

Public Assessment Report

Scientific discussion

**Pregamid 25 mg, 50 mg, 75 mg, 100 mg,
150 mg, 200 mg, 225 mg and 300 mg
hard capsules**

(pregabalin)

NL/H/3245/001-008/DC

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This module reflects the scientific discussion for the approval of Pregamid hard capsules. The procedure was finalised on 26 May 2015. 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
BCS	Biopharmaceutics Classification System
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 member states have granted a marketing authorisation for Pregamid 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules. The marketing authorisation holder is G.L. Pharma GmbH.

Pregabalin is indicated for:

- Epilepsy
Pregamid is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.
- Generalised Anxiety Disorder
Pregamid is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.
- Neuropathic pain
Pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults. The MEB has been informed that the application of this active substance for this indication is being protected by a patent of a third party.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lyrica hard capsules, which has been registered in the EEA by Pfizer Ltd since July 2004 through a centralised procedure (EU license number EU/1/04/279).

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania and Slovakia.

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

II. QUALITY ASPECTS

II.1 Introduction

Pregamid capsules contain a white to off-white powder.

Pregamid 25 mg is a hard capsule, size 4, with a white cap and a white body, with "25" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 50 mg is a hard capsule, size 3, with a white cap and a pinkish-orange body, with "50" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 75 mg is a hard capsule, size 4, with a brownish-red cap and a white body, with "75" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 100 mg is a hard capsule, size 3, with a brownish-red cap and a brownish-red body, with "100" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 150 mg is a hard capsule, size 2, with a white cap and a white body, with "150" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 200 mg is a hard capsule, size 1, with a pinkish-orange cap and a pinkish-orange body, with "200" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 225 mg is a hard capsule, size 1, with a pinkish-orange cap and a white body, with "225" printed in black ink on the body. The capsules contain a white to off-white powder.

Pregamid 300 mg is a hard capsule, size 0, with a brownish-red cap and a white body, with "300" printed in black ink on the body. The capsules contain a white to off-white powder.

The capsules are packed in PVC/Aluminium blisters.

Excipients of the capsule fill are maize starch, lactose monohydrate and talc. Excipients of the capsule shells are gelatin, titanium dioxide, and red and yellow iron oxide.

The capsule contents of the 25 mg and 50 mg strengths are dose proportional and the capsule contents of the 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strengths are dose proportional.

II.2 Drug Substance

The drug substance pregabalin is an established active substance, however not described in the European Pharmacopoeia (Ph.Eur.) or in another pharmacopoeia. The drug substance is sparingly soluble in water and exhibits pH dependent solubility with high solubility at very low and very high pH and low solubility at pH values in between. The drug substance exhibits polymorphism. Form I is produced. The drug substance has one chiral carbon atom. The drug substance corresponds to the S-enantiomer. A test for the R-isomer is included in the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of five steps. The proposed starting material is sufficiently justified. The solvents and intermediates have been specified. No metal catalysts are used.

The active substance was sufficiently characterized with regard to chemical structure and polymorphic form. Sufficient information is provided on impurities.

Quality control of drug substance

The drug substance specification of the MAH is in accordance with that of the ASMF holder. A suitable justification was provided for the absence of a test for the particle size distribution of the drug substance. In-house methods were adequately described and validated. The MAH provided batch analysis data on ten commercial-scale batches demonstrating compliance with the drug substance specification.

Stability of drug substance

Stability data on the active substance have been provided for four commercial-scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (six months). No significant changes were observed in the currently available stability data. The proposed re-test period of 24 months is justified. No specific storage conditions are needed.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The same excipients as in the reference product were selected and development focussed on the optimisation of the amounts of the individual excipients.

A full Biopharmaceutics Classification System (BCS)-based biowaiver has been requested. Dissolution of two batches of each strength of the test product was compared to that of two batches of the respective strength of the reference product in at pH 1.2, pH 4.5 and pH 6.8. In most cases, dissolution exceeded 85% in 15 minutes. In the other cases, f_2 values were calculated which

exceeded 50, thus showing similarity. Overall, the requirements for a BCS-based biowaiver have been met. Pregabalin is not regarded as a narrow therapeutic index drug.

A supportive bioequivalence study was carried out with the 300 mg strength. Comparative dissolution profiles of the biobatches obtained at pH 1.2, pH 4.5, and pH 6.8 are provided. Dissolution was similar in all media (>85% released in 15 min). The provided dissolution data support bioequivalence.

Manufacturing process

The manufacturing process consists of dry blending and capsule filling. It is considered to be a standard process. The manufacturing process was described in sufficient detail.

The manufacturing process was adequately validated with three common blend batches of the smallest commercial scale for the 25 mg and 50 mg strengths and three common blend batches of three different sizes at the lower commercial scale for the 75 mg to 300 mg strengths resulting in three batches per strength. All predefined acceptance criteria were met. All batches complied with the release specification.

Control of excipients

All excipients of the capsule fill are tested according to the Ph.Eur. An acceptable in house specification is presented for the capsule shells.

Quality control of drug product

The product specification includes tests for description, identification by HPLC and a colour reaction, assay, average mass of contents, uniformity of dosage units by mass variation, dissolution, related substances, and microbiological limits. The latter is not routinely performed. The release and shelf life specifications are identical. The drug product specification was adequately justified and is acceptable. Analytical methods were adequately described and validated. The methods for assay and related substances are considered to be stability indicating.

Batch analysis data showing compliance with the proposed release specification were provided for three batches of the smallest commercial batch size of each strength.

Stability of drug product

Stability data on the product was provided for three batches of the smallest commercial batch size of each strength stored at 25°C/60% RH (24 months), and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in PVC/aluminum blisters.

No significant changes are observed in the currently available stability data. An increasing trend is seen for impurities in the 25 mg and 75 mg strengths at accelerated conditions. This trend is not seen in the higher strengths at accelerated conditions and in all strengths at long term conditions. No trends are seen for the other parameters at both storage conditions. The photostability data demonstrate that the drug product is not sensitive to light.

Based on the provided stability data, a shelf life of 36 months is justified. No specific storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is of animal origin. Compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been confirmed. Magnesium stearate is of vegetable origin.

The suppliers of the gelatin for the hard capsules hold TSE Certificates of Suitability issued by the EDQM.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Pregamid hard capsules 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 Pregamid 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 member states 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 member states agreed that no further clinical studies are required.

For this generic application, a Biopharmaceutics Classification System (BCS)-based biowaiver was requested for all strengths. In addition a supportive bioequivalence study was submitted, which is discussed below.

IV.2 Pharmacokinetics

BCS-based biowaiver

The application for all concerned 25, 50, 75, 100, 150, 200, 225, 300 mg tablet strengths is based on a BCS-based biowaiver. The submitted bioequivalence study with the 300 mg tablet served as supportive data only and a biowaiver of strengths is not applied for. For this biowaiver to be granted, dose-proportionality among the different strengths is not required and instead a similarity in a qualitative and quantitative composition versus the reference product is a prerequisite.

All the strengths of Pregamid met all requirements for a BCS-based biowaiver as stated in the Guideline on the investigation of bioequivalence:

- the drug substance has been proven to exhibit high solubility and complete absorption (BCS-class 1)
- the active substance in test and reference products are identical
- drug substance does not belong to the group of 'narrow therapeutic index' drugs
- *in-vitro* dissolution characteristics of test and reference product are either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) at pH 1.2, 4.5 and 6.8.
- dissolution similarity has been shown between test and reference products
- the excipients of the all strengths of test products are qualitatively identical to the reference products and quantitatively very similar. None of the excipients is expected to affect bioavailability

Hence, a BCS-based biowaiver for all the different strengths including the 2 lower strengths (25 and 50 mg), can be granted.

Supportive bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Pregamid 300 mg (G.L. Pharma GmbH, Austria) is compared with the pharmacokinetic profile of the reference product Lyrica 300 mg hard capsules (Pfizer Limited, UK).

The choice of the reference product in the bioequivalence study is justified.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 20 healthy male subjects, aged 19-53 years. Each subject received a single dose (300 mg) of one of the 2 pregabalin formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16 and 24 hours after administration of the products.

The study design is acceptable to assess bioequivalence for the pregabalin formulations. Pharmacokinetic parameters can be adequately assessed with this study design, as the pregabalin t_{max} and $t_{1/2}$ was accounted for by the duration of the sampling period and sampling frequency. A bioequivalence study under fasting conditions is appropriate for an immediate release formulation.

Analytical/statistical methods

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

Results

A total of 20 healthy adult males enrolled in the study, 18 subjects completed both periods and were included in the pharmacokinetic and statistical analysis. One subject tested positive in the alcohol breath test in period 2, and one subject did not report to the facility for period 2.

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

Treatment N=18	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	60.9 $\pm$ 7.8	66.1 $\pm$ 10.4	8.5 $\pm$ 1.6	1.0 (0.5-3.0)	--
Reference	61.2 $\pm$ 8.7	66.1 $\pm$ 11.1	8.8 $\pm$ 1.3	1.0 (0.5-2.5)	--
*Ratio (90% CI)	1.00 (0.98-1.02)	1.00 (0.98-1.02)	0.95 (0.89-1.02)	--	--
CV (%)	--	--	--	--	--
AUC_{0-∞} area under the plasma concentration-time curve from time zero to infinity 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 t_{1/2} half-life CV coefficient of variation					

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Pregamid 300 mg is considered bioequivalent with Lyrica 300 mg hard capsules.

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 Pregamid.

- 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	• Pregnant and lactating women

The member states 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. A BCS-based has been granted for all strengths of Pregamid. A supportive bioequivalence study showed 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

The package leaflet (PL) has not been evaluated via a user consultation study. Instead the MAH has submitted a bridging report. With regard to the content of the PL reference is made to the leaflet of Lyrica, which has been successfully user tested. The readability of the company's layout has been established in previous user tests. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

A BCS-based biowaiver has been granted for all Pregamid strengths. A supportive bioequivalence study with the 300 mg capsule confirms bioequivalence.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pregamid with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 May 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached