Decentralised Procedure

Public Assessment Report

Pregabalin Teva
25/ 50/ 75/ 100/ 150/ 200/ 225/ 300 mg Hartkapseln

Pregabalin

DE/H/5003/001-008/DC

Applicant: Teva B.V., The Netherlands

Reference Member State	DE

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Pregabalin Teva 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg Hartkapseln
Name of the drug substance (INN name):	Pregabalin
Pharmaco-therapeutic group (ATC Code):	N03AX16
Pharmaceutical form(s) and strength(s):	Capsules, hard ; 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg
Reference Number(s) for the Decentralised Procedure	DE/H/5003/001-008/DC
Reference Member State:	DE
Concerned Member States:	**DE/H/5003/001,003,005/DC:** BE, BG, CY, CZ, DK, EE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT,SE, SI, SK, UK **DE/H/5003/002/DC:** BE, CY, DK, EL, FR, IE, IT, LU, MT, NL, PT, SE, UK **DE/H/5003/004,006/DC:** CY; DK, EL, FR, IE, IT, LU, MT, NL, PT, SE, UK **DE/H/5003/007/DC:** CY; DK, EL, IE, IT, LU, MT, NL, PT, SE, UK **DE/H/5003/008/DC:** BE, CY, DK, EL, ES, FR, HR, IE, IT, LU, MT, NL, PL, PT, SE, SI, SK, UK
Applicant (name and address)	Teva B.V. Swensweg 5, NL-2031 GA Haarlem, The Netherlands

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *"Pregabalin Teva 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg Hartkapseln"*, in the indications peripheral and central neuropathic pain, adjunctive therapy in adults with partial seizures with or without secondary generalisation and Generalised Anxiety Disorder (GAD) in adults, is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

N/A

II.2 About the product

This decentralised application concerns a generic version of pregabalin, under the trade names *"Pregabalin Teva 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg Hartkapseln"*. In this Assessment Report, the name *"pregabalin"* is used.

The originator product is *"Lyrica 25, 50, 75, 100, 150, 200, 225 and 300 mg hard capsules"* by Pfizer Ltd. UK, centrally registered across the EU since 6th July 2004.

With Germany as the Reference Member State in this Decentralized Procedure, Teva B.V., The Netherlands, applied for the Marketing Authorisations for DE/H/5003/001,003,005/DC in BE, BG, CY, CZ, DK, EE, EL, ES, FR, HR, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT,SE, SI, SK, UK for DE/H/5003/002/DC in BE, CY, DK, EL, FR, IE, IT, LU, MT, NL, PT, SE, UK for DE/H/5003/004,006/DC in CY; DK, EL, FR, IE, IT, LU, MT, NL, PT, SE, UK for DE/H/5003/007/DC in CY; DK, EL, IE, IT, LU, MT, NL, PT, SE, UK and for DE/H/5003/008/DC in BE, CY, DK, EL, ES, FR, HR, IE, IT, LU, MT, NL, PL, PT, SE, SI, SK, UK.

Pregabalin is an anticonvulsant used as an adjunct in the treatment of partial seizures with or without secondary generalisation in adults. It is also used in the treatment of generalised anxiety disorder, neuropathic pain, and fibromyalgia. Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

II.3 General comments on the submitted dossier

The submitted dossier is generally of adequate quality with regard to prevailing European requirements for essentially similar products.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

The submitted bioequivalence studies have been stated to have been carried out in accordance with the International conference on harmonisation (ICH) E6 'Guideline for Good Clinical Practice' and Declaration of Helsinki (Seoul, 2008).

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

The drug substance data is provided in the form of an Active Substance Master File. Letter of access as well as drug substance documentation is included in the dossier. The chemical-pharmaceutical documentation and Quality Overall Summary in relation to *Pregabalin Teva 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg Hartkapseln* are of sufficient quality in view of the present European regulatory requirements. The control tests and specifications for drug substance product are adequately drawn up. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

Drug Product

The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. The batch analysis results show that the finished products meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Presented stability data is acceptable and supports a shelf-life of 36 months for finished product packaged in PVC/Al blisters and HDPE bottles.

III.2 Non-clinical aspects

The pharmacological and toxicological properties of pregabalin are well known and have been adequately summarised in the Non-clinical Overview. In the Non-clinical Overview it is confirmed that impurities have been limited in accordance with European and ICH requirements.

The instructions on use of the compound during pregnancy and lactation and the preclinical safety data contained in the proposed SmPC and PL, respectively, essentially reflect the characteristics of the active substance and have been harmonised in this procedure with the currently approved product information of the reference product *"Lyrica"* (EMEA/H/C/546/WS/690).

Environmental Risk Assessment (ERA)

Since *"Pregabalin Teva 25/ 50/ 75/ 100/ 150/ 200/ 225/ 300 mg Hartkapseln"* is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics

To support the application, the applicant has submitted two bioequivalence studies:

In bioequivalence study No. 151-10, bioavailability of the intended *Pregabalin Teva 50 mg Hartkapseln* was compared to that of Lyrica 50 mg capsules. In study No. 152-10, bioavailability of the intended *Pregabalin Teva 300 mg Hartkapseln* was compared to that of Lyrica 300 mg capsules. Both studies had an open-label, single-dose, fasted, randomized, two-period, two-sequence, two-treatment, crossover design.

From the submitted bioequivalence studies (Nos. 151-10 and 152-10) bioequivalence of *Pregabalin Teva 50 mg Hartkapseln* with Lyrica 50 mg capsules, hard and *Pregabalin Teva 300 mg Hartkapseln* with Lyrica 300 mg capsules, hard, respectively can be concluded.

The results of study 151-10 with the 50 mg capsules, hard can be extrapolated to the 25 mg strength. The results of study 152-10 with the 300 mg capsules, hard can be extrapolated to the 75mg/100mg/150mg/200mg/225mg strengths, respectively according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or safety have been submitted.

User Testing
No weaknesses of the PL were identified during any test round. In both main test rounds, 100% of participants were able to find the information relating to each question and 100% of participants were able to answer each question correctly. The general impression of the PL (content, language and layout) was mostly positive. In conclusion, the user test is considered acceptable.

Summary Pharmacovigilance system
The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

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 effects • 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	• Haemangiosarcoma • Suicidality • Off-label use in paediatric patients • Medication error with pregabalin oral solution
Missing information	• Pregnancy and lactation

The applicant proposed routine pharmacovigilance and risk minimisation measures for all of the above safety concerns. No additional measures are proposed, which is endorsed.

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data. Bioequivalence of the intended *Pregabalin Teva 25 / 50 / 75 / 100 / 150 / 200 / 225 / 300 mg Hartkapseln* with the respective reference product, Lyrica 25/50/75/100/150/200/225/300 mg capsules can be concluded.
The RMP contains adequate pharmacovigilance and risk minimisation measures for a positive benefit risk ratio. The application is approved. For intermediate amendments see current product information.