LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Pregabalin Jubilant (pregabalin)

SE/H/1807/01-08/DC

This module reflects the scientific discussion for the approval of Pregabalin Jubilant. The procedure was finalised on 2019-03-05. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Pregabalin Jubilant, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, and 300 mg, hard capsule, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Jubilant Pharmaceuticals N.V., applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and Germany and United Kingdom as concerned member states (CMS).

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

No bioequivalence studies have been performed on Pregabalin capsules. A BCS-Class I Biowaiver is requested.

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/EC 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

Pharmacokinetic properties of the active substance
Absorption: 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.

Linearity: The pharmacokinetics of pregabalin is linear over the recommended daily dose range.

Elimination: The elimination half-life is 6.3 hours. Pregabalin is eliminated primarily by renal excretion as unchanged drug.

BCS-based biowaiver
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

According to the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr), a BCS class I-based biowaiver is applicable for an immediate release product if the drug substance is not considered to have a narrow therapeutic index and has been proven to exhibit high solubility and complete absorption (BCS class I). Also, in-vitro dissolution characteristics of the test and the reference product should be either very rapid or similarly rapid and the excipients that might affect bioavailability should be quantitatively and qualitatively the same.

The applicant has submitted a biowaiver justification in the Clinical overview, stating that the product is eligible for a BCS class I biowaiver based on high solubility, high permeability and rapid dissolution. The applicant also discusses the difference in excipients compared to the reference product and claims that pregabalin should not be considered a narrow therapeutic index drug.

The applicant states that pregabalin oral bioavailability is estimated to be ≥ 90% and is independent of dose (Lyrica® SmPC, Ben-Menachem 2004, Bockbrader 2010).

Discussion and overall conclusion
It can be concluded that the drug substance has been proven to exhibit high solubility and complete absorption (BCS class I).

Pregabalin is not considered to have a narrow therapeutic index in the sense that narrowed acceptance ranges would be necessary in bioequivalence studies performed with pregabalin.

The qualitative composition of the capsule content is the same for test and reference product. The capsule shell of both products contains sodium lauryl sulphate (SLS) which is mentioned in the bioequivalence guideline as a substance that might affect bioavailability. However, the amount is very low and it is not considered likely that this would affect the bioavailability. Thus, the differences in excipients are acceptable for a BCS class I substance.

"Very rapid" in vitro dissolution of the test and the reference product has been demonstrated.

In conclusion, the justification for a 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 Pregabalin Jubilant.

The applicant submitted an updated RMP in response to RMS comments. The submitted Risk Management Plan, version 1.3 signed 1st of March 2019:

Table SVIII.1: Summary of safety concerns as per published Lyrica – EPAR RMP summary dated 17-Dec-2018

Summary of safety concerns	
Important identified risks	• Dizziness, Somnolence, Loss of consciousness, Syncope and Potential for Accidental injury • Vision-related events • Discontinuation events • Drug Interactions (lorazepam, ethanol and CNS depressants • Congestive Heart Failure • Abuse and Drug Dependence • Euphoria
Important potential risks	• Suicidality • Off-label use in paediatric patients
Missing information	• Pregnancy and lactating women

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 submitted Risk Management Plan, version 1.3 signed 1st of March is considered acceptable.
All issues resolved.

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, product name, is found adequate. There are no objections to approval of product name, from a non-clinical and clinical point of view. The product information is acceptable.
The benefit/risk ratio is considered positive and Pregabalin Jubilant, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg, hard capsules is recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC 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 Pregabalin Jubilant, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg, 300 mg, hard capsules, was positively finalised on 2019-03-05.

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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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