LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lyribastad
(pregabalin)

SE/H/1636/01-08/DC

This module reflects the scientific discussion for the approval of Lyribastad. The procedure was finalised on 2017-10-04. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Lyribastad, 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg, capsule, hard is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, STADA Arzneimittel AG, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and AT, DK, FI as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lyrica, 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg, capsule, hard authorised in Union since 2004, with Pfizer Limited as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

Pregabalin has an oral bioavailability of ≥90 % independent of dose. Following an oral dose of pregabalin maximal plasma concentrations occur within one hour. The rate of pregabalin absorption is decreased when given with food but the extent of absorption is not significantly affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. The pharmacokinetics of pregabalin is linear over the recommended daily dose range. The terminal half-life is 6.3 hours. Pregabalin is eliminated primarily by renal excretion as unchanged drug.

No bioequivalence study has been submitted since the applicant applies for a BCS-based biowaiver. From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same. It should also be confirmed that the substance is not a narrow therapeutic index drug. These aspects are discussed below.

Absorption

According to the bioequivalence guideline complete absorption is considered to be established where measured extent of absorption is >85%. Data from absolute bioavailability or mass-balance studies could be used to support this claim. The applicant states that Pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose (Blommel 2007; Bockbrader 2010; Martindale 2016). Thus, oral bioavailability of pregabalin averaged ≥ 90% across the full dose range of 75 to 900 mg/d studied (Bockbrader 2010). This range includes and exceeds the efficacious dosage range (150-600 mg/d) studied in phase III pregabalin trials.

According to the SmPC and EPAR of Lyrica, pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose. Thus, it is agreed that pregabalin has complete absorption and can be classified as a BCS class I substance from a pharmacokinetic perspective.

Excipients

The qualitative composition of the capsule content is similar for the test and reference product, with maize starch replaced by pregelatinized starch. It is noted that the capsule shell of the reference product contains sodium lauryl sulphate (SLS) which is not included in the capsule shell of the test product. This difference is however considered negligible and not considered likely to affect the bioavailability. Thus, the differences in excipients are acceptable for a BCS class I substance.

Narrow therapeutic index
The applicant has submitted a justification that pregabalin does not have a narrow therapeutic index. It is agreed that pregabalin is not considered to be a drug with a narrow therapeutic index in the sense that the acceptance criteria would need to be tightened in a bioequivalence study. The recommended dose range is wide (150 mg/day – 600 mg/day) and the risks associated with a potentially small increase in exposure above the highest recommended exposure of the originator seems negligible. Thus, a BCS based biowaiver is possible in this aspect.

Pharmacokinetic conclusion
It is concluded that pregabalin has a fraction absorbed greater than or equal to 85% and thus can be classified as BCS class I substance from a pharmacokinetic point of view. It has also been sufficiently demonstrated that pregabalin is not a narrow therapeutic index drug. The differences in excipients are acceptable for a BCS class I substance. Quality aspects of BCS biowaiver are also fulfilled. Thus, the justification for BCS (Biopharmaceutics Classification System) based biowaiver CAN be accepted.

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 Lyribastad.

Safety specification

Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Weight gain • Peripheral oedema and oedema-related events • Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Discontinuation events • Drug interactions (lorazepam, ethanol and CNS depressants) • Euphoria • Hypersensitivity and allergic reactions • Congestive heart failure • Vision-related events • Abuse, misuse and drug dependence
Important potential risks	• Suicidality • Haemangiosarcoma • Off-label use in paediatric patients
Missing information	• Pregnancy and lactation

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 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 Lyribastad is found adequate. There are no objections to approval of Lyribastad from a non-clinical and clinical point of view. 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 Lyribastad, 25mg, 50mg, 75mg, 100mg, 150mg, 200mg, 225mg, 300mg, capsule, hard was positively finalised on 2017-10-04.

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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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