SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lymecycline Glenmark 300 mg hard capsules

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

Hard Capsules

Hard gelatin capsule of approximately 21.7 mm in size with pink body imprinted with ‘632’ in black ink and purple cap imprinted with ‘G’ in black ink, filled with yellow to dark yellow granules.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

{(Invented) name} is indicated for the treatment of the following infections in adults and children from the age of 12 years
• Moderate to severe acne vulgaris
• Acute exacerbation of chronic bronchitis
• Pneumonia caused by *Mycoplasma pneumoniae*, *Chlamydia psittaci* or *Chlamydia pneumoniae*
• Urogenital infections caused by *Chlamydia trachomatis*.

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 vulgaris is 1 capsule (300 mg) 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.

For other infections, the usual dosage is 1 capsule (300 mg) twice a day.

Elderly:

As with other tetracyclines, no specific dose adjustment is required.

Renal impairment

The excretion rate for tetracycline is reduced in case of renal impairment and thus normal dosage may lead to accumulation. In case of renal impairment it is recommended to lower the dose and possibly to control serum levels. Lymecycline is contraindicated in patients with severe renal impairment (see section 4.3).

Hepatic impairment

Use with caution: potential for accumulation with increased toxicity (see section 4.4).

Paediatric population:

Lymecycline is contraindicated in children under the age of 12 years (see section 4.3). For children and adolescents, over the age of 12 years, the adult dosage may be given.

Method of administration

Capsules should be swallowed whole with at least half a glass of water whilst in an upright position in order to reduce the risk of oesophageal irritation and ulceration.

4.3 Contraindications

- Hypersensitivity to the active substance or any other tetracycline or to any of the excipients listed in section 6.1.
- Patients with severe renal impairment.
- Children aged less than 12 years
- Pregnancy and breastfeeding
- Concurrent treatment with oral retinoids and vitamin A (over 10,000 IU/day) and use in association with systemic retinoids (see section 4.5 and 4.8).

4.4 Special warnings and precautions for use

Children under 12 years should only be treated with lymecycline on severe indication, due to deposition in the growing skeleton and the risk of enamel hypoplasia.

Bacterial resistance

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

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

Diarrhoea/Pseudomembranous colitis
Clostridium difficile-associated diarrhoea and pseudomembranous colitis have been reported for lymecycline. It is important to consider these diagnoses in patients who present with diarrhoea subsequent to the administration of lymecycline. In such circumstances, the use of supportive measures together with the administration of specific treatment for Clostridium difficile should be considered.

Hepatic and renal impairment
In patients with renal impairment there is a risk of accumulation in serum and tissues that may cause liver toxicity.

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.

Photosensitivity

Tetracyclines may cause photosensitivity reactions; 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.

Systemic lupus erythematosus

Lymecycline may cause exacerbation of systemic lupus erythematosus.

Myasthenia Gravis

Lymecycline can cause weak neuromuscular blockade, and therefore should be used with caution in myasthenia gravis.

Enamel hypoplasia
Tetracyclines are absorbed to some extent by developing bones and teeth, and may produce staining and enamel hypoplasia (see Contraindications).

4.5 Interaction with other medicinal products and other forms of interaction

The following combination is contraindicated
Oral retinoids and vitamin A (over 10,000 IU/day): Concomitant use of tetracycline and oral retinoids (acitretin and isotretinoin) and vitamin A (over 10,000 IU/day) should be avoided, as this leads to an increased risk of intracranial hypertension (see section 4.3).

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.
- Diuretics.

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 recognized 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, activated charcoal, cholestyramine, bismuth chelates: In concomitant treatment, the absorption of tetracyclines is reduced. Drugs that increase gastric pH can reduce the absorption of tetracyclines. These products should be taken at least 3 hours apart.

An increase in the effects of peroral anticoagulants of coumarine type may occur with concomitant administration of tetracyclines.

Although not reported for lymecycline capsules, a few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent usage of tetracycline or oxytetracycline with oral contraceptives.

Paediatric population

Interaction studies have only been performed in adults.

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).

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

Fertility
The effect of lymecycline on fertility in humans is unknown.

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.

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

System Organ Class (SOC)	**Frequency**	**Adverse Reaction**
Blood and the lymphatic system disorders	Unknown	Neutropenia, Thrombocytopenia
Immune system disorders	Unknown	Anaphylactic reaction, Hypersensitivity, Urticaria, Angioneurotic oedema
Psychiatric disorders	Unknown	Depression Nightmares
Nervous system disorders	Common	Headache*
	Unknown	Dizziness, Intracranial hypertension*

Eye disorders	Unknown	Visual disturbance*
Gastrointestinal disorders	Common	Nausea, Abdominal pain, Diarrhoea
	Unknown	Epigastralgia, Glossitis, Vomiting, Enterocolitis
Hepatobiliary disorders	Unknown	Jaundice
Skin and subcutaneous tissue disorders	Unknown	Erythematous rash, Photosensitivity, Pruritus, Stevens Johnson syndrome
General disorders and administration site conditions	Unknown	Pyrexia
Investigations	Unknown	Transaminases increased, Blood alkaline phosphatase increased, Blood bilirubin increased

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

General tetracycline 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.
- haemolytic anemia, eosinophilia and other haematological disorders.

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

Extra-renal hyperazotemia linked to an anti-anabolic effect which can be intensified in the case of simultaneous use of diuretics has been reported with use of tetracyclines.

As with all antibiotics overgrowth of non-susceptible organisms may cause candidiasis, pseudomembranous colitis (*Clostridium difficile* overgrowth), glossitis, stomatitis, and 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 national reporting system listed in Appendix V.

4.9 Overdose

Tetracycline has relatively low acute toxicity.

Symptoms

Nausea, vomiting and diarrhoea.

Injuries to the liver and kidneys have been observed in patients with renal impairment following ingestion of high doses. Pregnant women are particularly susceptible to liver damage.

Treatment

Supportive care should be instituted. Ventricular emptying, activated carbon, antacids if indicated. Dialysis can be considered through cases of massive overdose and kidney failure.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antibacterials for systemic use, tetracyclines

ATC code: J01AA04

Mechanism 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 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 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 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 *Propionibacterium sp.* 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 *Propionibacterium*, or between *Propionibacterium sp.* and other skin commensals.

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

Strains of *Propionibacterium* 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:

Streptococcus pneumonia: sensitive ≤ 1, resistant > 2

Haemophilus influenza: sensitive ≤ 1, resistant > 2

Moraxella catarrhalis: sensitive ≤ 1, resistant > 2

Susceptibility
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 indications:

Commonly susceptible species
***Gram-positive* 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* anaerobes**
Propionibacterium acnes (isolates from acne)* +

* 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

During absorption lymecycline is quickly hydrolysed to active tetracycline and other, inactive, constituents. Free tetracycline, which is quickly absorbed, gives therapeutic serum concentrations (> 1 microg/ml) for at least 12 hours. Therapeutic serum concentrations are reached within one hour and maximum serum concentrations (2 – 3 microg/ml) are reached within 2 - 3 hours. Doubling the dose gives 80 % increase in serum concentrations. Absorption is insignificantly affected by milk or other types of food. The degree of protein binding is 45% and the half-life is 10 – 12 hours. Approximately 60 % of the oral dose is excreted in the urine in active form.

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

Capsule content:
Magnesium stearate (E470b)
Silica, Colloidal hydrated (E551)

Capsule shell:
Gelatin (E441)
Titanium dioxide (E171)
Erythrosine (E127)
Indigotine (E132).

Printing ink:
Shellac (E904)
Propylene Glycol (E1520)
Black Iron Oxide (E172)
Potassium hydroxide (E525).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store below 25^{o}C in the original package in order to protect from moisture.

6.5 Nature and contents of container

Aluminium-Aluminium blister pack

Aluminium-PVC/PVDC blisters packed in aluminium pouch

Pack sizes of 28, 56 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precaution for disposal

No special requirements for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

< [To be completed nationally]>

8. MARKETING AUTHORISATION NUMBER(S)

< [To be completed nationally]>

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORIZATION

Date of first authorization: *< [To be completed nationally]>*

10. DATE OF REVISION OF THE TEXT

2024-07-03