white polypropylene securitainer and sealed with a white low density polyethylene snap-on cap together with a silica gel sachet and leaflet.

1 000 capsules are packed into amber polyvinyl chloride Xactic containers and sealed with a white high density polyethylene screw cap together with a silica gel sachet and leaflet.

1 000 capsules are packed in a white high density polyethylene container and sealed with a white polypropylene cap, together with a white silica gel capsule and a leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Limited

1 New Road,

Erand Gardens,

Midrand, 1685

Customer Care: 0860 ADCOCK/ 232625

8. REGISTRATION NUMBER

28/20.1.1/0059

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 26 April 1994

10. DATE OF REVISION OF THE TEXT

20 September 2022

Namibia: NS2 04/20.1.1/0022

adcock ingram