CBG MEB

Public Assessment Report

Scientific discussion

Pregabaline Hetero 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules

(pregabalin)

NL/H/3278/001-008/DC

Date: 13 December 2016

This module reflects the scientific discussion for the approval of Pregabaline Hetero hard capsules. The procedure was finalised on 4 August 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
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 Pregabaline Hetero 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules from Hetero Europe S.L.

The product is indicated for:

- Epilepsy
  Pregabaline Hetero is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

- Generalised Anxiety Disorder
  Pregabaline Hetero 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 decentralised 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 has been registered in the EEA by Pfizer Ltd since 6 July 2004 via a centralised procedure (EU/1/04/279).

The concerned member states (CMS) involved in this procedure were the Czech Republic (only 75 mg and 150 mg strength), Germany, Spain (only 25 mg, 75 mg, 150 mg and 300 mg strength) and Iceland.

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

II. QUALITY ASPECTS

II.1 Introduction

Pregabaline Hetero is a hard capsule filled with white to off- white powder. Each capsule contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin:

Pregabaline Hetero 25 mg is a white cap/white body size ‘4’ hard gelatin capsule imprinted with ‘138’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 50 mg is a white cap/white body size ‘4’ hard gelatin capsules imprinted with ‘139’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 75 mg is an orange cap/white body size ‘4’ hard gelatin capsules imprinted with ‘140’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 100 mg is an orange cap/orange body size ‘3’ hard gelatin capsules imprinted with ‘141’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 150 mg is a white cap/white body size ‘2’ hard gelatin capsules imprinted with ‘142’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero is a 200 mg orange cap/orange body size ‘1’ hard gelatin capsules imprinted with ‘143’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 225 mg is a light orange cap/white body size ‘1’ hard gelatin capsules imprinted with ‘144’ on cap and ‘J’ on body with black ink.

Pregabaline Hetero 300 mg is an orange cap/white body size '0' hard gelatin capsules imprinted with '145' on cap and 'J' on body with black ink.

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

The excipients are:
Capsule content – mannitol, maize starch and talc
Capsule shell – gelatine, titanium dioxide (E171) and iron oxide red (E172) (only for 75 mg, 100 mg, 200 mg, 225 mg, 300 mg)
Printing Ink – shellac, black iron oxide (E172), propylene glycol and potassium hydroxide

The capsule content of the 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg strengths is dose proportional. The capsule content of the 25 mg strength is not dose proportional to the other strengths as the relative amount of mannitol is larger.

II.2 Drug Substance

The drug substance is pregabalin, an established active substance 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 has one chiral carbon atom so theoretically, there are two isomers (enantiomers) possible. 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
A five stage manufacturing process is used. Tests for solvents are included in the drug substance specification. The active substance was sufficiently characterised with regard to chemical structure and polymorphic form. Sufficient information is provided on impurities.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. 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 ASM provided batch analysis data on three commercial scale batches and the MAH provided batch analysis data on two commercial scale batches demonstrating compliance with the proposed drug substance specification.

Stability of drug substance
Stability data on the active substance have been provided for three commercial scale batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). No significant changes were observed in the currently available stability data. The proposed retest period of 36 months is justified. No specific storage conditions are needed.

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 choice of excipients is justified and their functions explained. The development focussed on the optimisation of the amounts of the individual excipients. The capsule content of the 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg are dose proportional and manufactured using the same manufacturing process. The capsule content

of the 25 mg strength is not dose proportional to the other strengths as the relative amount of mannitol is larger. The pharmaceutical development of the product has been adequately performed.

Bioequivalence studies were carried out with the 25 mg and the 300 mg strength. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition. For the other strengths a biowaiver is requested. The biowaiver is based on the bioequivalence study with the 300 mg product. Comparative dissolution profiles (>85% in 15 min) of the bio-batches at pH 1.2, 4.5, and 6.8 have been demonstrated.

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 batches of pilot scale for all strengths. 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 finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, average weight of filled capsule, average net fill content, water content, uniformity of dosage units, dissolution, related compounds, assay, and microbial limit tests. The release and shelf life specifications are identical, except for one of the related substances (total impurities). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three commercial scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product was provided for three production batches of each strength stored at 25°C/60% RH (24 months), and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. Tablets were stored in the proposed packaging. No clear changes are observed in the currently available stability data. The proposed shelf life of 36 months can be granted. No specific storage restrictions are considered necessary. The photostability data demonstrate that the drug product is not sensitive to light.

Results of an in-use stability study shows that the product remains stable in opened HDPE bottles up to 3 months. Hence the proposed in-use period of 3 months can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Certificates of suitability issued by the EDQM have been provided for the gelatin 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 member states consider that Pregabaline Hetero 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 Pregabaline Hetero 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 hard capsules 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, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Initially the MAH submitted one bioequivalence study with the 300 mg formulation. A biowaiver for the lower strengths was sufficiently justified, except for the 25 mg formulation. Pregabaline Hetero 25 mg differs qualitatively from the other strengths. The MAH therefore provided the results of a second study, with the 25 mg formulation. Both studies were conducted under fasted conditions as this is the most sensitive condition to detect difference between the test and reference products.

The following studies were submitted:

- a bioequivalence study in which the pharmacokinetic profile of the test product Pregabaline Hetero 300 mg hard capsules (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Lyrica 300 mg hard capsules (Pfizer Ltd, UK).
- a bioequivalence study in which the test product Pregabaline Hetero 25 mg hard capsules (Hetero Europe S.L., Spain) is compared to reference product Lyrica 25 mg hard capsules (Pfizer Ltd, UK).

The choice of the reference products in the bioequivalence studies has been justified. The formula and preparation of the bioequivalence batches are identical to the formula proposed for marketing.

Biowaiver
A biowaiver was granted for the additional 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths. The different capsule strengths are manufactured by the same manufacturing site using the same manufacturing process, and contain the same excipients. The qualitative composition of the 50 mg to 300 mg strengths is dose proportional. Similarity between the 300 mg biobatch and additional 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg tablets has been demonstrated at all three pH conditions (>85% in 15 min). The results of the bioequivalence study with 300 mg can therefore be extrapolated to the 50-225 mg capsule.

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

Study I - 300 mg hard capsules

A balanced, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 18-43 years. Each subject received a single dose (300 mg) of one of the 2 pregabalin formulations. The tablet was orally administered with 240 mL of drinking water. The subjects fasted from food until 4 hours after dosing. Drinking water restriction was maintained one hour before dosing to one hour after dosing and all the subjects were refrained from taking water during this period. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose (60 minutes) and 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2,5, 3, 4, 5, 6, 8, 12, 16, 24 and 36 hours after administration of the products.

The overall study design is acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

Results

All 28 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 300 mg pregabalin under fasted conditions.

Treatment N=28	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	63235 ± 8220	64872 ± 8656	8037 ± 1772	1.25 (0.50-3.00)
Reference	64143 ± 7630	65549 ± 8072	7827 ± 1857	1.25 (0.67-3.00)
***Ratio (90% CI)**	0.98 (0.97-1.00)	0.99 (0.97-1.01)	1.03 (0.97-1.08)	--
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **$AUC_{0-\infty}$** area under the plasma concentration-time curve from time zero to infinity **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Study II - 25 mg hard capsules

A balanced, open label, randomised, two-treatment, two-period, two-sequence, single dose, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male subjects, aged 18-42 years. Each subject received a single dose (25 mg) of one of the 2 pregabalin formulations. The tablet was orally administered with 240 mL of drinking water. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose (60 minutes) and 0.167, 0.333, 0.5, 0.667, 0.833, 1, 1.25, 1.5, 1.75, 2, 2,5, 3, 4, 5, 6, 8, 12, 16, 24 and 36 hours after administration of the products.

The overall study design is acceptable considering the absorption rate and half-lives. Also the washout period is acceptable.

Results

28 subjects were eligible for pharmacokinetic analysis. Two subjects were withdrawn from the study due to a positive breathing test for alcohol consumption on the day of check-in.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 25 mg pregabalin under fasted conditions.

Treatment N=28	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	5359 ± 797	827 ± 183	0.68 (0.33-2.0)

Reference	5441 ± 853	837 ± 149	0.83 (0.50-1.75)
***Ratio (90% CI)**	0.99 (0.96-1.01)	0.98 (0.92-1.04)	--
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			

**ln-transformed values*

Conclusion on bioequivalence studies

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80–1.25. Bioequivalence between the Pregabaline Hetero 300 mg hard capsules and the reference Lyrica 300 mg hard capsules has been proven after single dose under fasting conditions. Based on the second submitted bioequivalence study, Pregabaline Hetero 25 mg hard capsules is considered bioequivalent with Lyrica 25 mg hard capsules under fasting.

The MEB has been assured that the bioequivalence studies have 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 Pregabalin Hetero.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Discontinuation events • Weight gain • Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury • Vision-related events • Congestive heart failure • Peripheral oedema and oedema-related events • Drug interactions (lorazepam, ethanol and CNS depressants • Euphoria • Hypersensitivity and allergic reactions • 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. The MAH demonstrated through 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Lyrica. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pregabaline Hetero 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 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.

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 Pregabaline Hetero with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 August 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
Minor change to an approved test procedure	NL/H/3278/ 1-8/IA/002	IA	29-8-2016	28-9-2016	Approval	No
To include an additional batch size	NL/H/3,5/IA /001	IA	29-8-2016	28-9-2016	Approval	No