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, red cap and yellow body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Acne
- Ear, nose and throat infections
- Acute exacerbation of chronic bronchitis
- Gastro-intestinal infection
- Urinary tract infection
- 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 1 capsule daily: treatment
should be continued for at least 8 weeks.

For other infections, the usual dosage is 1 capsule b.d. If higher doses are required, 3-
4 capsules may be given over 24 hours. Lower doses may be given for prophylaxis.
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 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:
Oral use

Warfarin*:* In healthy male volunteers, the co-administration of amlodipine does not significantly alter the effect of warfarin on prothrombin response time. Co- administration of amlodipine with warfarin did not change the warfarin prothrombin response time.

Cyclosporin*:* Pharmacokinetic studies with cyclosporin have demonstrated that amlodipine does not significantly alter the pharmacokinetics of cyclosporine.

Drug/Laboratory test interactions: None known.

4.3 Contraindications

Hypersensitivity to the active substance or any other tetracycline or to any of the
excipients listed in section 6.1.

Its use is contraindicated in children aged under 8 years due to the risk of permanent
dental staining and enamel hypoplasia.

4.4 Special warnings and precautions for use

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

Care should be exercised in administering tetracyclines to patients with hepatic impairment. Tetracyclines may cause photosensitivity reactions; however, very rare cases have been reported with lymecycline.

May cause exacerbation of systemic lupus erythematosus. Can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.

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, magnesium, bismuth and zinc salts, antacids, Bismuth containing ulcer-healing drugs, iron preparations and quinapril. These products should not be taken within two hours before or after taking Lymecycline.

Unlike earlier tetracyclines, absorption of Lymecycline is not significantly impaired by moderate amounts of milk.

Concomitant use of oral retinoids should be avoided as this may increase the risk of benign intracranial hypertension. An increase in the effects of anticoagulants may occur with tetracyclines. Concomitant use of diuretics should be avoided.

4.6 Fertility, pregnancy and lactation

Tetracyclines are selectively absorbed by developing bones and teeth and may cause dental staining and enamel hypoplasia. In addition these compounds readily cross the placental barrier and therefore Lymecycline should not be given to pregnant or lactating women.

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.

System Organ Class	Frequency	Adverse Reaction

Blood and lymphatic system disorders	Unknown	Neutropenia Thrombocytopenia
Eye disorders	Unknown	Visual disturbance
Gastrointestinal disorders	Common (≥1/100 and <1/10)	Nausea Abdominal pain Diarrhoea
	Unknown	Epigastralgia Glossitis Vomiting Enterocolitis
General disorders and administration site conditions	Unknown	Pyrexia
Hepatobiliary disorders	Unknown	Jaundice Hepatitis
Immune system disorder	Unknown	Anaphylactic reaction Hypersensitivity Urticaria Angioneurotic oedema
Investigations	Unknown	Transaminases increased Blood alkaline phosphatase increased Blood bilirubin increased
Nervous system disorders	Common (≥1/100 and <1/10)	Headache
	Unknown	Dizziness Intracranial hypertension
Skin and subcutaneus tissues disorders	Unknown	Erythematous rash Photosensitivity Pruritus

		Stevens Johnson syndrome

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, 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 at: www.mhra.gov.uk/yellowcard

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

Mode 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

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

No specific information is presented given the vast experience gained with the use of tetracyclines in humans over the last forty years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate

Colloidal hydrated silica

The capsule shells contain

Gelatin

Purified water

Indigocarmine (E132)

Titanium dioxide (E171)

Erythrosine (E127)

Quinoline yellow (E104)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package in order to protect from light. Should be kept out of the sight and reach of children.

6.5 Nature and contents of container

Alu/Alu blisters. Pack sizes: Blister with 7 capsules (4 x 7's pack or 8x7's blister in a carton).

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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