Public Assessment Report

Decentralised Procedure

Lymecycline 408mg Capsules, hard
(lymecycline)

Procedure No: UK/H/4170/001/DC

UK Licence No: PL 30306/0367

Actavis Group PTC ehf
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Lymecycline 408mg Capsules, hard (PL 30306/0367; UK/H/4171/001/DC). It explains how the application for Lymecycline 408mg Capsules, hard was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Lymecycline 408mg Capsules, hard.

For practical information about using Lymecycline 408mg Capsules, hard, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as ‘Lymecycline Capsules’ in this report.

What are Lymecycline Capsules and what are they used for?
Lymecycline Capsules is a generic medicine'. This means Lymecycline Capsules is similar to a ‘reference medicine’ already authorised in the UK called Tetralysal 300mg hard capsule (PL 10590/0019), which was granted to Galderma (UK) Limited on 25 September 1995.

Lymecycline Capsules are used in adults and children over 12 years of age to treat acne; which appears as blackheads and whiteheads which people often refer to as pimples or spots. This medicine can also be used to treat other infections such as
• acute sinusitis
• bronchitis
• infections in the abdomen
• some types of eye infections called trachoma
• soft tissue infections.

How do Lymecycline Capsules work?
Lymecycline Capsules contain the active ingredient, lymecycline, which belongs to a group of medicines called tetracycline antibiotics. These medicines kill bacteria.

How are Lymecycline Capsules used?
Lymecycline Capsules are available as hard capsules and are taken by mouth. The capsules should always be taken with a glass of water.

This medicine should always be taken exactly as advised by the patient’s doctor. If unsure, the patient should check with his/her doctor or pharmacist.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, the duration of treatment and the need for any specific monitoring of certain parameters or for diagnostic tests.

Lymecycline Capsules can only be obtained with a prescription.

What benefits of Lymecycline Capsules have been shown in studies?
As Lymecycline Capsules is a generic medicine, studies in patients have been limited to tests to determine that Lymecycline Capsules is bioequivalent to the ‘reference medicine’, Tetralysal 300mg hard capsule (Galderma (UK) Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

In addition, the Marketing Authorisation Holder (Actavis Group PTC ehf) has provided data from the published literature on lymecycline.
What are the possible side effects of Lymecycline Capsules?
Like all medicines, Lymecycline Capsules can cause side effects although not everybody gets them.

For the full list of all side effects reported with Lymecycline Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Lymecycline Capsules.

Why are Lymecycline Capsules approved?
It was concluded that, in accordance with EU requirements, Lymecycline Capsules have been shown to have comparable quality and to be comparable to Tetralysal 300mg hard capsule (Galderma (UK) Limited). Therefore, the MHRA decided that, as for Tetralysal 300mg hard capsule (Galderma (UK) Limited), the benefits outweigh the identified risks and recommended that Lymecycline Capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Lymecycline Capsules?
Safety information has been included in the Summary of Product Characteristics and the package leaflet for Lymecycline Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Lymecycline Capsules
A Marketing Authorisation was granted in the UK on 10 August 2012.

The full PAR for Lymecycline Capsules follows this summary.

For more information about treatment with Lymecycline Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2015.
SCIENTIFIC DISCUSSION

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Scientific discussion

I  INTRODUCTION
On 14 June 2012, Malta and the UK agreed to grant a Marketing Authorisation (MA) to Actavis Group PTC ehf for the medicinal product Lymecycline 408mg Capsules, hard. The MA was granted via a Decentralised Procedure (DCP), with the UK as Reference Member State (RMS UK/H/4171/01-3/DC). After the national phase, an MA was granted in the UK on 10 August 2012 (PL 30306/0367). This product is a prescription-only medicine.

This is a generic application for Lymecycline 408mg Capsules, hard submitted under Article 10(1) of Directive 2001/83/EC, as amended. The application refers to the UK reference product Tetralysal 300mg hard capsule (PL 10590/0019) authorised to Galderma (UK) Limited on 25 September 1995. The reference product has been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired.

Lymecycline belongs to the pharmacotherapeutic group ‘tetracyclines’ with the ATC code = J01AA04. 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.

Lymecycline is indicated for the treatment of infections caused by tetracycline sensitive organisms including the following:
- moderate to severe acne
- acute sinusitis
- acute exacerbation of chronic bronchitis
- *Helicobacter pylori* infection
- urogenital infections caused by *Chlamydia trachomatis*
- trachoma
- rickettsial fever
- soft tissue infection

The application is supported by a bioequivalence study comparing the test product, Lymecycline 408mg (equivalent to 300mg tetracycline base) with the reference product Tetralysal 300mg hard capsule (Galderma (UK) Limited) under fasting conditions. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

No new non-clinical or clinical efficacy studies were conducted for this application, which is acceptable given that the application is based on essential similarity to products that have been licensed for over 10 years.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA
The submitted documentation concerning the proposed product is of sufficient quality and meets the current EU regulatory requirements.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is a hard gelatin capsule with a blue cap and white body
Each capsule contains 408mg of lymecycline equivalent to 300mg tetracycline base.

The product also contains silica colloidal, hydrated, magnesium stearate, titanium dioxide (E171), gelatin, Indigo Carmine FD&C Blue (E132), black iron oxide (E172), titanium dioxide (E171) and yellow iron oxide (E172). Appropriate justification for the inclusion of each excipient has been provided.

The finished product is licensed for marketing in blister strips composed of aluminium form packing bottom strip with a heat-sealed aluminium foil top layer. The blister strips are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons and are packaged in pack sizes of 16, 20, 28, 56 and 100 capsules.

The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed however, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuff.
II.2 DRUG SUBSTANCE

**Lymecycline**

**rINN name:** Lymecycline  
**Chemical name:** N6[[4Dimethylamino),4,4a,5,5a,6,11,12a octahydro-3,6,10,12,12apentahydroxy-6-methyl-1,11-dioxo-2-aphthacenyl]carbonyl]-amino[methyl]-L-lysine.  
**Molecular formula:** C29H38N4O10  
**Molecular weight:** 602.63

![Chemical structure of Lymecycline](image)

**General properties**

**Description:** Lymecycline is a yellow hygroscopic powder  
**Solubility:** Very soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride

Lymecycline, the active substance, is the subject of a European Pharmacopoeia (EP) monograph.

**Manufacture**

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 pharmaceutical ingredient. 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. Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards. 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.

II.3 MEDICINAL PRODUCT

**Pharmaceutical development**

Details of the pharmaceutical development of the medicinal product have been supplied and are satisfactory. The objective was to develop a robust, stable, generic formulation, bioequivalent to the innovator product, Tetralysal 300 mg hard capsules (Galderma (UK) Limited). Lymecycline is converted to tetracycline in the intestinal tract. 408mg of lymecycline is equivalent to 300mg of tetracycline base.

Comparative dissolution and impurity profiles were provided for the test and reference products and were found to be similar.

The following excipients; FD&C Blue (E132), yellow iron oxide and black iron oxide, each comply with
their individual in-house specifications; which are satisfactory. The remaining excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Appropriate justification for the inclusion of each excipient has been provided.

With the exception of gelatin, none of the excipients used contain material derived from animal or human origin. The applicant has provided from each supplier, Certificates of Suitability issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM), confirming that the gelatin has been manufactured in-line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE). Furthermore, no genetically modified organisms are used in the manufacture of any of the excipients.

**Manufacture**
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted on commercial-scale batches and are satisfactory. The validation data demonstrated consistency of the manufacturing process.

**Control of Finish Product**
Finished product specifications are provided for both release and shelf-life, and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and adequately validated, as appropriate. Satisfactory batch analysis data are provided. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container-Closure System**
The finished product is licensed for marketing in blister strips composed of an aluminium form packing bottom strip with a heat-sealed aluminium foil top layer. The blister strips are placed with the Patient Information Leaflet (PIL) into cardboard outer cartons and are packaged in pack sizes of 16, 20, 28, 56 and 100 capsules. The Marketing Authorisation Holder (MAH) has stated that not all pack sizes may be marketed. However, the MAH has committed to submitting the proposed packaging/labelling for any pack size before it is marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 1 year has been approved. Storage conditions are “Store below 25°C” and “Store in the original package in order to protect from light”.

**Bioequivalence Studies**
The application is supported by a bioequivalence study comparing the test product, Lymecycline 408 mg Capsules, hard with the reference product Tetralysal 300 mg Capsules (Galderma (UK) Limited) under fasting conditions.

An evaluation of the bioequivalence study can be found in the Clinical Aspects section of this report.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
It is recommended that a Marketing Authorisation is granted for Lymecycline 408mg Capsules, hard.
II.5  Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PILs are available on the MHRA website. The current labelling is presented below:
Lymecycline 408mg Capsules, hard

Each capsule contains 408mg of lymecycline equivalent to 300mg tetracycline base. Read the package leaflet before use. Use as directed by your doctor.

Keep out of the sight and reach of children.

Store below 25°C. Store in the original package in order to protect from light.

MA holder
Actavis Group PTC eif.
Reykjavikurvegi 76-78
220 Hafnarfjörður
Iceland
PL 30305/0367

Actavis, Barnstaple, EX31 2SS, UK
III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of lymecycline are well known. No new non-clinical data have been submitted for these applications and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology

Not applicable, see Section III.1 Introduction, above.

III.3 Pharmacokinetics

Not applicable, see Section III.1 Introduction, above.
III.4 Toxicology
Not applicable, see Section III.1 Introduction, above.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the product is intended for substitution with product that is already marketed, no increase in environmental exposure to lymecycline is anticipated. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Lymecycline 408mg Capsules, hard, from a non-clinical point of view.

IV. CLINICAL ASPECTS
IV.1 Introduction.
The clinical pharmacology of lymecycline is well-known.

A satisfactory clinical overall summary is provided, and has been prepared by an appropriately qualified physician. The curriculum vitae of the expert has been provided.

IV.2 Pharmacokinetics
The clinical pharmacokinetic properties of lymecycline are well known, with the exception of data from the bioequivalence study detailed below, no new pharmacokinetic data are provided or required for this application.

The application is supported by one single dose bioequivalence study comparing the test product, Lymecycline 408 mg Capsules, hard (equivalent to 300 mg tetracycline base) with the reference product Tetralysal® (lymecycline) 300 mg capsules of Galderma (UK) Limited, in healthy adult subjects under fasting conditions.

Study 1
This study was a randomized, open label, two treatment, two period, two sequence, single dose, crossover, bioequivalence study of lymecycline 300 mg capsules of Actavis Group PTC ehf, Iceland (Test product) and Tetralysal® (lymecycline) 300 mg capsules of Galderma (UK) Limited, UK (Reference product), in healthy adult subjects, under fasting conditions.

The study was conducted in compliance with Good Clinical Practice (ICH-GCP) and Good Laboratory Practice.

Study design
Subjects were admitted to the study facility on the evening before the start of the study and fasted overnight for 10hrs. Subjects then received a single oral dose of study medication with 240ml of water.

Serial blood sampling before dosing and up to 48 hours after drug administration was carried out.

A washout period of 7 days was maintained between dosing periods in each group which is sufficient time for lymecycline to be eliminated from the body.
A validated LC/MS/MS analytical methodology was used for quantification of lymecycline from the human plasma samples. Primary variables analysed were: C_{max}, AUC_{(0-t)} and AUC_{(0--)}, AUC_{0-t}/AUC_{0--}, T_{max}, Kel, t1/2.
Pre-defined bioequivalence acceptance criteria
Bioequivalence of the test product versus the reference products was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 80-125% for log-transformed $C_{\text{max}}$ and AUC ratios.

Results:
Bioequivalence results for log-transformed test/reference ratios with 90% Confidence Intervals:

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Ratio (%)</th>
<th>90% Confidence Intervals</th>
<th>Intra-variation Coefficient (%)</th>
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<tbody>
<tr>
<td>$AUC_{\text{gt}}$</td>
<td>103.17</td>
<td>98.16 - 108.44</td>
<td>10.96</td>
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<tr>
<td>$C_{\text{max}}$</td>
<td>101.98</td>
<td>97.06 - 107.15</td>
<td>10.88</td>
</tr>
</tbody>
</table>

Conclusion on bioequivalence study:
The results of the bioequivalence study show that $C_{\text{max}}$ and AUC of the test product fall within the acceptance criteria range of 80-125% in line with the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98). Therefore the test product Lymecycline 408 mg hard capsules is bioequivalent with the reference product Tetralysal 300 mg tablets (Galderma (UK) Limited).

Safety
A total of 6 adverse events were reported in the study. They were mild to moderate in intensity and were completely resolved.

IV.3 Pharmacodynamics
The clinical pharmacodynamic properties of lymecycline are well-known. No new pharmacodynamic data have been submitted and none are required for this application.

IV.4 Clinical Efficacy
No new efficacy data have been submitted and none are required for this application.

IV.5 Clinical Safety
No new safety data have been submitted and none are required for this generic application. As lymecycline is a well-known product with an acceptable adverse event profile, this is satisfactory.

IV.6 Risk Management Plan
Suitable justification has been provided for not submitting a Risk Management Plan for this application which was received prior to 21 July 2012, the date from which pharmacovigilance regulations in accordance with Directive 2010/84/EU came into force. As the safety profile of the active substance is well-established, a Risk Minimisation Plan is not considered necessary. Routine Pharmacovigilance activities in accordance with EU regulations are considered sufficient.

IV.7 Discussion of the clinical aspects
The application contains an adequate review of published clinical data and bioequivalence has been shown. There are no objections to the approval of Lymecycline 408mg Capsules, hard from a clinical point of view.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package
leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Lymecycline 408mg Capsules, hard 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 this type of application. As the pharmacokinetics, pharmacodynamics and toxicology of lymecycline are well-known, no additional data were required.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Lymecycline 408 mg Capsules, hard with the reference product Tetralysal 300mg capsules under fasting conditions.

SAFETY
The safety profile of lymecycline is well-known. With the exception of the safety data generated during the bioequivalence no new safety data were submitted and none are required for this type of application. No new or unexpected safety issues were raised during the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with lymecycline is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product Information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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<tbody>
<tr>
<td>To increase the shelf life from 12 months to 15 months. Consequently section 6.3 (Shelf-life) of the SmPC has been updated.</td>
<td>UK/H/4171/001/IB/001</td>
<td>SmPC</td>
<td>19/10/2012</td>
<td>09/11/2012</td>
<td>Approval</td>
<td>No</td>
</tr>
<tr>
<td>To update sections 4.2, 4.8, 5.1 and 6.6 of the Summary of Product Characteristics (SmPC) in line with the Quality Review of Documents (QRD) template. Consequentially the Patient Information Leaflet (PIL) has been updated.</td>
<td>UK/H/4171/001/IB/005</td>
<td>SmPC and PIL</td>
<td>27/04/2015</td>
<td>11/05/2015</td>
<td>Approval</td>
<td>Yes (Annex 1.1)</td>
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</tbody>
</table>
Annex 1.1

Our Reference: PL 30306/0367, Application 10
Product: Lymecycline Capsules 408mg
Marketing Authorisation Holder: Actavis Group PTC ehf
Active Ingredient(s): LYMECYCLINE.

Type of Procedure: Mutual Recognition
Submission Type: Variation
Submission Category: Type IB
Submission Complexity: Standard
EU Procedure Number (if applicable): UK/H/4171/001/IB/005

Reason:
To update sections 4.2, 4.8, 5.1 and 6.6 of the Summary of Product Characteristics (SmPC) in line with the Quality Review of Documents (QRD) template. Consequentially, the Patient Information Leaflet (PIL) has been updated.

Linked / Related Variation(s) or Case(s):

Supporting Evidence
Revised SmPC fragments (sections), and leaflet have been provided.
QRD template

Evaluation
The updated sections of the SmPC and leaflet are in line with the QRD template and are therefore acceptable.

Conclusion
The updated sections of the SmPC and the leaflet are satisfactory and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision – Approved 11/05/2015