SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DOXYCYL CAPSULES, 50 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule of DOXYCYL CAPSULES contains 50 mg doxycycline as doxycycline hyclate.
Contains sugar: Lactose monohydrate 77,6 mg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsules
A yellow granular powder encapsulated within a no. 4 opaque capsule, with a red cap and brown body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOXYCYL CAPSULES is indicated for the treatment of acne.

4.2 Posology and method of administration

Posology

50 mg (1 capsule) twice daily.

Method of administration

For oral administration
DOXYCYL CAPSULES may be taken one hour before or two hours after meals. It should be taken with adequate liquid with the patient in an upright position and well before retiring for the night, to avoid lodging of capsules in the distal oesophagus, as this may result in local corrosive irritation and ulceration.
DOXYCYL CAPSULES should be given with plenty of fluid. It may be given with food if gastric irritation occurs.

4.3 Contraindications

- Hypersensitivity to doxycycline or any of the excipients listed in section 6.1.
- DOXYCYL CAPSULES should not be used in pregnancy, as it crosses the placenta and is deposited in foetal bones and teeth. Pregnant woman 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 discolouration of the child's teeth may occur, as well as impaired bone growth (see section 4.6).
- DOXYCYL CAPSULES 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.
- Potentially hepatotoxic medication should not be given with DOXYCYL CAPSULES.
- The administration of DOXYCYL CAPSULES is contraindicated in patients with porphyria.

4.4 Special warnings and precautions for use

Paediatric population

The use of DOXYCYL CAPSULES 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) and should therefore not be used during these periods (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 in patients with impaired hepatic function

Do not use concomitantly with hepatotoxic medicines.

Use with care in patients with liver function impairment.

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 DOXYCYL CAPSULES. 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 DOXYCYL CAPSULES 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 such as DOXYCYL CAPSULES (see section 4.8). If serious skin reactions occur, DOXYCYL CAPSULES should be discontinued immediately and appropriate therapy should be instituted.

Photosensitivity
Patients who may be exposed to direct sunlight should be warned of the risk of photosensitivity (see section 4.8). Patients likely to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with DOXYCYL CAPSULES and treatment should be discontinued at the first evidence of skin erythema.

Photoonycholysis has also been reported in patients receiving doxycycline such as DOXYCYL CAPSULES (see section 4.8).

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

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, 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 medicines.

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 medicines 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 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
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 CAPSULES.). 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 (e.g., DOXYCYL CAPSULES). 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 medicine cessation patients should be monitored until they stabilise. Concomitant use of isotretinoin or other systemic retinoids and DOXYCYL CAPSULES should be avoided because isotretinoin is also known to cause benign intracranial hypertension (pseudotumor cerebri). (See section 4.5).

Diagnostic tests
DOXYCYL CAPSULES 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 CAPSULES.

Myasthenia gravis
Care is advisable in patients with symptoms of myasthenia gravis as this may be aggravated in patients with this problem.

Cross-sensitisation between tetracyclines is common.

Methoxyflurane
Caution is advised in administering tetracyclines (e.g.,DOXYCYL CAPSULES) with methoxyflurane (see section 4.5).

Jarisch-Herxheimer reaction
Some patients with spirochete infections may experience a Jarisch-Herxheimer reaction shortly after doxycycline (e.g., DOXYCYL CAPSULES) treatment is started. Patients should be reassured that this is a usually self-limiting consequence of antibiotic treatment.

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

Paediatric population
DOXYCYL CAPSULES is not indicated for treating commonly occurring infections in children under 12 years of age (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction
The absorption of DOXYCYL CAPSULES is reduced by divalent and trivalent cations such as aluminium, bismuth, calcium, iron, magnesium and zinc, and therefore concomitant administration of DOXYCYL CAPSULES with antacids, kaolin, 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 CAPSULES.

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

CAPSULES.

Sodium bicarbonate and colestipol are reported to reduce DOXYCYL CAPSULES absorption.

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

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

Alcohol may decrease the half-life of DOXYCYL CAPSULES.

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

DOXYCYL CAPSULES may produce increased concentrations of lithium and digoxin.

It has been reported that DOXYCYL CAPSULES increase the toxic effects of ergot alkaloids and methotrexate.

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

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

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

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 CAPSULES dose may be required.

There is a possible increased risk of benign intra-cranial hypertension when DOXYCYL CAPSULES given with retinoids. Concomitant use should be avoided. Each of these medicines used alone has been associated with benign intracranial hypertension (pseudotumor cerebri) (see section 4.4).

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

Antibacterials inactivate oral typhoid vaccines. Avoid administration of vaccine during treatment with DOXYCYL CAPSULES.

Laboratory test interactions
False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test (see section 4.4).

4.6 Fertility, pregnancy and lactation

Fertility

Data on fertility is not currently available.

Pregnancy

DOXYCYL CAPSULES should not be used in pregnancy, as it crosses the placenta and is deposited in foetal bones and teeth. Pregnant woman 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 discolouration of the child's teeth may occur, as well as impaired bone growth (see section 4.3).

Breastfeeding

DOXYCYL CAPSULES are 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 DOXYCYL CAPSULES and in such cases; patients must be informed to refrain from driving or operating machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

MeDRA System Organ Class	**Frequent**	**Less frequent**	**Not known Cannot be estimated from the available data.**
Infections and infestations		Vaginal infection Oral candidiasis, vulvovaginitis, and pruritis ani can occur due to overgrowth of Candida albicans. Oral candidiasis results in soreness, redness and thrush in the mouth, which may extend into the trachea and bronchi	
Metabolism and nutrition disorders		Porphyria, decreased appetite	Vitamin deficiency may occur
Blood and lymphatic system disorders		Haemolytic anaemia, neutropenia, thrombocytopenia, eosinophilia	
Immune system disorders	Hyper-sensitivity reactions (incl. anaphylactic shock, anaphylactic reaction, anaphylactoid reaction, Henoch-Schonlein purpura, angioneurotic oedema, fixed drug	Jarisch Herxheimer reaction[B] (see section 4.4)	

	eruptions, hypotension, pericarditis, angioedema, asthma, dyspnoea, serum-sickness, peripheral oedema, tachycardia and urticaria		
Endocrine disorders		Brown-black microscopic discolouration of thyroid glands	
Nervous system disorders	Headache	Anxiety, bulging fontanelles in infants, benign intracranial hypertension (pseudotumor cerebri[A])	
Ear and labyrinth disorders		Tinnitus[D]	
Eye disorders		Visual disturbance[D]	
Vascular disorders		Flushing	
Gastro-intestinal disorders	Nausea, vomiting, dry mouth	Dyspepsia (heartburn/ gastritis), pancreatitis, glossitis, pseudo membranous colitis, *Clostridium difficile colitis,* oesophageal ulcer, oesophagitis, enterocolitis, inflammatory lesions (with monilial overgrowth) in the	Tooth discolouration[E]

		anogenital region, dysphagia, abdominal pain, diarrhoea, stomatitis, discolouration of the tongue	
Hepato-biliary disorders		Hepatotoxicity, abnormal hepatic function, hepatitis, jaundice, hepatic failure	
Skin and sub-cutaneous tissue disorders	Exfoliative dermatitis, exacerbation of systemic lupus erythematosus, (see section 4.3), photosensitivity reaction, rash including maculo-papular and erythematous rashes	Skin hyperpig-mentation[C,] erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis and photo-onycholysis have been reported, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	
Musculo-skeletal and connective tissue disorders		Arthralgia, myalgia	
Renal and urinary system disorders		Increased blood urea[F]	

[A] In association with tetracyclines, including doxycycline, benign intracranial hypertension has been reported with possible symptoms of headache, vomiting, visual disturbances including blurred vision, scotoma, diplopia or permanent loss of vision. The manifestation of clinical symptoms, including headache or visual disturbances, should suggest a possible diagnosis of intracranial

hypertension. If an increase in intracranial pressure is suspected during treatment with DOXYCYL CAPSULES, administration should be discontinued.

[B] In the setting of spirochete infections treated with DOXYCYL CAPSULES.

[C] With chronic use of DOXYCYL CAPSULES.

[D] Associated with Benign intracranial hypertension (pseudotumor cerebri)

[E] DOXYCYL CAPSULES are 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).

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

The use of expired DOXYCYL CAPSULES may lead to the Fanconi-type syndrome which is characterised by polyuria and polydipsia with nausea, vomiting, proteinuria, glucosuria, acidosis, amino-aciduria, hypophosphataemia and 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 and supportive and gastric lavage is indicated.

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 consequent 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*:
Haemophilus ducreyi, Actinomyces israelli, Francisella tularensis and *Treponema pertenue.*

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* and *Streptococcus.*

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Black oxide (C.I. 77499)
Gelatin
Lactose monohydrate
Magnesium stearate
Ponceau 4R (C.I. 16255)
Purified talc
Red oxide (C.I. 77491)
Starch maize dried
Titanium dioxide (C.I. 77891)
Yellow oxide (C.I. 77492)

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.
Keep in original packaging until required for use.
Protect from light.

6.5 Nature and contents of container

30 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.

30 capsules, together with a leaflet, are packed in a white polypropylene container and sealed with a white low density polyethylene screw cap or a white polypropylene cap.

Not all packs 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

27/20.1.1/0495

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 01 April 1993

10. DATE OF REVISION OF THE TEXT

20 September 2022

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