Please note: This application for registration is submitted as a duplicate and hence [PRODUCT NAME] is used in 1.3 to indicate the names as proposed:

Master (Proposed proprietary name)	**Duplicate (Proposed proprietary name)**
Lymac 300 mg: 51/20.1.1/0887	Lymecycline 300 mg Unicorn: 51/20.1.1/0888

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

[Product name] hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 408 mg of lymecycline equivalent to 300 mg tetracycline base.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

[Product name] hard capsules.

Hard gelatin capsule, blue cap and white body.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Infections caused by susceptible strains of pathogens:

Upper and lower respiratory tract infections: Sinusitis, pharyngitis, mycoplasma pneumoniae, psittacosis and chronic bronchitis.

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

Soft tissue: Acne.

Ophthalmic infections: Trachoma and inclusion conjunctivitis.

Intestinal infections: Cholera, Whipple's disease and tropical sprue.

Miscellaneous infections: Rickettsial-infections, brucellosis, tularemia, actinomycosis, Lyme disease, yaws, relapsing fever, leptospirosis during the early infective phase.

4.2 Posology and method of administration

Posology

The usual dose for ADULTS is 300 mg every 12 hours (depending on the severity of the infection). The maximum dose should not exceed 3 g daily for adults and 50 mg/kg body mass per day for children.

Special populations

Paediatric population

Use in children under the age of 12 years is not recommended.

Method of administration

The capsules should be swallowed whole with adequate liquid either one hour before meals or two hours after meals to avoid lodging of capsules in the distal oesophagus as this may result in local corrosive irritation and ulceration.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Its use is contraindicated in patients with overt renal insufficiency and in children aged under 12 years due to the risk of permanent dental staining and enamel hypoplasia.
- Concurrent treatment with oral retinoids (see section 4.5).
- Should not be given to patients with systemic lupus erythematosus.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Oesophageal irritation and ulceration

Solid dosage forms of the tetracyclines may cause oesophageal irritation and ulceration. To avoid oesophageal irritation and ulceration, adequate fluids (water) should be taken with [Product name] (see section 4.2).

Caution should be exercised if the product is administered to patients with impaired renal or hepatic function.

Hepatotoxicity

Overdosage could result in hepatotoxicity.

Antibiotic resistance

Prolonged use of broad spectrum antibiotics may result in the appearance of resistant organisms and superinfection.

Phototoxicity

Due to the risks of photosensitivity, it is recommended to avoid exposure to direct sunlight and ultraviolet light during the treatment which should be discontinued if erythematous cutaneous manifestations occur.

Expired medication

The use of expired tetracyclines can lead to renal tubular acidosis (Pseudo-Fanconi syndrome) readily reversible when treatment is discontinued altogether.

Systemic lupus erythematosus

May cause exacerbation of systemic lupus erythematosus.

Myasthenia gravis

Can cause weak neuromuscular blockade so should be used with caution in myasthenia gravis.

Hepatic impairment

Care should be exercised when administering tetracyclines to patients with hepatic impairment.

Paediatric population

The product should not be used in children below 12 years of age due to the risk of permanent dental staining and enamel hypoplasia (see section 4.2).

Elderly population

Elderly patients are susceptible to hepatotoxic medicines and antianabolic effects of tetracyclines.

4.5 Interaction with other medicines and other forms of interaction

Simultaneous administration of iron preparations and anti-acids, magnesium/aluminium and calcium hydroxides, oxides, salts, cholestyramine, bismuth chelates, sucralfate and quinapril may decrease tetracycline absorption. Enzyme inducers such as barbiturates, carbamazepine, phenytoin may accelerate the decomposition of tetracycline due to enzyme induction in the liver thereby decreasing its half-life. These products should not be taken within two hours before or after taking [Product name].

Patients should not receive antacid therapy or milk concomitantly.

Concomitant use of oral retinoids and vitamin A (above 10 000 IU/day) should be avoided as this may increase the risk of benign intracranial hypertension. An increase in the effects of anticoagulants may

occur with tetracyclines with an increased risk of haemorrhage. Concomitant use of diuretics should be avoided.

Do not use concomitantly with hepatotoxic medicines.

Bacteriostatic medicines including lymecycline may interfere with the bacteriocidal action of penicillin and beta-lactam antibiotics. It is advisable that tetracycline-class drugs and penicillin should not therefore be used in combination.

Tetracyclines and methoxyflurane used in combination have been reported to result in fatal renal toxicity.

Tetracyclines may diminish the effectiveness of oral contraceptives.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental dyschromia and enamel hypoplasia (see section 4.3).

Pregnancy

Tetracyclines readily cross the placental barrier. Therefore, [Product name] should not be administered to pregnant women.

Breastfeeding

Tetracyclines are distributed into milk. Therefore, [Product name] 300 should not be administered to breast-feeding women (risk of enamel hypoplasia or dental dyschromia in the infant) (see section 4.3).

Fertility

No data on the effect on fertility is available.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. [Product name] can cause visual disturbances and dizziness so patients should be warned not to drive or operate machinery until they know what effect [Product name] has on them.

4.8 Undesirable effects

Tabulated list of adverse reactions

The most frequently reported adverse events with [Product name] are gastrointestinal disorders of nausea, abdominal pain, diarrhoea and nervous system disorder of headache. The most serious adverse events reported with [Product name] are Stevens Johnson syndrome, anaphylactic reaction, angioedema and intracranial hypertension.

System Organ Class	**Frequency**	
	Adverse reactions	**Frequency**
Blood and lymphatic system disorders	Neutropenia Thrombocytopenia Haemolytic anaemia Eosinophilia	Unknown
Immune system disorder	Anaphylactic reaction Hypersensitivity Urticaria Angioedema Maculopapular rashes	Unknown

	Exfoliative dermatitis Pericarditis Henoch-Schönlein purpura (anaphylactoid purpura)	
Nervous system disorders	Headache	Frequent
	Dizziness Intracranial hypertension	Unknown
Eye disorders	Visual disturbance	Unknown
Gastrointestinal disorders	Nausea Abdominal pain Diarrhoea	Frequent
	Epigastralgia Glossitis Vomiting Enterocolitis	Unknown
Hepatobiliary disorders	Jaundice Hepatitis	Unknown
Skin and subcutaneous	Erythematous rash	Unknown

tissues disorders	Photosensitivity of the skin and nails; onycholysis and nail discoloration may occur Pruritus Stevens Johnson syndrome	
General disorders and administration site conditions	Pyrexia	Unknown
Investigations	Transaminases increased Blood alkaline phosphatase increased Blood bilirubin increased	Unknown

c. Description of selected adverse reactions

Increased severity of uraemia and hepatotoxicity in patients with renal disease given high doses has been reported.

Vitamin deficiencies may result during prolonged administration.

A Jarisch-Herxheimer-like reaction has been reported in patients with relapsing fever treated with tetracycline.

In the elderly a negative nitrogen balance may be induced.

Benign intracranial hypertension and bulging fontanelles in infants were reported with tetracyclines with possible symptoms of headaches, visual disturbances including blurring of vision, scotomata, diplopia or permanent visual loss.

The following adverse effects were reported with tetracyclines in general and may occur with [Product name]: dysphagia, oesophagitis, oesophageal ulceration, pancreatitis, teeth discolouration, hepatitis, hepatic failure. Dental dyschromia and/or enamel hypoplasia may occur if the product is administered in children younger than 12 years of age.

Overgrowth of non-susceptible organisms may cause candidiasis, pseudomembranous colitis (Clostridium Difficile overgrowth), glossitis, stomatitis, vaginitis or staphyloccocal enterocolitis.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reaction Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Signs and symptoms

See section 4.8.

Treatment / Management

If adverse reactions or idiosyncrasy occur, discontinue medication. Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification/ Category and Class: A20.1.1 – Broad and medium spectrum antibiotics.

Pharmacotherapeutic group: Tetracyclines

ATC Code: J01AA04

Mechanism of action

Tetracyclines provide bacteriostatic action at the available plasma and tissue concentrations and are effective against intracellular and extracellular organisms. Their mechanism of action is based on an inhibition of ribosomal protein synthesis. Tetracyclines block the access of the bacterial aminoacyl-tRNA to the mRNA-ribosome complex by binding to the 30S subunit of the ribosome, thus preventing the addition of amino acids to the growing peptide chain in protein synthesis. When given at therapeutically attainable concentrations their toxic effect is limited to the bacterial cells.

The exact mechanisms by which tetracyclines reduce lesions of *acne vulgaris* have not been fully elucidated; however, the effect appears to result in part from the antibacterial activity of the medicines. Following oral administration, the medicines inhibit the growth of susceptible organisms (mainly *Propionibacterium acnes*) on the surface of the skin and reduce the concentration of free fatty acids in sebum. The reduction in free fatty acids in sebum may be an indirect result of the inhibition of lipase-producing organisms which convert triglycerides into free fatty acids or may be a direct result of interference with lipase production in these organisms. Free fatty acids are comedogenic and are believed to be a possible cause of the inflammatory lesions, e.g. papules, pustules, nodules, cysts, of

acne. However, other mechanisms also appear to be involved because clinical improvement of *acne vulgaris* with oral tetracycline therapy does not necessarily correspond with a reduction in the bacterial flora of the skin or a decrease in the free fatty acid content of sebum.

Species for which acquired resistance may be a problem
Gram-positive aerobes
S. aureus (methicillin susceptible)
S. aureus (methicillin resistant) +
Coagulase-negative staphylococci (methicillin susceptible)
Coagulase-negative staphylococci (methicillin resistant) +
Corynebacterium spp
Gram-negative aerobes
None of relevance
Anaerobes
*Propionibacterium acnes (isolates from acne)** +
Other (microaerophile)
None of relevance
Inherently resistant species
None of relevance

5.2 Pharmacokinetic properties

Lymecycline is more readily absorbed from the gastro-intestinal tract than tetracycline, with a peak serum concentration of approximately 2 mg/L after 3 hours following a 300 mg dose. In addition, similar

blood concentrations are achieved with small doses. When the dose is doubled an almost correspondingly higher blood concentration has been reported to occur.

Lymecycline is distributed into pleural and peritoneal fluid, saliva, semen and prostatic fluid. It passes the placental barrier readily (amniotic fluid) and is also present in milk of lactating patients.

The serum half-life of lymecycline is approximately 10 hours.

It is concentrated by the liver and excreted into the bile. Enterohepatic circulation is an important step in the metabolic pathway. Excretion in the urine is by glomerular filtration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal, hydrated

Magnesium stearate

The hard capsule shells contains:

titanium dioxide (E171)

gelatin

indigo carmine FD&C Blue (E132)

black iron oxide (E172)

titanium dioxide (E171)

yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Alu/Alu blister: 15 months

6.4 Special precautions for storage

Alu/Alu blister: Store at or below 25 °C.

As with all medicines, [Product name] should be kept out of the sight and reach of children.

6.5 Nature and contents of container

Alu/Alu blister strips of 28 or 30 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Austell Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown

JOHANNESBURG

2193

South Africa

Tel: 0860287835

8. REGISTRATION NUMBER

[PRODUCT NAME]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 July 2021

10. DATE OF REVISION OF THE TEXT

07 March 2022