Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rimicorim 300mg Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, Hard
Hard gelatin capsule with yellow body and red cap imprinted with "NM".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lymecycline is indicated for the treatment of moderate to severe acne vulgaris (please see section 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.

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

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
Capsules should be taken with at least half a glass of water whilst in an upright position. They should be taken with a light meal without dairy products.

4.3 Contraindications

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

Its use is contraindicated in patients with severe renal impairment, in pregnancy and lactation, use in association with systemic retinoids (see 4.5 and 4.8 sections), concomitant treatment with oral retinoids and in children less than 12 years
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

Solid dosage forms of 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).

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.
The excretion rate for tetracycline is reduced in case of renal insufficiency and thus normal dosage may lead to accumulation.
In patients with renal impairment it is recommended to lower the dose.
May cause exacerbation of systemic lupus erythematosus.
Can cause weak neuromuscular blockade so should be used with caution in Myasthenia Gravis.
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.
Tetracyclines may cause photosensitivity reactions; however, very rare cases have been reported with lymecycline.
Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking tetracyclines.
Patients should know 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.
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, activated charcoal, , sucralfate and quinapril.

<u>The following combinations should therefore be avoided:</u>
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.
Lithium: 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.
Methoxyflurane: Concurrent use with the anaesthetic methoxyflurane increases the risk of kidney failure and has been reported to result in fatal renal toxicity.

<u>Combinations where dose adjustment is recommended:</u>
Zinc, calcium, iron: 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.Concomitant use of systemic retinoids including 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 (see section 4.8).
Although not reported for lymecycline capsules, a few cases of pregnancy or breakthrough bleeding have been attributed to the concurrent use of tetracycline or oxytetracycline with oral contraceptives.
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

<u>Pregnancy</u>
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).

<u>Breastfeeding</u>
Tetracycline can also be excreted into breast milk and new-born infants may be at risk of adverse effects such as dental staining and enamel hypoplasia. Hence, lymecycline should not be administered to breast-feeding women (see section 4.3).

Fertility

The effect of lymecycline on fertility in humans 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 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.

Tabulated list of adverse reactions

The list of undesirable effects shown below is presented by system organ class, MedDRA preferred term, and frequency. 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	Unknown:	Neutropenia Thrombocytopenia
Eye disorders	Unknown:	*Visual disturbance
Gastrointestinal disorders	Common:	Nausea, Abdominal pain, Diarrhoea
	Unknown:	Glossitis, enterocolitis, vomiting, Epigastralgia, , oesophageal ulcer and oesophagitis.
General disorders and administration site conditions	Unknown:	Pyrexia
Hepatobiliary disorders	Unknown:	Jaundice, Hepatitis
Immune system disorder	Unknown:	Hypersensitivity, Urticaria, Angioneurotic oedema, Anaphylacticreaction
Investigations	Unknown:	Transaminases increased, Blood alkaline phosphatase increased, Blood bilirubin increased
Nervous system disorders	Common:	Headache
	Unknown:	Dizziness, *Intracranialhypertension
Skin and subcutaneous tissues disorders	Unknown:	Erythematous rash, Photosensitivity reactions, Pruritus, Stevens Johnson syndrome
Psychiatricdisorders	Unknown	Depression, Nightmare

*(The occurrence of clinical symptoms including visual disturbance 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

Description of selected adverse events with tetracyclines therapy in general:

- 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.

- Systemic Lupus Erythematosus
- Pancreatitis
- Haemolytic anaemia, eosinophilia and other hematologic disorders have been reported with tetracycline therapy.

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

- 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: http.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

Mode of action

Tetracyclines provide bacteriostatic action at the available plasma and tissue concentrations and are effective against intracellular andextracellular 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 lipaseproducing 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.
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 (>1microgram/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.

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

Colloidal Silicon Dioxide (Aerosil 200)
Magnesium Stearate
Capsules shell components
Gelatin
Water
Erythrosine (E127)
Quinoline yellow (E104)
Titanium dioxide (E171)
Indigo Carmine (E 132)

Printing Ink Composition
Shellac
Propylene Glycol
Black Iron Oxide (E172)
Potassium Hydroxide

6.2 Incompatibilities

Not applicable

6.3 Shelf life

12 months

6.4 Special precautions for storage

Do not store above 25°C. Store in the original packaging.

6.5 Nature and contents of container

Capsules are packed in Aluminium/Aluminium blisters containing 28 or 56 capsules. Not all pack sizes will be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Brown & Burk IR Limited

22 Northumberland Road
Ballsbridge
Dublin 4
Ireland

8 MARKETING AUTHORISATION NUMBER

PA23148/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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