Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lycimor 300 mg Capsules, Hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard
Hard gelatine capsule size 0, blue cap and white body

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lymecycline is indicated for the treatment of moderate to severe acne vulgaris (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology
Adults
The usual dosage for the long-term treatment of moderate to severe acne is 1 capsule daily. Treatment should be continued for at least 8 weeks to 12 weeks, however it is important to limit the use of antibiotics to the shortest possible period and discontinue their use when further improvement is unlikely. The treatment should not exceed a duration of 6 months.

Elderly
As for other tetracyclines, no specific dose adjustment is required.

Paediatric population
The safety and efficacy of Lycimor in children under the age of 12 years have not been established. No data are available.
For children over the age of 12 years, the adult dosage may be given.
For children under the age of 8 years, see section 4.3.

Renal impairment
The excretion rate for tetracycline is reduced in case of renal insufficiency and thus normal dosage may lead to accumulation. In case of renal insufficiency it is recommended to lower the dose and possibly to control serum levels.

Method of administration
The capsules must be taken with at least half a glass of water whilst in an upright position in order to reduce the risk of oesophageal irritation and ulceration. It should be taken with a light meal without dairy products.

4.3 Contraindications

Lycimor is contraindicated in:
- hypersensitivity to the active substance, any other tetracycline or to any of the excipients listed in section 6.1
- patients with severe renal impairment
- children aged under 8 years due to the risk of permanent dental staining and enamel hypoplasia
- pregnancy and during breast-feeding
- concurrent treatment with oral retinoids and use in association with systemic retinoids (see sections 4.5 and 4.8).

4.4 Special warnings and precautions for use

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

Cross-resistance between tetracyclines may develop in micro-organisms, and cross sensitisation in patients.

Tetracyclines should only be used with caution in patients with hepatic dysfunction, lest accumulation occurs with increased toxicity. Careful monitoring of dosage by serum levels is necessary. High dosage of tetracyclines may be hepatotoxic and great care should be used with concurrent administration of other hepatotoxic drugs.

Tetracyclines may cause photosensitivity reactions, manifested by an exaggerated sunburn; however, very rare cases have been reported with lymecycline. Patients should be informed that this reaction may occur and be warned to avoid direct exposure to natural and artificial sunlight and that treatment should be discontinued at the first evidence of skin erythema or skin discomfort.

May cause exacerbation of systemic lupus erythematosus.

Can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.

Tetracyclines are absorbed to some extent by developing bones and teeth and may produce staining and enamel hypoplasia.

Tetracyclines should only be administered with great caution in patients with renal insufficiency, lest accumulation occurs with increased toxicity. Dosage may require reduction. High dosage of tetracyclines may be nephrotoxic.

Diarrhoea/pseudomembranous colitis caused by *Clostridium difficile* may occur. Patients with diarrhoea should therefore be monitored closely.

Bulging fontanelles in infants and benign intracranial hypertension in adults has been reported during treatment with tetracyclines. Therefore treatment should cease if evidence of raised intracranial pressure develops during treatment with lymecycline.

Regarding moderate acne vulgaris, lymecycline is indicated only if topical treatment is not effective.

4.5 Interaction with other medicinal products and other forms of interaction

The absorption of tetracyclines may be affected by the simultaneous administration of calcium, aluminium, didanosine, magnesium, bismuth and zinc salts, antacids, bismuth containing ulcer-healing drugs, iron preparations and quinapril.

The following combinations should be avoided:

- Antacids: Antacids containing di- or tri-valent cations form chelate complexes with tetracyclines, resulting in reduced absorption. Sodium bicarbonate has been reported to inhibit the absorption of tetracyclines due to change in pH.
- Quinapril: Quinapril tablets contain magnesium which forms chelate complexes with tetracycline resulting in reduced absorption.
- Didanosine: Didanosine in tablet form contains trivalent cations which form chelate complexes with tetracycline resulting in reduced absorption. There are however no experimental studies.
- Systemic retinoids including oral retinoids and vitamin A (more than 10,000 IU/day): Increased risk of benign intracranial hypertension.
- Diuretics: Association with rises in blood urea nitrogen levels.

Some adverse effects have been reported with tetracycline therapy when used in combination with lithium; an interaction between lithium and the tetracycline class is a recognised interaction. Specifically, a combination of lymecycline with lithium may cause an increase in serum lithium levels.

Combinations where dose adjustment is recommended:

- Zinc, calcium, iron, sucralfate: In concomitant treatment, the absorption of tetracyclines is reduced. These products should not be taken within two to three hours before or after taking lymecycline capsules.
- Anticoagulants: An increase in the effects of oral coumarin-type anticoagulants may occur with tetracyclines increasing the risk for bleeding.

An increase in the effects of anticoagulants may occur with tetracyclines.

Concomitant use of diuretics should be avoided because of their association with rises in blood urea nitrogen levels.

Lymecycline could cause false-positive urine glucose determinations. It could also interfere with fluorometric determinations of urine catecholamines resulting in falsely increased values (Hingerty's method).

4.6 Fertility, pregnancy and lactation

Pregnancy
The effect of tetracycline on embryofoetal development in animals has not been reported.
Tetracyclines readily cross the placenta barrier.
Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental staining and enamel hypoplasia.
Therefore, lymecycline should not be administered to pregnant women (see section 4.3).

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

Fertility
In humans, the effect of lymecycline on fertility is unknown. In the rat, tetracyclines caused a reduction in the weight of the testis, epididymis and seminal vesicle. In addition a reduction in sperm motility, percentage live spermatozoa and changes in testicular histopathology were noted.

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.

4.8 Undesirable effects

The most frequently reported adverse events with lymecycline are gastrointestinal disorders of nausea, abdominal pain, diarrhoea (these symptoms can be alleviated by taking the capsules in with a meal) and nervous system disorder of headache.

The most serious adverse events reported with lymecycline are Stevens-Johnson syndrome, anaphylactic reaction, angioneurotic oedema and intracranial hypertension.

The following definitions of frequencies are used:
Common (≥1/100 to <1/10)
Not known (cannot be estimated from the available data)

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	Not known	Neutropenia Thrombocytopenia
Immune system disorders	Not known	Anaphylactic reaction Hypersensitivity Urticaria Angioneurotic oedema
Psychiatric disorders	Not known	Depression Nightmare
Nervous system disorders	Common	*Headache
	Not known	Dizziness **Intracranial hypertension
Eye disorders	Not known	*Visual disturbance

Gastrointestinal disorders	Common	Nausea Abdominal pain Diarrhoea
	Not known	Epigastralgia Glossitis Vomiting Enterocolitis
Hepatobiliary disorders	Not known	Jaundice Hepatitis
Skin and subcutaneous tissues disorders	Not known	Erythematous rash Photosensitivity Pruritus Stevens-Johnson syndrome
General disorders and administration site conditions	Not known	Pyrexia
Investigations	Not known	Transaminases increased Blood alkaline phosphatase increased Blood bilirubin increased

*The occurrence of clinical symptoms including visual disturbance or headache should raise the possibility of the diagnosis of intracranial hypertension.
**The treatment should be interrupted if raised intra-cranial pressure is suspected during lymecycline treatment.

General tetracyclines adverse events
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 lymecycline: dysphagia, oesophagitis, oesophageal, ulceration, pancreatitis, teeth discolouration, hepatic failure, systemic lupus erythematosus.

Dental dyschromia and/or enamel hypoplasia may occur if the product is administered in children younger than 8 years of age.

Haemolytic anaemia, eosinophilia and other hematologic disorders have been reported with tetracycline treatment.

Extra-renal hyperazotemia linked to an anti-anabolic effect which may be intensified by the association with diuretics has been reported with tetracycline treatment.

As with all antibiotics 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 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 via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

There is no specific treatment, but gastric lavage should be performed as soon as possible. Supportive measure should be instituted as required and a high fluid intake maintained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 drugs. Following oral administration, the drugs 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.

Mechanism of resistance
Tetracycline resistance in propionibacteria is usually associated with a single point mutation within the gene encoding 16S rRNA. Clinical isolates resistant to tetracycline were found to have cytosine instead of guanine at a position cognate with *Escherichia coli* base 1058. There is no evidence that ribosome mutations can be transferred between different strains or species of propionibacteria, or between propionibacteria and other skin commensals.

Resistance to the tetracyclines is associated with mobile resistance determinants in both staphylococci and coryneform bacteria. These determinants are potentially transmissible between different species and even different genera of bacteria.

In all three genera, cross-resistance with the macrolide-lincosamide-streptogramin group of antibiotics cannot be ruled out.

Strains of propionibacteria resistant to the hydrophilic tetracyclines are cross-resistant to doxycycline and may or may not show reduced susceptibility to minocycline.

Breakpoints
No breakpoints are listed for *Propionibacterium acnes* in the current EUCAST tables.

Susceptibility to tetracyclines of species relevant to the approved indication

Commonly susceptible species
Gram-positive Anaerobes
Propionibacterium acnes (clinical isolates)*

*Even if resistance to cutaneous propionibacteria is detected, this does not automatically translate into therapeutic failure, since the anti-inflammatory activity of the tetracyclines is not compromised by resistance in the target bacteria.

5.2 Pharmacokinetic properties

During absorption lymecycline is quickly hydrolysed to active tetracycline and other, inactive, constituents. Free tetracycline, which is quickly absorbed, gives therapeutic serum concentrations (>1 microgram/ml) for at least 12 hours. Therapeutic serum concentrations are reached within one hour and maximum serum concentrations (2-3 microgram/ml) are reached within 2-3 hours. Doubling the dose gives 80% increase in serum concentrations.

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

5.3 Preclinical safety data

There are no non-clinical data of relevance to the prescriber which are additional to that already included in other sections of this SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Silica colloidal, hydrated
Magnesium stearate

Capsule Body:
Titanium dioxide (E171)
Gelatine

Capsule Cap:
Indigo carmine (E132)
Black iron oxide (E172)
Titanium dioxide (E171)
Yellow iron oxide (E172)
Gelatine

6.2 Incompatibilities

Not applicable

6.3 Shelf life

15 months

6.4 Special precautions for storage

Store below 25°C
Store in the original package in order to protect from light.

6.5 Nature and contents of container

Al/Al blister

Blister: 16, 20, 21, 28, 56 and 100 capsules, hard.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA1986/118/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

October 2022