SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Lymecycline 408 mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains 408 mg of lymecycline equivalent to 300 mg tetracycline base.
Capsule length: 24 mm.

Excipient with known effects:
Tartrazine (E 102): 0.066 mg / capsule (see section 4.4).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule, hard.

Hard gelatin capsule, with a red cap, and a yellow body, containing a yellow powder.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Lymecycline 408 mg Capsule, 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:

- Acne, moderate to severe.
- Acute sinusitis.
- Acute exacerbation of chronic bronchitis.
- *Helicobacter pylori* infection.
- Urogenital infections caused by *Chlamydia trachomatis*.
- 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 (408 mg) daily; treatment should be continued for at least eight (8) weeks.

For other infections, the usual dosage is one capsule (408 mg) twice a day. In the event higher doses are required, 3 – 4 capsules (1224 mg – 1632 mg) may be given over 24 hours.

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

*Elderly:*
As with other tetracyclines, no specific dosage adjustment is required.

*Renal impairment:*
Lymecycline is contraindicated in patients with overt renal insufficiency (see section 4.3).

*Hepatic impairment:*
Use with caution; potential for accumulation with increased toxicity (see section 4.4).

*Paediatric population:*
Not recommended for children under the age of 12 years. For children and adolescents over the age of 12 years, the adult dosage may be given.

**Method of administration**

Lymecycline 408 mg capsule, hard are for oral administration. The capsules should always be taken with a glass of water.

4.3 **Contraindications**

Lymecycline 408 mg capsule 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 less than 12 years.
- Pregnancy, and during lactation in women breast – feeding infants.
4.4 **Special warnings and precautions for use**

Prolonged usage of an anti-infective may result in the development of infection due to organisms resistant to the anti-infective used in therapy.

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

Tetracyclines should only be used with caution in patients with hepatic dysfunction, in case accumulation occurs, resulting in 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; however, very rare cases have been reported with Lymecycline.

Lymecycline may cause exacerbation of systemic lupus erythematosus.

Lymecycline can cause weak neuromuscular blockade, and therefore 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.

**Excipients**

This medicinal product contains Tartrazine, E 102, 0.066 mg / capsule: this may cause allergic reactions.

4.5 **Interaction with other medicinal products and other forms of interaction**

The absorption of tetracyclines may be affected by the simultaneous administration of aluminium, bismuth, calcium, magnesium, and zinc salts, antacids, bismuth containing ulcer healing drugs, iron preparations, and quinapril. These products should not be taken within two (2) hours before, or two (2) hours after taking Lymecycline 408 mg capsules hard.

In contrast to earlier tetracyclines, the absorption of Lymecycline is not significantly impaired by moderate amounts, such as a glass, of milk.

The concomitant usage 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 concomitant administration of tetracyclines.

The concomitant usage of diuretics should be avoided.

Although not reported for Lymecycline, a few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent usage of tetracycline or oxytetracycline with oral contraceptives.
The plasma levels of tetracyclines may be decreased with concurrent usage of barbiturates, carbamazepine, or phenytoin.

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

4.6 Fertility, pregnancy and lactation

Pregnancy: Tetracyclines readily cross the placental barrier. Tetracyclines are selectively absorbed by developing bones and teeth, and may cause dental staining and enamel hypoplasia. Therefore the administration of lymecycline to pregnant women is contraindicated (see section 4.3).

Breast-feeding: Tetracyclines are distributed into milk. Due to the risk of enamel hypoplasia or dental dyschromia in the infant, lymecycline is contraindicated in breast-feeding women (see section 4.3).

Fertility: The effect of lymecycline on fertility in humans is unknown. However, tetracycline hydrochloride had no effect on fertility in male and female rats at a daily dose 25 times higher than that proposed for humans.

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. However, Lymecycline may cause dizziness and visual disturbances (see section 4.8), therefore patients should be cautioned to make sure they are not affected before driving or operating machines.

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).
<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Not known</td>
<td>Neutropenia</td>
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<tr>
<td></td>
<td></td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Not known</td>
<td>Visual disturbances</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Epigastralgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Glossitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enterocolitis</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Not known</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Not known</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Not known</td>
<td>Anaphylactic reaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urticaria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Angioneurotic oedema</td>
</tr>
<tr>
<td>Investigations</td>
<td>Not known</td>
<td>Transaminases increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood alkaline phosphatase increased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood bilirubin increased</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Not known</td>
<td>Dizziness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intracranial hypertension</td>
</tr>
<tr>
<td>Skin and subcutaneous tissues disorders</td>
<td>Not known</td>
<td>Erythematous rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Photosensitivity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Stevens Johnson syndrome</td>
</tr>
</tbody>
</table>

*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 eight (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 staphylococcal 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 therapy; however gastric lavage should be performed as soon as possible. Supportive measures 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 exert bacteriostatic action at the available plasma and tissue concentrations and are effective against intracellular and extracellular organisms. The mechanism of action is mediated via inhibition of ribosomal protein synthesis. Tetracyclines block access of the bacterial aminoacyl – t RNA to the mRNA – ribosome complex by binding to the 30S subunit of the ribosome, thereby preventing addition of amino acids to the growing peptide chain in protein synthesis. Administration at therapeutically attainable concentrations limits their toxic effects to the bacterial cells.

The exact mechanism of action whereby tetracyclines reduce lesions of acne vulgaris has not been fully elucidated; the effect appears to result in part from the antibacterial activity of the drugs. Post 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 consequence of interference with lipase producing organisms that convert triglycerides into free fatty acids, or may be as a consequence of interference in lipase production in these organisms. Free fatty acids are comedogenic and are believed to be a possible cause of inflammatory lesions, i.e. papules, pustules, nodules, cysts, of acne. However, other mechanisms also appear to be involved, since clinical improvement of acne vulgaris with oral tetracycline therapy does not necessarily correspond either with a reduction in the bacterial flora of the skin, or with a decrease in the free fatty acid content of sebum.

Mechanism of resistance:

Tetracycline resistance in Propionibacterium sp. is generally 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 Propionibacterium, or between Propionibacterium sp. and other skin commensals.

Resistance to the tetracyclines is associated with mobile resistance determinants in both Corynebacterium sp. and Staphylococcus sp. 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 excluded.

Strains of Propionibacterium sp. resistant to the hydrophilic tetracyclines are cross resistant to doxycycline, and may, or may not, show reduced susceptibility to minocycline.

**Breakpoints:**

Clinical minimal inhibitory concentration (MIC) breakpoints established by EUCAST for Lymecycline (based on sensitivities for tetracycline) are:

- Staphylococcus sp.: sensitive ≤ 1, resistant > 2
- Streptococcus sp., A, B, C, G: sensitive ≤ 1, resistant > 2
- Streptococcus pneumoniae: sensitive ≤ 1, resistant > 2
- Haemophilus influenza: sensitive ≤ 1, resistant > 2
- Moraxella catarrhalis: sensitive ≤ 1, resistant > 2
- Neisseria gonorrhoeae: sensitive ≤ 0.5, resistant > 1
- Neisseria meningitides: sensitive ≤ 1, resistant > 2

**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 required, 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 infection is questionable.

Susceptibility to tetracyclines of species relevant to the approved indications:

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram – positive aerobes</strong></td>
<td>None of relevance</td>
</tr>
<tr>
<td><strong>Gram – negative aerobes</strong></td>
<td>None of relevance</td>
</tr>
<tr>
<td><strong>Anaerobes</strong></td>
<td></td>
</tr>
<tr>
<td>Propionibacterium acnes (clinical isolates)*</td>
<td></td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>None of relevance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem (defined as &gt; 10% resistant within any EU country)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram – positive aerobes</strong></td>
<td></td>
</tr>
<tr>
<td>Staph. aureus (methicillin susceptible)</td>
<td></td>
</tr>
<tr>
<td>Staph. aureus (methicillin resistant)+</td>
<td></td>
</tr>
<tr>
<td>Coagulase – negative Staphylococcus sp. (methicillin susceptible)</td>
<td></td>
</tr>
<tr>
<td>Coagulase – negative Staphylococcus sp. (methicillin resistant)+</td>
<td></td>
</tr>
</tbody>
</table>
Corynebacterium sp.

Species for which acquired resistance may be a problem (defined as > 10 % resistant within any EU country

Gram – negative aerobes
None of relevance

Anaerobes

Propionibacterium acnes (isolates from acne)*

Other (microaerophilic)
None of relevance

Inherently resistant species
None of relevance

However, even if resistance to cutaneous Propionibacterium sp. 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

Absorption:
Following oral dosing lymecycline is readily absorbed, with or without the presence of food, approximately 90 % administered dose is absorbed via an active transport mechanism. Lymecycline is more readily absorbed from the gastrointestinal tract than tetracycline, with peak serum concentrations of ca 2 mg / L after 3 hours following a 300 mg dose. Similar blood concentrations are reported to occur with smaller doses. Doubling the dose reportedly results in a correspondingly higher blood concentration. Time to tmax is about 3 h, and the serum half life of lymecycline is approximately 10 hours.

Distribution:
Lymecycline is lipid soluble. Volume of distribution is 1.3 – 1.7 L / Kg, and it is approximately 45 % protein bound.

Biotransformation:
Lymecycline undergoes transformation to teracycline in vivo, and is excreted unchanged thereafter.

Elimination:
Principal route of elimination is via renal excretion, with some 25 – 30 % of the dose being excreted via the renal route, and biliary excretion also plays a role.

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.

Environmental Risk Assessment (ERA):
This is a generic medicinal product, containing lymecycline. As such, it will simply replace already existing products in the market, without leading to additional prescribing and usage of lymecycline. As such it will not result in any additional environmental exposure to lymecycline, or the in vitro produced tetracycline. Therefore there is no requirement for any additional environmental risk assessment.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Colloidal anhydrous silica
Magnesium stearate

Capsule cap:
Gelatin
Indigo carmine, E 132
Erythrosine, E 127
Titanium dioxide, E 171

Capsule body:
Gelatin
Tartrazine, E 102
Titanium dioxide, E 171

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
2 years

6.4 Special precautions for storage
Store below 25°C.
Store in the original package.

6.5 Nature and contents of container
Aluminium (Al) – Aluminium (Al) blister strips.
Packs containing 7, 14, 28, 56, and 112 capsules.
Not all pack sizes may be marketed.
6.6 Special precautions for disposal and other handling

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

Morningside Healthcare Ltd
115, Narborough Road,
Leicester, LE3 0PA,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117 / 0096

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23/08/2016

10 DATE OF REVISION OF THE TEXT

23/08/2016