LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lymecycline Glenmark
(lymecycline)

SE/H/2129/01/DC

This module reflects the scientific discussion for the approval of Lymecycline Glenmark. The procedure was finalised on 2022-03-23. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Lymecycline Glenmark, 300 mg, capsule, hard.

The active substance is tetracycline, lymecycline. A comprehensive description of the indication and posology is given in the SmPC.

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

The application for Lymecycline Glenmark, 300 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Glenmark Arzneimittel GmbH, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and LU as concerned member states (CMS).

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

The reference product used in the bioequivalence study is Tetralysal, 300 mg, capsule, hard, from France with Galderma as marketing authorisation holder.

European Reference Product (ERP)
A European Reference Product is used in CMS LU: Tetralysal, 300 mg, capsule, hard, authorised in Sweden since 1969, with Galderma Nordic AB as marketing authorisation holder.
The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

Pharmacodynamic, pharmacokinetic and toxicological properties of lymecycline are well known. As lymecycline is a widely used, well-known active substance, no further studies are required, and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Lymecycline Glenmark is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Lymecycline Glenmark from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Lymecycline hard capsules with the reference product Tetralysal hard capsules.

Pharmacokinetic properties of the active substance
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.

Study C1B00259
Methods
This was a single-dose, two-way crossover study conducted in 48 (46 completed) healthy volunteers, comparing Lymecycline 408 mg hard capsules (equivalent to 300 mg tetracycline base) with Tetralysal, 300 mg, hard capsules (strength expressed as tetracycline) under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of tetracycline were determined with an LC/MS/MS method. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 6th August and 14th September 2020.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1.

Table 1: Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for tetracycline, n=46

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**37368 ± 10037**	**2424 ± 519**	**3.75 (1.33-6.02)**
Reference	**37353 ± 9900**	**2415 ± 489**	**4.00 (2.00-5.50)**
***Ratio (90% CI)**	**99.83 (92.51-107.72)**	**99.93 (93.24-107.10)**	**-**

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*

For AUC_{0-t} and C_{max} of tetracycline the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). It is acceptable to base bioequivalence on the active metabolite tetracycline as, according to the SmPC of the reference product, lymecycline is metabolised to active tetracycline during absorption. The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Lymecycline hard capsules are considered bioequivalent with Tetralysal hard capsules.

Pharmacodynamics/Clinical efficacy/Clinical safety
The application contains an adequate review of published clinical data.
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted.
Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 the product.

Safety specification

Important identified risk(s)	• None
Important potential risk(s)	• None
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 satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.3 signed 17 January 2022 is considered acceptable.

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, Lymecycline Glenmark, is found adequate. There are no objections to approval of Lymecycline Glenmark, 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/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Lymecycline Glenmark, 300 mg, capsule, hard was positively finalised on 2022-03-23.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	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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