CBG MEB

Public Assessment Report

Scientific discussion

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

(pregabalin)

NL/H/3655/001-008/DC

Date: 24 March 2017

This module reflects the scientific discussion for the approval of Linefor hard capsules. The procedure was finalised on 5 October 2016. 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
NTID	Narrow Therapeutic Index Drug
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 Linefor 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules from Pharmaceutical Works Polpharma S.A.

Pregabalin is indicated for:

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

- Generalised Anxiety Disorder
  Pregabaline Torrent 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 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 through a centralised procedure (EU/1/04/279).

The concerned member states (CMS) involved in this procedure were Bulgaria (50 mg, 75 mg, 150 mg), Czech Republic (50 mg, 75 mg, 150 mg and 300 mg) and Poland (all strengths).

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

II. QUALITY ASPECTS

II.1 Introduction

Linefor 25 mg is a white hard gelatin capsule overprinted with “25” on the body containing a white or almost white powder or slightly compacted agglomerates.
Linefor 50 mg is a white hard gelatin capsule overprinted with “50” on the body containing a white or almost white powder or slightly compacted agglomerates.
Linefor 75 mg is a hard gelatin capsule, with white body overprinted “75” and red-brown cap containing a white or almost white powder or slightly compacted agglomerates.
Linefor 100 mg is a hard red-brown hard gelatin capsules overprinted with “100” on the body containing a white or almost white powder or slightly compacted agglomerates.
Linefor 150 mg is a white hard gelatin capsule overprinted “150” on the body containing a white or almost white powder or slightly compacted agglomerates.
Linefor 200 mg is a light brown hard gelatin capsule overprinted with “200” on the body containing a white or almost white powder or slightly compacted agglomerates. The capsule size is No
Linefor 225 mg is a hard gelatin capsule with white body overprinted “225” and light brown cap containing a white or almost white powder or slightly compacted agglomerates.
Linefor 300 mg is a hard gelatin capsule with white body overprinted “300” and red-brown cap containing a white or almost white powder or slightly compacted agglomerates.

The capsules are packed in Aluminium//transparent PVC/PVDC blisters.

The excipients are:

Capsule content - lactose monohydrate, maize starch, talc

Capsule shell -
25 mg, 50 mg, 150 mg:
Titanium dioxide (E171)
Gelatin

75 mg, 100 mg, 300 mg:
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)
Gelatin

200 mg, 225 mg:
Titanium dioxide (E171)
Red iron oxide (E172)
Yellow iron oxide (E172)
Black iron oxide (E172)
Gelatin

Printing Ink:
Shellac glaze 45% in ethanol
Black iron oxide (E172)
Propylene glycol
Ammonium hydroxide

The capsule contents of the 50, 75, 100, 150, 200, 225, 300 mg strengths are dose proportional. A separate, non-proportional powder blend is used for the 25 mg strength.

II.2 Drug Substance

The active substance is pregabalin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is sparingly soluble in water. Pregabalin contains one chiral centre in its structure and exists as S(+) and R(-) isomers. The drug substance manufacturers produce the S-isomer. Polymorph form I is manufactured.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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
Manufacturer-I
The manufacturing process consists of two parts. No class I solvents are used in the manufacture. The active substance has been adequately characterised and acceptable specifications for the starting material, solvents and reagents used in the manufacturing process have been adopted.

Manufacturer-II
The manufacturing process consists of four synthesis steps. No class I solvents and are used. The active substance has been adequately characterised and acceptable specifications for the starting material, solvents and reagents used in the manufacturing process have been adopted.

Quality control of drug substance
The drug substance specification complies with the Ph. Eur., with additional tests and limits. The MAH's specification of the drug substance is in line with the specification for the drug substance of the ASMF holders. The drug substance specification is acceptable.

Batch analysis results (certificates of analysis) have been provided for a total of 5 batches of pregabalin originating from both manufacturers.

Stability of drug substance
Manufacturer-I
Stability data on the active substance have been provided for 6 commercial size batches stored at 25ºC ± 2ºC/60% ± 5%RH (56 or 36 months) or 40ºC ± 2ºC/75% ± 5%RH (6 months). Stability data have been provided using adequate stability indicating methods. The claimed re-test period of 60 months is acceptable.

Manufacturer-II
Long-term stability data at 25ºC/60% RH for up to 24 months and accelerated stability data at 40°C/75% RH for up to 6 month are provided of four production scale batches. Based on the stability results the proposed re-test period of 24 months is acceptable.

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 formulation development was based on the innovator, which is available in the same product strengths.
Initial trials involved the development of laboratory scale batches of all capsule strengths starting from common granulate, however, a change of formulation for 25 mg strength was necessary (increase of capsule fill weight). The other strengths are dose proportional and they are manufactured from a common blend by the same manufacturing process. Particle size of active substance has no influence on dissolution profiles and capsules' parameters.
Dissolution profiles of the Linefor products and Lyrica reference products were considered comparable as 85% of pregabalin was dissolved after 15 minutes in all cases.
The dissolution profiles of the biobatch and the other Linefor strengths are similar in all media investigated as more than 85% of the drug is dissolved within 15 minutes for all capsules in all media.
A bioequivalence study was performed with the 300 mg strength, and a biowaiver of strength has been granted for the other strengths, except for the 25 mg for which a Biopharmaceutics Classification System (BCS)-based biowaiver was granted (see section IV 'Clinical aspects).
Formulation development has been adequately performed.

Manufacturing process
The manufacturing processes consists of sifting, mixing, encapsulation and packing. The process is sufficiently detailed described and is considered to be a standard process. No process validation data has been provided. Process validation will be performed on the first three consecutive commercial scale batches.

Control of excipients
With the exception of hard gelatin capsule shells and the printing ink, all excipients are controlled conform Ph. Eur. The specifications and compositions of the printing ink and capsules are acceptable as the used colorants are EU approved and ingredients comply with relevant Ph. Eur. monographs.

Quality control of drug product
The product specification includes tests for appearance, appearance of content, capsules average weight, uniformity of dosage units (mass variation), identification of pregabalin, identification of titanium dioxide, identification of iron oxide, water content in capsule filling, related substances, assay, dissolution and microbial examination. The release and shelf-life requirements/limits are identical and generally acceptable. The analytical methods have been adequately described and validated.
Batch analysis data are presented on two production scale batches for each strength and the biobatch. All results comply with the specification.

Stability of drug product
Stability data on the product has been provided on two pilot scale batches of each strength and the biobatch stored at 30ºC ± 2ºC/60% ± 5%RH (24 months) and 40ºC ± 2ºC/75% ± 5%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/PVC/PVDC blisters. In addition, forced degradation, photostability and thermal

cycling stability studies have been provided. The proposed shelf life of 36 months for PVC/PVDC-Alu blister pack and the proposed storage conditions “This medicinal product does not require any special storage conditions” are acceptable.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The only excipient derived from TSE-relevant animal species used in the manufacture of pregabalin capsules is gelatin. TSE CEPs have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Linefor hard capsules have 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 Linefor 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, the MAH has submitted:

- a bioequivalence study with Linefor 300 mg
- a request for a BCS-based biowaiver for the 25 mg strength
- a request for a biowaiver of strength for the 50 mg, 75 mg, 100 mg, 150 mg, 200 mg and 225 mg strengths.

IV.2 Pharmacokinetics

IV.2.1 Bioequivalence study

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Linefor 300 mg (Pharmaceutical Works Polpharma S.A, Poland) is compared with the pharmacokinetic profile of the reference product Lyrica 300 mg hard capsules (Pfizer Ltd, UK).

The choice of the reference products in the bioequivalence studies is accepted, as Lyrica has been registered through a centralised procedure. 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 22 healthy subjects (14 males/8 females), age 34.4 years. Each subject received a single dose (300 mg) of one of the 2 pregabalin formulations. The capsule was orally administered with 200 ml water. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.0, 1.25, 1.50, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0 and 24.0 hours after administration of the products.

The design of the bioequivalence study is acceptable. Pregabalin may be taken regardless of food. Thus, a study under fasting conditions is appropriate as this is the most sensitive condition to detect difference between the test and reference products. The wash-out period of 7 days is sufficient to avoid the carry-over effect considering the half-life of pregabalin is 6 hours. Furthermore, the sampling period was long enough and the sampling scheme was adequate to estimate the pharmacokinetic parameters.

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
Twenty-one subjects completed both study periods and their data were used for the statistical analysis. One subject was withdrawn after study period 1 due to an adverse event (moderate somnolence).

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

Treatment N=21	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	53.9 ± 9.2	57.9±10.3	7.8±1.7	1 (0.5-4.0)	--
Reference	53.6 ± 9.6	57.5±10.6	8.0±1.7	1 (0.5-6.0)	--
***Ratio (90% CI)**	1.01 (0.98-1.03)	1.01 (0.98-1.04)	0.98 (0.92-1.05)	--	--

$AUC_{0-\infty}$ 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

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC0-t, AUC0-∞ and Cmax are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Linefor 300 mg is considered bioequivalent with Lyrica 300 mg hard capsules.

Safety
Fourteen subjects experienced a total of thirty mild and two moderate adverse event over the course of the study. In total, there were fifteen mild adverse events considered related to the oral

administration of Linefor and seventeen adverse events, i.e. fifteen mild and two moderate adverse events, considered related to the oral administration of Lyrica. No serious adverse event occurred.

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.2.2 Biowaiver of strengths

The 50, 75, 100, 150, 200, 225 and 300 mg strengths are dose-proportional, are manufactured by the same manufacturing site using the same manufacturing process, and contain the same excipients. Dissolution tests were performed using basket apparatus at 75 rpm, while a rotation speed of 100 rpm is recommended by the guideline in case of a basket apparatus. The use of a lower rotation speed is not considered an issue since the dissolution at 75 rpm across pH range of 1.2-7.4 was already very rapid (>85% in 15 min).
The biowaiver for the 50, 75, 100, 150 and 225 mg capsules is considered acceptable.

IV.2.3 BCS-based biowaiver for 25 mg strength

The 25 mg and 50 mg capsules are of same weight, and therefore the criteria of dose-proportionality for biowaiver from 300 mg study is not met. Thus, a Biopharmaceutics Classification System (BCS)-based biowaiver is requested for the 25 mg strength.

The BCS is a scientific framework to classify drugs on the basis of their aqueous solubility, permeability and dissolution. Drug substances can be classified in 3 classes according to the BCS:
- Class 1: High Solubility – High Permeability
- Class 2: Low Solubility – High Permeability
- Class 3: High Solubility – Low Permeability

The BCS-based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as an innovator product. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH also showed that the composition of the generic and innovator product is similar.

BCS classification and eligibility of the drug substance
Narrow Therapeutic Index
Criteria to categorise a drug as a narrow therapeutic index drug (NTID) are not defined in EU guidelines. However taking into consideration other, non-EU guidelines and the reference product SmPC, it is concluded that:
1) pregabalin does not require plasma level monitoring,
2) the difference between the lowest (150 mg daily) and the highest (600 mg daily) recommended daily dose is relatively high
3) there are no data on pregabalin being classified as NTID by any regulatory agency or in literature.

Pregabalin is therefore not considered a NTID.

Absorption
Pregabalin human absorption is reported to be ≥90%. The human oral bioavailability was based on percentage of dose excreted unchanged in the urine (averaged 91.1% in one single dose study; 90% in the mass balance study). Therefore pregabalin can be classified as a substance of complete absorption according to EU BCS classification.

Solubility
The lowest observed solubility of a drug substance pregabalin at 37°C was about 30.70 mg/mL in pH 7.4. Pregabalin is an amino acid therefore its lowest aqueous solubility occurs at its isoelectric point (≈ pH 7.4). It has two ionizable groups therefore the pKa1 of the carboxylic acid is about 4.2 and the pKa2 of amino moiety is about 10.6. Considering the highest single dose of pregabalin hard capsules is 300 mg daily, pregabalin can be classified as highly soluble according to EU BCS classification.

BCS classification and eligibility of the drug product

Composition

The qualitative composition of Linefor compared to Lyrica shows that the same excipients are used in both formulations. The excipients are not known to have influence on bioavailability and are used in typical amounts. Lactose monohydrate has no significant influence on drug permeability.

Dissolution

Dissolution of Lyrica 25 mg capsules and Linefor 25 mg capsules are very rapid (>85% in 15 min) at pH 1.2, 4.5, 6.8 and 7.4, and therefore considered as similar.

Conclusion

The MAH has sufficiently substantiated with data from the literature and with own in-house tests that pregabalin can be considered a BCS class I drug. In addition, the claim that pregabalin is not a drug with a narrow therapeutic index is supported. The qualitative composition of Lyrica and Linefor 25 mg strength is identical. The quantitative differences in the inactive excipients are not expected to result in differences in the efficacy or safety between the two products.
Dissolution tests were performed using basket apparatus at 75 rpm, while a rotation speed of 100 rpm is recommended by the guideline in case of a basket apparatus. However, as indicated above under 'IV.2.2 Biowaiver of strengths', this is not considered an issue since the dissolution at 75 rpm across pH range of 1.2-7.4 was already very rapid (>85% in 15 min). The BCS-based biowaiver for the 25 mg capsules is considered acceptable.

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 Linefor.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Weight gain - Oedema - Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury - Withdrawal symptoms - Interactions with other medicines - Euphoria - Hypersensitivity reactions, including allergic reactions - Congestive heart failure - Vision-related events - Abuse, misuse and drug dependence
Important potential risks	- Cancer of the blood vessels - Thoughts of self-harming or suicide - Off-label use in children
Missing information	- Pregnancy and breastfeeding

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 a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. A BCS-based biowaiver was granted for the 25 mg capsules. Dissolution is rapid and similar, and a difference in bioavailability is not expected. 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. The MAH submitted a bridging report. Reference is made to the Lyrica PL; the content of the two leaflets is very similar. Regarding layout and style the leaflet for Linefor is very similar to a successfully user tested PL for Eplerenone 25 mg, 50 mg film-coated tablets. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Linefor 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, based on a bioequivalence study for the 300 mg strength and a biowaiver for the remaining strengths, except the 25 mg strength. For this strength the MAH submitted an argumentation for not performing a bioequivalence study. The MAH applied for a BCS (class I)-based biowaiver, based on criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98). The BCS-based biowaiver is fully justified and accepted.

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 Linefor with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 October 2016.

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