COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Prelexa 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules (pregabaline)

NL License RVG: 126029 - 126036

Date: 17 January 2022

This module reflects the scientific discussion for the approval of Prelexa. The marketing authorisation was granted on 26 November 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Prelexa 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules, from Maddox Pharma Swiss B.V.

This product is indicated for the following conditions:

Neuropathic pain
Prelexa is indicated for the treatment of peripheral and central neuropathic pain in adults.

Epilepsy
Prelexa is indicated as an adjuvant therapy in adults with partial epilepsy with or without secondary generalised attacks.

Generalised anxiety disorder
Prelexa is indicated for the treatment of generalised anxiety disorder (GAD) in adults.

A comprehensive description of the indications and posology is given in the SmPC.

This national procedure concerns a generic application claiming essential similarity with the innovator product Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules, which were registered through a centralized procedure (EU/1/04/279) by Pfizer Limited on 6 July 2004.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Prelexa are hard capsules, specific appearance information can be found below:

Prelexa 25 mg hard capsules:
White, with imprint “PGB 25”in black ink.

Prelexa 50 mg hard capsules:
White, with imprint “PGB 50” in black ink and marked with a black band.

Prelexa 75 mg hard capsules:
White and orange, with imprint “PGB 75” in black ink.

Prelexa 100 mg hard capsules:

Orange, with imprint “PGB 100” in black ink.

Prelexa 150 mg hard capsules:
White, with imprint “PGB 150” in black ink.

Prelexa 200 mg hard capsules:
Light orange, with imprint “PGB 200” in black ink.

Prelexa 225 mg hard capsules:
White and light orange, with imprint “PGB 225” in black ink.

Prelexa 300 mg hard capsules:
White and orange, with imprint “PGB 300” in black ink.

The hard capsules contain 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin respectively.

The hard capsules are packed in PVC/aluminium blisters and HDPE bottles.

The excipients are:

Prelexa 25 mg, 50 mg and 150 mg hard capsules:
Capsule core – mannitol (E421), pre-gelatinised corn starch, corn starch and talc (E533B).

Capsule shell – gelatine (E441) and titanium dioxide (E172).

Imprinting ink – shellac, iron oxide black (E172) and potassium hydroxide.

Prelexa 75 mg, 100 mg, 200 mg, 225 mg and 300 mg hard capsules:
Capsule core - mannitol (E421), pre-gelatinised corn starch, corn starch and talc (E533B).

Capsule shell – gelatine (E441), titanium dioxide (E171) and iron oxide red (E172).

Imprinting ink – shellac, iron oxide black (E172) and potassium hydroxide.

The capsule content of the 25 mg and 50 mg strength is dose/weight proportional and the capsules of the 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strengths are dose/weight proportional.

II.2 Drug Substance

The active substance is pregabalin, an established substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white crystalline powder, sparingly soluble in water. The drug substance exhibits polymorphism and stereoisomerism which are adequately controlled. The polymorphic form of pregabalin is form I, and is consistently manufactured and remains stable during storage.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is in line with the Ph.Eur. monograph and the requirements as described on the CEP's. An in-house related substances method is described for the one of the drug substance manufacturers material, which has been justified and cross validated with the Ph.Eur. method. The specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of each drug substance manufacturer.

Stability of drug substance

The active substance from manufacturer I is stable for three years when stored in a polyethylene bag in an aluminium/polyethylene bag placed in a fibre drum. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

The active substance from manufacturer II is stable for 60 months when stored in double polyethylene bags (outer black) in a triple laminated bag placed in a polyethylene container. This aspect has been evaluated within the scope of the CEP procedure by the EDQM and the conclusion is taken from the CEP.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation development was based on the reference product. Compared to the composition of the reference product, the test product contains mannitol instead of lactose monohydrate. The excipients were chosen to enhance the flow of blend and to improve the stability of the drug product.

Two comparative bioequivalence (BE) studies have been performed, one with a pilot scale batch of the 50 mg strength and one with a pilot scale batch of the highest strength of 300

mg. Both studies were performed versus capsules of the same strengths of the reference product. A comparative multimedia dissolution study at three pH's of the BE test products was performed and a dissolution study for the biowaivers of the other strengths. In addition, a comparative multimedia dissolution study was performed in support of the claimed manufacturing site. In all studies, all profiles in all media demonstrated dissolution of more than 85% after 15 minutes.

The pharmaceutical development of the drug product has been adequately performed. The applicant has adequately confirmed that the drug products from both manufacturers are of identical composition and are manufactured according to identical procedures. Thus, it has been adequately justified that the batches from manufacturer II that were used for the BE study and the biowaiver of strength study are representative for the proposed manufacturer.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process is considered a standard process consisting of five phases: dispensing, sieving, mixing, mixing with talc and encapsulation. The manufacturing process description provides the appropriate target values of the process parameters, equipment used, environmental conditions and IPC tests. The critical steps are the blend mixing duration control and the sieving control. A clear description of the container closure integrity test for the blister primary packaging has been provided. Process validation data on the product has been provided for 28 batches.

Control of excipients

The excipients comply with the Ph.Eur. except for a co-processed excipient for which an in-house specification is applicable. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average mass, identification, uniformity of dosage units, disintegration, assay, related compounds, dissolution and microbiological quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate risk assessment on nitrosamines has been provided and sufficient information about the elemental impurities assessment and the fact that no test and acceptance criteria are added for chirality and polymorphism.

The analytical methods have been adequately described. For the method validations the applicant has provided sufficient information. Batch analytical data from the proposed production site has been provided on more than three pilot scaled and full scaled batches for each strength, demonstrating compliance with the proposed release specification.

Stability of drug product

Stability data on the product has been provided for 11 batches (25 mg, 50 mg, 75 mg, 150 mg and 300 mg strengths) and eight batches (100 mg and 225 mg strengths) from the proposed manufacturer. Furthermore, stability data on the product has been provided for six batches (25 mg, 50 mg and 75 mg strengths), three batches (100 mg, 150 mg and 200 mg strengths)

and four batches of the 300 mg strength from a previous manufacturing site. Stability testing is performed at accelerated (40°C ±2°C/75% ±5% RH), intermediate (30°C ±2°C/65% ±5%RH, performed for one batch of the 25 mg and four batches of the 50 mg strengths) and long term at 30°C ±2°C/75% ±5%RH (for all strengths except the 25 mg and 50 mg in blisters) and at 25°C ±2°C/60% ±5%RH.

The intermediate storage conditions of 30°C ±2°C/75% ±5%RH are accepted. The batches were stored in Al/PVC blister and HDPE bottles. Photostability studies were performed in accordance with ICH Q1B recommendations and showed that the product is stable when exposed to light.

Because the stability results of the 25 mg and 50 mg batches, manufactured at a previous manufacturing site, stored at 30°C ±2°C/75±5% RH in blisters, demonstrate out of specification results for an impurity, it was concluded that the 25 mg and 50 mg strengths are less stable in Al/PVC packaging compared to the other strengths and the HDPE containers. As a consequence, for the 25 mg and 50 mg strength in Al/PVC blisters a shelf life of 24 months is claimed with the following storage statement: “Do not store above 25°C”. For the 75, 100, 150, 200, 225 and 300 mg strength in Al/PVC blisters a shelf life of 24 months is claimed with the following storage statement: “Do not store above 30°C”. This is considered to be acceptable.

For the HDPE bottles for all strengths a shelf life of 24 months is claimed without any special storage conditions. This is considered in line with the EMA Guideline on Declaration of Storage Conditions and the stability results and accepted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM on gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Prelexa has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Prelexa 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Lyrica which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pregabalin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Prelexa 50 mg and 300 mg hard capsules (Maddox Pharma Swiss B.V.) is compared with the pharmacokinetic profile of the reference product Lyrica 50 mg and 300 mg hard capsules (Pfizer Ltd.) respectively.

The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The design of the studies is acceptable.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

<u>Biowaiver</u>
Bioequivalence studies have been submitted for the 50 mg and 300 mg strengths. Bioequivalence studies were not carried out on the other strengths, since all conditions listed in section 4.1.6 of the Guideline on the Investigation of Bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1 are fulfilled for the additional strengths compared to the tested strengths:

- All strengths are manufactured by the same manufacturing process.
- Qualitative composition of the different strengths is the same.
- Composition of the 25 mg and 50 mg strengths are quantitatively proportional.

- Composition of the 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strengths are quantitatively proportional.
- Comparative dissolution profiles across the physiological pH range indicate that the dissolution profiles are similar when compared between the proposed strengths.

The dissolution properties of one batch of each strength of the Prelexa 50 mg and 300 mg product were investigated under three pH conditions, and were compared with the dissolution of the Lyrica 50 mg and 300 mg test bio-batches under the same conditions. This was considered acceptable and a biowaiver for the 25 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths was granted.

Bioequivalence studies

Pharmacokinetic BE study I (Prelexa 50 mg VS Lyrica 50 mg hard capsules, fasting conditions)

Design
A randomised, two-treatment, two-period, two-sequence single-dose crossover bioequivalence study was carried out under fasting conditions in 32 healthy male subjects, aged 20-40 years. Each subject received a single dose (50 mg) of one of the two pregabalin formulations. The capsule was orally administered with 240 ml water after an overnight fast. Fasting continued until four hours after drug administration. Water was allowed *ad libitum* until one hour pre-dose and beginning one hour after drug administration. There were two dosing periods, separated by a washout period of eight days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after drug administration.

Results
Out of a total of 32 subjects, 29 subjects were eligible for pharmacokinetic analysis. One subject was withdrawn due to elevated blood pressure, another subject was withdrawn because of a seizure disorder. Finally, one subject withdrew consent before dosing.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin (50 mg) under fasted conditions.

Treatment N=29	**AUC_{0-t} (µg.h/ml)**	**t_{max} (h)**	**C_{max} (µg/ml)**
Test	11.49 ± 1.397	0.75 (0.5 – 1.75)	1.89 ± 0.410
Reference	11.36 ± 1.315	1 (50.5 – 1.75)	1.85 ± 0.440
Geometric mean Ratio (90% CI)	101.02 (98.40 – 103.71)	--	102.57 (95.99 – 109.61)

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 concentration
CI	confidence interval

**ln-transformed values*

Pharmacokinetic BE study II (Prelexa 300 mg VS Lyrica 300 mg hard capsules, fasting conditions)

Design

A randomised, two-treatment, two-period, two-sequence single-dose crossover bioequivalence study was carried out under fasting conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (300 mg) of one of the two pregabalin formulations. The capsule was orally administered with 240 ml water after an overnight fast. Fasting continued until four hours after drug administration. Water was allowed *ad libitum* until one hour pre-dose and beginning one hour after drug administration. There were two dosing periods, separated by a washout period of nine days.

Blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00 and 48.00 hours after drug administration.

Results

Out of a total of 36 subjects, 35 subjects were eligible for pharmacokinetic analysis. One subject did not check in for period II and was withdrawn.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of pregabalin (300 mg) under fasted conditions.

Treatment N=35	**AUC_{0-t}** (µg.h/ml)	**t_{max}** (h)	**C_{max}** (µg/ml)
Test	66.70 ± 10.38	1.5 (0.5 – 3.50)	8.56 ± 1.44
Reference	67.05 ± 10.74	1.75 (0.5 – 2.50)	8.55 ± 1.68
Geometric mean Ratio (90% CI)	99.57 (97.85 – 101.32)	--	100.56 (95.51 – 105.88)

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 concentration
CI	confidence interval

**ln-transformed values*

<u>Conclusion on bioequivalence studies</u>:

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 80.00 – 125.00%. Based on the submitted bioequivalence studies Prelexa is considered bioequivalent with Lyrica.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Prelexa.

Table 3. Summary table of safety concerns as approved in RMP

Important identified risks	• Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Discontinuation events • Interaction with other medications (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 lactation

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lyrica. No new clinical studies were conducted. The MAH demonstrated through two bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

User consultation with target patient groups on the package leaflet (PL) has not been performed for Prelexa. However, as Prelexa is a generic formulation of Lyrica, the product information of Prelexa is identical to Lyrica. The absence of a user consultation study or bridging report is therefore considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Prelexa 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Lyrica 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules. Lyrica is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Prelexa with the reference product, and have therefore granted a marketing authorisation. Prelexa was authorised in the Netherlands on 26 November 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type C.I.2.a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the reference product	SmPC	23-12-2021	Approval	
Type B.II.b.2.c.1	Replacement or addition of a manufacturer responsible for importation and/or batch release	PL	29-11-2021	Approval	