LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Lymelysal
(lymecycline)

SE/H/1585/01/DC

This module reflects the scientific discussion for the approval of Lymelysal. The procedure was finalised on 2016-09-29. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Lymelysal, 300 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. Each capsule contains 408 mg of lymecycline equivalent to 300 mg tetracycline. The applicant, 2care4 ApS applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Tetralysal, 300 mg, capsules, hard authorised in DK since 1962, with Galderma Nordic AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Tetralysal, 300 mg, capsules, hard from UK with Galderma (UK) Limited as marketing authorisation holder.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Lymecycline is metabolised to active tetracycline during absorption. Following an oral dose of lymecycline maximal plasma concentrations of tetracycline occur at approximately 2-3 hours. The absorption of lymecycline is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. The terminal half-life of tetracycline is 10-12 hours.

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Lymecycline, 300 mg, capsules (408 mg lymecycline corresponding to 300 mg tetracycline base) with Tetralysal, 300 mg, capsules (408 mg lymecycline corresponding to 300 mg tetracycline base) under fasting conditions. Blood samples were collected pre-dose and up to 48 hours post-dose. The study design is considered acceptable. Plasma concentrations of tetracycline were determined with an adequately validated LC/MS/MS method. According to the SmPC of the reference product, the parent drug lymecycline is metabolised to the active metabolite tetracycline during absorption. It is therefore considered acceptable to measure the active metabolite instead of the parent drug. This has also been agreed for previous lymecycline generics. For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tetracycline, n=23.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**26380±5840**	**1795±390**	**3.67 (1.00-5.00)**
Reference	**25488±6501**	**1795±465**	**3.67 (1.50-5.00)**
***Ratio (90% CI)**	**103.88 (97.45-110.74)**	**100.78 (94.59-107.37)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum plasma concentration			

**calculated based on ln-transformed data*

Based on the submitted bioequivalence study, Lymelysal is considered bioequivalent with Tetralysal.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Lymelysal.

Safety specification

Summary table of safety concerns as approved in the RMP.

Summary of safety concerns	
Important identified risks	- Hypersensitivity - *Clostridium difficile*-associated diarrhoea and pseudomembranous colitis - Photosensitivity - Benign intracranial hypertension when used concomitantly with systemic retinoids - Dental staining and enamel hypoplasia in the foetus or child when used during pregnancy, breast feeding or in use by children under 12 years old
Important potential risks	 - Emergence of bacterial resistance - Toxicity in patients with hepatic impairment - Liver toxicity in patients with renal impairment - Exacerbation of systemic lupus erythematosus - Neuromuscular blockade when used in patients with myasthenia gravis
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The MAH has satisfactory responded to the questions raised and updated the RMP accordingly. The RMP is approved

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 language used for the purpose of user testing the PIL was English.
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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lymelysal, is found adequate. There are no objections to approval of Lymelysal from a non-clinical and clinical point of view.

Bioequivalence between the test and reference product has been adequately demonstrated.

The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Lymelysal, 408 mg, capsule, hard was positively finalised on 2016-09-29.

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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