SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Lymecycline 408mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

Hard gelatin capsule, blue cap and white body

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lymecycline 408 mg Capsules, hard is indicated for the treatment of the following infections caused by tetracycline sensitive organisms (please see section 4.4 and 5.1) including the following:

- Moderate to severe acne
- Ear, nose and throat infections
- Acute exacerbation of chronic bronchitis
- Helicobacter pylori infection
- Urogenital infections caused by *Chlamydia trachomatis*
- Non-gonococcal urethritis
- Trachoma
- Rickettsial fever

- Soft tissue infection

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 chronic treatment of acne is 408 mg daily: treatment should be continued for at least 8 weeks.

For other infections, the usual dosage is 408 mg twice a day. If higher doses are required, 1224-1632 mg may be given over 24 hours.

The capsules should always be taken with a glass of water.

In the management of sexually transmitted disease both partners should be treated.

Older people:
As for other tetracyclines, no specific dose adjustment is required.

Paediatric population
The safety and efficacy of Lymecycline 408 mg Capsules in children aged under 12 years of age 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.

Method of administration

Lymecycline 408mg Capsules, hard is for oral administration. The capsules should be taken with a glass of water in order to reduce the risk of oesophageal irritation and ulceration (see section 4.4).

4.3 Contraindications

Lymecycline 408 mg Capsules, hard is contraindicated in:
- hypersensitivity to lymecycline or any other tetracycline or to any of the excipients listed in section 6.1
- patients with overt renal insufficiency
- children aged under 8 years due to the risk of permanent dental staining and enamel hypoplasia
- pregnancy and during lactation in women breast feeding infants
- concurrent treatment with oral retinoids (see section 4.5).

4.4 Special warnings and precautions for use

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 this medicinal product (see section 4.2).

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

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

Renal impairment
Caution should be exercised if the product is administered to patients with impaired renal functions.

Hepatic impairment
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.

Hepatotoxicity
High dosage of tetracyclines may be hepatotoxic and great care should be used with concurrent administration of other hepatotoxic drugs.

Phototoxicity
Tetracyclines may cause photosensitivity reactions; however, very rare cases have been reported with lymecycline. 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.

Paediatric population
Tetracyclines are absorbed to some extent by developing bones and teeth and may produce staining and enamel hypoplasia. 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 4.3).

4.5 Interaction with other medicinal products 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 cycline 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 Lymecycline 408 mg Capsules, hard.

Some adverse effects are reported with tetracycline therapy in general in case of combination with lithium; an interaction between lithium and the tetracycline class is a recognised interaction. A combination of lymecycline with lithium may cause an increase in serum lithium levels.

Unlike earlier tetracyclines, absorption of lymecycline is not significantly impaired by moderate amounts (e.g. a glass) of milk.

Concomitant use of oral retinoids should be avoided as this may increase the risk of benign intracranial hypertension.

Concomitant use of 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.

Bacteriostatic medicinal products 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.

Concurrent use with the anaesthetic methoxyflurane increases the risk of kidney failure and has been reported to result in fatal kidney failure.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy: 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).

Breast-feeding: 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: 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

4.8 Undesirable effects

The most frequently reported adverse events with lymecycline are gastrointestinal disorders of nausea, abdominal pain, diarrhoea 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.

Adverse reactions are ranked by frequency, the most frequent first, using the following convention:
Very Common: (≥1/10),
Common: (≥1/100 to <1/10),
Uncommon: (≥1/1,000 to <1/100),
Rare: (≥1/10,000 to <1/1,000),
Very rare (<1/10,000) and
Not known (cannot be estimated from the available data).

System Organ Class	Frequency	Adverse Reaction
Blood and lymphatic system disorders	Not known	Neutropenia Thrombocytopenia
Eye disorders	Not known	Visual disturbance*
Gastrointestinal disorders	Common	Nausea Abdominal pain Diarrhoea
	Not known	Epigastralgia Glossitis Vomiting Enterocolitis
General disorders and administration site conditions	Not known	Pyrexia

Hepatobiliary disorders	Not known	Jaundice Hepatitis
Immune system disorder	Not known	Anaphylactic reaction Hypersensitivity Urticaria Angioneurotic oedema
Investigations	Not known	Transaminases increased Blood alkaline phosphatase increased Blood bilirubin increased
Nervous system disorders	Common	Headache
	Not known	Dizziness Intracranial hypertension
Skin and subcutaneus tissues disorders	Not known	Erythematous rash Photosensitivity Pruritus Stevens Johnson syndrome
Psychiatric disorders	Not known	Depression Nightmare

*The manifestation of clinical symptoms, including vision disorders, or headache, must suggests the possibility of a cranial hypertension diagnosis. If increased intracranial pressure is suspected during treatment with lymecycline, administration should be stopped.

General tetracyclines adverse events:
Benign intracranial hypertension and bulging fontanelles in infants were reported with tetracyclines with possible symptoms of headaches, vomiting, 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, hepatitis, hepatic failure.

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

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 the Yellow Card Scheme; website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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
For tetracycline resistance in anaerobic and most aerobic bacteria, the breakpoints as set by the NCCLS are:

Susceptible	MIC $\leq$ 4 mg/L
Intermediate	MIC 8 mg/L
Resistant	MIC $\geq$ 16 mg/L

In cutaneous propionibacteria, mutational resistance is associated with MICs of tetracycline $\geq$ 2mg/L.

Susceptibility table
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Susceptibility to tetracyclines of species relevant to the approved indication

Commonly susceptible species
Gram-positive aerobes
None of relevance
Gram-negative aerobes
None of relevance
Anaerobes
Propionbacterium acnes (clinical isolates)*
Other
None of relevance
Species for which acquired resistance may be a problem (defined as >10% resistant within any European country)
Gram-positive aerobes
S. aureus (methicillin susceptible)
S. aureus (methicillin resistant) +
Coagulase-negative staphylococci (methicillin susceptible)
Coagulase-negative staphylococci (methicillin resistant) +
Corynebacterium spp

Species for which acquired resistance may be a problem (defined as >10% resistant within any European country)
Gram-negative aerobes
None of relevance
Anaerobes
Propionibacterium acnes (isolates from acne)* +
Other (microaerophile)
None of relevance
Inherently resistant species
None of relevance

However, even if resistance to cutaneous propionibacteria is detected, this does not automatically translate into therapeutic failure, since the antiinflammatory activity of the tetracyclines is not compromised by resistance in the target bacteria.

5.2 Pharmacokinetic properties

After oral dosing it is absorbed readily with or without the presence of food.

Lymecycline is more readily absorbed from the gastro-intestinal tract than tetracycline, with a peak serum concentration of approximately 2mg/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.

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 FD&C Blue (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 strip

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva UK Limited
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Castleford,
WF10 5HX,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

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