Public Assessment Report

Decentralised Procedure

LYMECYCLINE 408MG CAPSULES

Procedure No: UK/H/1889/002/DC

UK Licence No: PL 20620/0023

NRIM Limited

Medicines and Healthcare products Regulatory Agency
LAY SUMMARY

On 11 July 2012, Belgium, Denmark, Finland, France, Ireland, Italy, Norway, Sweden and the UK agreed to grant a Marketing Authorisation to NRIM Limited for the medicinal product Lymecycline 408mg Capsules (PL 20620/0023; UK/H/1889/002/DC). The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a Marketing Authorisation was granted in the UK on 13 September 2012.

The main use of Lymecycline is the treatment of moderate to severe acne. Acne appears as blackheads and whiteheads, which people often refer to as pimples or spots. Lymecycline attacks the bacteria that are one of the main causes of acne. The name of these bacteria is Propionibacterium acnes.

Lymecycline belongs to a group of medicines called tetracycline antibiotics.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Lymecycline 408mg Capsules outweigh the risks; hence, a Marketing Authorisation was granted.
TABLE OF CONTENTS

Module 1: Information about initial procedure  Page 3
Module 2: Summary of Product Characteristics  Page 4
Module 3: Patient Information Leaflets  Page 22
Module 4: Labelling  Page 24
Module 5: Scientific Discussion  Page 28

1 Introduction
2 Quality aspects
3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6  Steps taken after initial procedure
## Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Lymecycline 408mg Capsules</th>
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<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Lymecycline</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Hard capsules</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>408mg lymecycline (equivalent to 300mg tetracycline base)</td>
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<tr>
<td><strong>MA Holder</strong></td>
<td>NRIM Limited, Unit 15 Moorcroft, Harlington Road, Hillingdon, UB8 3HD</td>
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<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>UK</td>
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<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Belgium, Denmark, Finland, France, Ireland, Italy, Norway and Sweden</td>
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<tr>
<td><strong>Procedure Number</strong></td>
<td>UK/H/1889/002/DC</td>
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<tr>
<td><strong>Timetable</strong></td>
<td>Day 210 – 11 July 2012</td>
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Module 2

Summary of Product Characteristics

The current approved UK version of the Summary of Product Characteristics (SmPC) for this product is available on the MHRA website.
Module 3
Patient Information Leaflet

The current approved UK version of the Patient Information Leaflet (PIL) for this product is available on the MHRA website.
Module 4
Labelling

Lymecycline 300 Cap 14 x 4
Size: 125 x 65 x 88 mm
Carton Cutter Guide

Lymecycline 408mg Capsules

56 Capsules

Lymecycline (equivalent to 300mg tetracycline base)

NRI

Each capsule contains mg erythromycin equivalent to 50mg tetracycline.
For oral administration Do not exceed 2 capsules in any 24-hour period.

Keep out of reach of children. Read the package leaflet before use.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Lymecycline 408mg Capsules (PL 20620/0023; UK/H/1889/002/DC) could be approved. This application were submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Belgium, Denmark, Finland, France, Ireland, Italy, Norway and Sweden as Concerned Member States (CMS).

These are prescription-only medicines indicated for the treatment of moderate to severe acne vulgaris.

This was an application made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Tetralysal 300mg Capsules (Galderma Nordic AB), which were initially granted in Denmark in May 1962.

Lymecycline is a semisynthetic tetracycline antibiotic with improved oral absorption, enhanced tissue penetration, and slower elimination relative to tetracycline. Lymecycline has been in clinical use for several decades in the proposed indications and has a well-established benign side-effect profile.

Lymecycline is generally bacteriostatic against a wide variety of organisms, both gram-positive and gram-negative. These drugs enter gram-negative bacteria by passive diffusion through the hydrophilic channels formed by the porin proteins of the outer cell membrane and by active transport via an energy-dependent system that pumps all tetracyclines across the cytoplasmic membrane. Entry of these drugs into gram-positive bacteria requires metabolic energy, but is not as well understood. This system is also believed to exist in gram-positive bacteria.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

One bioequivalence study was performed, which compared the pharmacokinetics of Lymecycline Capsules (the test product) versus Tetralysal Capsules (the reference product – Galderma UK Limited). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for these product types at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved with the end of procedure (Day 210) on 11 July 2012. After a subsequent national phase, the licence was granted in the UK on 13 September 2012.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Lymecycline 408mg Capsules</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Lymecycline</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Tetracyclines (J01AA)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Hard capsules, 408mg (equivalent to 300mg lymecycline base)</td>
</tr>
<tr>
<td>Reference numbers for the Mutual Recognition Procedure</td>
<td>UK/H/1889/002/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Belgium, Denmark, Finland, France, Ireland, Italy, Norway and Sweden</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 20620/0023</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>NRIM Limited, Unit 15 Moorcroft, Harlington Road, Hillingdon, UB8 3HD</td>
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</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Lymecycline

rINN: Lymecycline

Chemical name: N6-[[[4-Dimethylamino),4,4a,5a,6,11,12a octahydro-3,6,10,12,12apentahydroxy-6-methyl-1,11-dioxo-2-aphthacenyl]carbonyl]-amino[methyl]-L-lysine.

Structure:

Molecular formula: C_{29}H_{38}N_{4}O_{10}
Molecular weight: 602.63
Appearance: A yellow hygroscopic powder.
Solubility: Very soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride.

Lymecycline is the subject of a European Pharmacopoeia monograph.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients, namely colloidal silicon dioxide (Aerosil 200), magnesium stearate, gelatin, water, erythrosine (E127), quinoline yellow (E104), titanium dioxide (E171), indigo carmine (E132), shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide.
All excipients comply with their respective European Pharmacopoeia monograph, with the exception of quinoline yellow (E104) which complies with a suitable in-house specification. Suitable batch analysis data have been provided for all excipients, showing compliance with their respective specifications.

With the exception of gelatin, none of the excipients are sourced from animal or human origin. The suppliers of gelatin have provided European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability to show that the gelatin is sourced in-line with current requirements for the minimisation of transmission of BSE/TSE. No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product that could be considered a generic medicinal product of the innovator product Tetralysal 300mg Capsules (Galderma Nordic AB).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed product and its respective innovator product.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the finished product. The manufacturing process has been validated and has shown satisfactory results. The marketing authorisation holder has committed to providing validation data for the first full-scale batches, as soon as these become available.

**Finished Product Specification**

The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of analysis have been provided for all working standards used.

**Container-Closure System**

The finished product is packaged in aluminium/aluminium blisters, which are packed into cartons in pack sizes of 28 or 56 capsules per carton.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

**Stability of the product**

Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months, with the storage conditions “Do not store above 25°C. Store in the original packaging.”

**Bioequivalence/bioavailability**

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the bioequivalence study.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Quality Overall Summary (Expert report)
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of lymecycline are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of this application, the Marketing Authorisation Holder has submitted the following bioequivalence study:

An open-label, randomised, two-period, two-treatment, two-sequence, single-dose, crossover study to compare the pharmacokinetics of the test product Lymecycline Capsules (NRIM Limited, UK) versus the reference product Tetraysal Capsules (Galdema Limited, UK) in healthy adult subjects under fasted conditions.

Volunteers were dosed with 408mg (equivalent to 300mg tetracycline base) of either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 36 hours post dose. The two treatment arms were separated by a 7-day washout period.
The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) for plasma levels of tetracycline are presented below:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
</tr>
<tr>
<td>C_max (ng/mL)</td>
<td>1490.3078</td>
<td>1449.4784</td>
</tr>
<tr>
<td>AUC_{0-t} (ng.hr/mL)</td>
<td>20367.8772</td>
<td>19754.1936</td>
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The 90% confidence intervals for C_max and AUC for test versus reference products are within predefined acceptance criteria. The data support the claim that the test product is bioequivalent to the reference product.

**Efficacy**

No new data on the efficacy have been submitted and none are required for this type of application.

**Safety**

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.

**SmPC, PIL and Labels**

The SmPC, PIL and labels are medically acceptable. The SmPC is consistent with that for the originator product.

**Pharmacovigilance System and Risk Management Plan**

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product.

**Clinical Expert Report**

The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Conclusion**

The grant of a Marketing Authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Lymecycline 408mg Capsules are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s product and the reference product Tetralysal Capsules (Galderma Limited, UK).

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the originator product are interchangeable. Extensive clinical experience with lymecycline is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is therefore considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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