SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE
CYCLIDOX CAPSULES (Capsules)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains doxycycline hydrochloride equivalent to 100 mg doxycycline.
Contains sugar: Lactose 161,6 mg
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Capsules.
CYCLIDOX CAPSULES are no. 2, opaque white, hard gelatine capsules printed "CYCLIDOX 100" in red and containing a yellow powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Infections caused by susceptible strains of pathogens:
Upper and lower respiratory tract: Sinusitis, pharyngitis, pneumonia (Legionella and Mycoplasma) and psittacosis.
Genito-urinary tract: Non-specific urethritis, 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 prophylaxis: For short-term prophylaxis of malaria in areas where a high level of chloroquine resistance has been reported and the traveller cannot tolerate mefloquine or other medicines for the prophylaxis of malaria.
Miscellaneous: Rickettsial infections (including Rocky Mountain spotted fever, murine typhus, recrudescent epidemic typhus, scrub typhus, Q fever), anthrax, brucellosis, tularaemia, actinomycosis, Lyme disease, yaws and relapsing fever. Leptospirosis, during the early infective phase.

4.2 Posology and method of administration
Posology
CYCLIDOX CAPSULES may be taken with food or milk to prevent gastric irritation, but not with preparations, e.g., antacids containing calcium or other di/trivalent metals.
Adults: 100 mg every 12 hours during the first 24 hours, followed by 100 mg once a day, or twice daily in severe infections.
Medication should be carried out for at least 24-48 hours after fever and other symptoms have disappeared.
Malaria prophylaxis: For adults, the recommended dose is 100 mg daily. For children over 8 years of age, the recommended dose is 2 mg/kg given once daily up to the daily adult dose. Prophylaxis should begin 1-2 days before travel to the malarious area. Prophylaxis should be continued daily during travel in the malarious area and for 4 weeks after the traveller leaves the malaria area. The duration of prophylactic treatment should not exceed 4 months.

Paediatric population
CYCLIDOX CAPSULES is contraindicated in children under the age of 12 years (see section 4.3).

Method of administration
For oral administration.

4.3 Contraindications
- Hypersensitivity to doxycycline (as in CYCLIDOX CAPSULES), any of the tetracyclines or any of the other ingredients in the capsules (see section 6.1).
- The use of medicines of the tetracycline class (such as CYCLIDOX CAPSULES) during tooth development (pregnancy, infancy and childhood to the age of 12 years) may cause permanent discolouration of the teeth (yellow-grey-brown). This is frequent during long-term use but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. CYCLIDOX CAPSULES is contra-indicated in these groups of patients.
- Children under 12 years of age: Contraindicated in children under the age of 12 years. As with other tetracyclines, doxycycline (as in CYCLIDOX CAPSULES) forms a stable calcium complex in any bone-forming tissue. A decrease in the fibula growth rate has been observed in prematures given oral tetracyclines in doses of 25 mg/kg every 6 hours. This reaction was shown to be reversible when the medicine was discontinued (see above about use during tooth development).
- Pregnancy: Doxycycline (as in CYCLIDOX CAPSULES) is contraindicated in pregnancy. The risks associated with the use of tetracyclines during pregnancy are predominantly due to effects on teeth and skeletal development (see above about use during tooth development) (see section 4.6).
- Nursing mothers: Tetracyclines, such as doxycycline (as contained in CYCLIDOX CAPSULES), are excreted into milk and are therefore contraindicated in nursing mothers (see above about use during tooth development) (see section 4.6).
- Patients with systemic lupus erythematosus.
- Patients with porphyria (see section 4.4).
- Doxycycline (as in CYCLIDOX CAPSULES) is contraindicated in patients with renal impairment. Potentially hepatotoxic medicine should not be given with doxycycline (see section 4.4).
- Preparations containing iron, aluminium, calcium or magnesium decrease the absorption of doxycycline, therefore do not give to patients receiving antacid therapy or calcium-containing foods.

4.4 Special warnings and precautions for use
- Use in patients with renal impairment: Excretion of doxycycline by the kidney is about 40 % / 72 hours in patients with normal renal function. This percentage excretion may fall to a range as low as 1-5 % / 72 hours in patients with severe renal insufficiency (creatinine clearance below 10 mL/min). Studies have shown no significant difference in the serum half-life of doxycycline in patients 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 (as in CYCLIDOX CAPSULES) in patients with impaired renal function (see section 4.3)
- Porphyria: There have been reports of porphyria in patients receiving tetracyclines (see section 4.3)
- *Photosensitivity:* Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some patients taking tetracyclines, including doxycycline (as in CYCLIDOX CAPSULES). 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.
- Use in patients with impaired hepatic function: CYCLIDOX CAPSULES should be administered with caution to patients with hepatic impairment or those receiving potentially hepatotoxic medicines. Abnormal hepatic function has been reported and has been caused by both the oral and parenteral administration of tetracyclines, including doxycycline (as contained in CYCLIDOX CAPSULES).
- *Microbiological overgrowth:* The use of antibiotics may occasionally result in over-growth 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 (as in CYCLIDOX CAPSULES), 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.
- *Oesophagitis:* Instances of oesophagitis and oesophageal ulcerations have been reported in patients receiving medicines of the tetracycline class, including doxycycline (as in CYCLIDOX CAPSULES). Most of these patients took medicines immediately before going to bed or with inadequate amounts of fluid.
- Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in patients receiving full therapeutic medicines. These conditions disappeared rapidly when the medicine was discontinued.
- *Venereal disease:* When treating venereal diseases, 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 (such as doxycycline in CYCLIDOX CAPSULES) to patients with myasthenia gravis.
- *Systemic lupus erythematous:* Tetracyclines (such as doxycycline in CYCLIDOX CAPSULES) can cause exacerbation of systemic lupus erythematosus (SLE).
- *Methoxyflurane:* Caution is advised in administering tetracyclines (such as doxycycline in CYCLIDOX CAPSULES) with methoxyflurane (see section 4.5).
- Pseudotumor cerebri may occur.

Information for patients - Malaria prophylaxis:
No present-day antimalarial medicine, including doxycycline (as in CYCLIDOX CAPSULES), guarantees protection against malaria. Should flu-like symptoms appear, the patient must inform the doctor that he/she has been in a malarious area.

The prevention of mosquito bites should form 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 in years when rainfall is low.
- High risk patients should avoid malaria areas altogether.

High risk patients include:
- babies and young children less than 5 years of age,
- pregnant women,
- immuno-compromised individuals such as those on long-term steroids, cancer patients and those on chemotherapy, Aids patients and those who have had their spleens removed.

- Not going outside between dusk and dawn, when mosquitoes are most active.
- Applying insect repellent to exposed skin and clothing.
- Wearing long sleeves and trousers at night.
- Using mosquito nets, screens, coils and pads.

Paediatric population
Tooth discolouration, enamel hypoplasia and retarded bone growth may occur in children under 12 years of age (these effects may also occur in the foetus if given to pregnant women) (see section 4.3).

4.5 Interaction with other medicines and other forms of interaction
- 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.
- Bacteriostatic medicines may interfere with the bactericidal action of penicillin, therefore it is advisable to avoid giving doxycycline in conjunction with penicillin.
- Absorption of doxycycline may be impaired by concurrently administered antacids containing aluminium, calcium, magnesium or other medicines containing these cations; oral zinc, iron salts or bismuth preparations. Dosages should be maximally separated.
- Phenobarbitone, carbamazepine, primidone and phenytoin may increase the metabolism of doxycycline (reduced half-life). An increase in the daily dosage of doxycycline (as in CYCLIDOX CAPSULES) should be considered.
- Alcohol may decrease the half-life of doxycycline.
- The concurrent use of tetracyclines and methoxyflurane has been reported to result in fatal renal toxicity (see section 4.4)

- Doxycycline may decrease the efficacy of oral contraceptives.
- 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.
- 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 concurrent use is advised and an increase in doxycycline dose may be required.
- *Laboratory test interactions:*

False elevations of urinary catecholamine levels may occur due to interference with the fluorescence test.
- Absorption of CYCLIDOX CAPSULES is diminished by milk, alkalis, antacids, aluminium hydroxide and other di- and trivalent cations such as calcium, iron and magnesium if they are given concomitantly.
- Doses of anticoagulants, such as warfarin, may need to be reduced if given concomitantly with CYCLIDOX CAPSULES.
- Penicillin should not be given concomitantly with CYCLIDOX CAPSULES as antagonism in action may occur.
- The metabolism of CYCLIDOX CAPSULES may be enhanced by inducers of hepatic enzymes such as alcohol (chronic use), anti-epileptics including carbamazepine, phenobarbitone and phenytoin, and rifampicin.

4.6 Fertility, pregnancy and lactation
- *Pregnancy:* CYCLIDOX CAPSULES is contraindicated in pregnancy (see section 4.3).
- *Lactation:* Doxycycline (as in CYCLIDOX CAPSULES) is excreted into milk and are therefore contraindicated in nursing mothers (see section 4.3).

4.7 Effects on ability to drive and use machines
The effect of doxycycline, as in CYCLIDOX CAPSULES, on the ability to drive or operate heavy machinery has not been studied. There is no evidence to suggest that CYCLIDOX CAPSULES may affect these abilities.

4.8 Undesirable effects
a. Summary of the safety profile
Frequency unknown: cannot be estimated from the available data.

b. Tabulated summary of adverse reactions

MedDRA system organ class	Frequency	Adverse reactions
Infections and infestations	Frequency unknown	Overgrowth of non-susceptible organisms may cause candidiasis, glossitis, staphylococcal enterocolitis, pseudomembranous colitis (with Clostridium difficile overgrowth) and inflammatory lesions (with candidal overgrowth) in the anogenital region.
Blood and the lymphatic system disorders	Frequency unknown	Haemolytic anaemia, thrombocytopenia, neutropenia, porphyria and eosinophilia. Vitamin deficiencies may occur.
Immune system disorders	Frequency unknown	Hypersensitivity reactions, including anaphylactic shock, anaphylaxis, anaphylactoid reactions, anaphylactoid purpura; hypotension; pericarditis; angioneurotic oedema; exacerbation of systemic lupus erythematosus; dyspnoea; serum sickness; peripheral oedema; tachycardia and urticaria.
Endocrine disorders	Frequency unknown	When given over prolonged periods, tetracyclines have been reported to produce brown-black microscopic discoloration of thyroid tissue. No abnormalities of thyroid function are known to occur.
Nervous system disorders	Frequency unknown	Headache. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported in some individuals receiving full therapeutic dosages of tetracyclines. These are reversible on stopping the medicine. Symptoms include blurring of vision, scotomata and diplopia. Permanent visual loss has been reported.
Ear and labyrinth disorders	Frequency unknown	Tinnitus.
Gastrointestinal disorders	Frequency unknown	Gastrointestinal symptoms are usually mild and seldom necessitate discontinuation of treatment. Abdominal pain, stomatitis, anorexia, nausea, vomiting, diarrhoea, dyspepsia and rarely dysphagia. Oesophagitis and oesophageal ulceration have been reported in patients receiving doxycycline. A significant proportion of these cases occurred with the hydrochloride salt in the capsule form (see section 4.4). Tetracyclines may cause discoloration of teeth and enamel hypoplasia, but usually only after long-term use.
Hepatobiliary disorders	Frequency unknown	Transient increases in liver function tests, hepatitis, jaundice, hepatic failure and pancreatitis have been reported rarely.
Skin and subcutaneous tissue disorders	Frequency unknown	Rashes including maculopapular and erythematous rashes occur, exfoliative dermatitis, erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis, photo-onycholysis. Photosensitivity (see section 4.4).
Musculoskeletal, connective tissue disorders	Frequency unknown	Arthralgia and myalgia.
Renal and urinary disorders	Frequency unknown	Increased blood urea (see section 4.4).
Reproductive system and breast disorders	Frequency unknown	Vaginitis.
General disorders and administrative site conditions	Frequency unknown	The use of doxycycline beyond the indicated date of expiry may lead to the Fanconi type syndrome which is characterised by polyuria and polydipsia with nausea, vomiting, proteinuria, glucosuria, acidosis and aminoaciduria. CYCLIDOX CAPSULES has anti-anabolic action, which may cause a rise in blood urea. In the elderly a negative nitrogen balance may be induced.

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

4.9 Overdose
See section 4.8. Treatment is supportive and symptomatic.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics.
Pharmacotherapeutic group: Tetracyclines; ATC code: J01AA02

Mechanism of action:
Doxycycline is a broad-spectrum tetracycline antibiotic and inhibits bacterial protein synthesis (30S ribosomes). CYCLIDOX CAPSULES is particularly effective in vitro against the following organisms (in vitro activity does not necessarily imply *in vivo* activity): *Vibrio cholerae, Ureaplasma urealyticum, Mycoplasma pneumoniae, Chlamydia trachomatis, Chlamydia psittaci, Borrelia recurrentis, Calymmatobacterium granulomatis, Borrelia burgdorferi, penicillin-sensitive Neisseria gonorrhoeae* and *Rickettsiae*. CYCLIDOX CAPSULES 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* and *Erysipelothrix rhusiopathiae*.
CYCLIDOX CAPSULES may also show some effect against the following organisms: *Bacteroides species* and *Fusobacterium nucleatum*.
* = in vitro sensitivity tests must be performed.

Resistant Pathogens: Many strains of the following are resistant: Staphylococci, Enterococci, Proteus vulgaris, Fungi and yeast (except Actinomyces), Pseudomonas aeruginosa (all strains), Streptococcus pneumoniae, E. coli, and Shigella.

Doxycycline is well absorbed. After an oral dose of 200 mg of doxycycline, plasma concentrations reach a maximum of 3 µg/mL at 2 hours and are well maintained, and thus dosage once daily is usually adequate. Absorption is diminished by the presence of iron, aluminium, calcium and magnesium. Doxycycline is widely distributed into pleural and peritoneal fluid, saliva, semen and prostatic fluid. It passes the placental barrier readily and is also present in the milk of lactating patients. It is concentrated by the liver and excreted, by way of the bile, into the intestine from which it is partially reabsorbed. Conventional doses of doxycycline are not excreted to the same extent as other tetracyclines and it does not accumulate significantly in the blood of patients with renal failure. Extrarenal infections in individuals may be treated with doxycycline when indicated. Doxycycline is excreted in the faeces, largely as an inactive conjugate or chelate. It also has less impact on the intestinal microflora.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule content:
Lactose
Magnesium stearate
Purified talc
Starch maize dried

Capsule shell:
Gelatine {printing ink: titanium dioxide CI77891}; methyl paraben 0,8 % and propyl paraben 0,2 % {as preservatives}

6.2 Incompatibilities
None known.

6.3 Shelf life
60 months (White HDPE jars).
36 months (PVC/PVDC/Al blister packs & White polypropylene securitainers with LDPE/MDPE lids).

6.4 Special precautions for storage
Store at or below 25 °C and protect from light.

6.5 Nature and contents of container
- Blister strips of 6's or 10's comprised of 250 um clear PVC/PVDC on 20 um printed aluminium foil.
- White, polypropylene securitainers with LDPE/MDPE lids with a foam insert
- 1 kg white, HDPE screw-on type neck finish jar

Pack sizes: 6, 14, 30, 100, 500 and 1 000 capsules
- Blister packs: 6, 14, 30 and 100 capsules
- Securitainers: 100 and 500 capsules
- Jars: 1 000 capsules

Not all pack sizes may be marketed.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Trinity Pharma (Pty) Ltd.
3 Gwen Lane, 4th Floor, Sandton, Gauteng
2031

8. REGISTRATION NUMBER(S)
Q/20.1.1/283

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
28 March 1983

10. DATE OF REVISION OF THE TEXT
26 January 2023

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