LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Pregabalin Medical Valley (pregabalin)

SE/H/1465/08/DC

This module reflects the scientific discussion for the approval of Pregabalin Medical Valley. The procedure was finalised on 2022-11-30. 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 Pregabalin Medical Valley, 225 mg, Capsule, hard.

The active substance is pregabalin. 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 is an extension, new strength, of the previously authorised products: Pregabalin Medical Valley, 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 300 mg, capsule, hard, marketed by Medical Valley Invest AB since 2016.

The application for Pregabalin Medical Valley, 225 mg, Capsule, hard, is a generic application submitted according to Article 10(1) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Lyrica, 225 mg, capsule, hard, authorised in the Union since 2004, with Upjohn EESV as marketing authorisation holder.

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

Pharmacology/Pharmacokinetics/Toxicology

Pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin 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 Pregabalin Medical Valley 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 Pregabalin Medical Valley from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
No bioequivalence study has been submitted since the applicant applies for a biowaiver based on the Biopharmaceutics Classification System (BCS).

Pharmacokinetic properties of the active substance

Absorption: Pregabalin has an oral bioavailability of >90 %. Following an oral dose of pregabalin maximal plasma concentrations occur within 1 hour.

The pharmacokinetics of pregabalin is not affected by food, and therefore there are no restrictions with respect to food in the SmPC of the originator. Concomitant food intake decreases the C_{max} by 25-31 %. However, because only the rate and not the extent of pregabalin bioavailability is affected by food, pregabalin can be given without regard to the timing of meals.

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

Elimination: The terminal half-life is 6 hours.

Discussion and overall conclusion

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 comparative, *in vitro* study of dissolution with different pH were used as dissolution method, which correspond to the physiological range. In the selected experimental conditions, similar dissolution profiles for Lyrica 225 mg hard capsules and Pregabalin Medical Valley 225 mg hard capsules were obtained.

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). It can be concluded that the extent of absorption is above 85% and thus, pregabalin can be classified as a BCS class I substance from a pharmacokinetic perspective.

None of the excipients included in the drug product are known to influence bioavailability.

The quality criteria for biowaiver (solubility and dissolution) have also been fulfilled.

For quality aspects of biowaiver, see the quality assessment report. Similar in vitro dissolution characteristics 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. Pregabalin Medical Valley capsule, hard, 225 mg, is considered bioequivalent with Lyrica capsule, hard,, 225 mg.

Pharmacodynamics/Clinical efficacy/Clinical safety
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 Pregabalin Medical Valley.

Safety specification

Summary of safety concerns	
Important identified risks	• Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Discontinuation events • Drug interactions (lorazepam, ethanol and CNS depressants) • Euphoria • Congestive heart failure • Vision-related events • Abuse and drug dependence
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 3.0 signed 3rd November 2021 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 PL was Spanish.

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, Pregabalin Medical Valley, is found adequate. There are no objections to approval of Pregabalin Medical Valley, from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and 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 Pregabalin Medical Valley, 225 mg, Capsule, hard was positively finalised on 2022-11-30.

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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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