LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Pregabalin 1A Farma (pregabalin)

SE/H/1711/01-08/E/01

This module reflects the scientific discussion for the approval of Pregabalin 1A Farma. The Public Assessment Report was written in August 2016 by the previous RMS DK after initial procedure DK/H/2596/001-008/MR. RMS transfer from DK to SE was completed 2017-12-19. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Pregabalin 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules, from Pharmathen S.A.

The product is indicated for: Neuropathic pain, epilepsy and Generalised Anxiety Disorder.
A comprehensive description of the indications and posology is given in the SmPC.

The active substance, pregabalin, is a gamma-aminobutyric acid analogue ((S)-3-(aminomethyl)-5-methylhexanoic acid). Pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system.

This mutual recognition procedure concerns a generic application claiming essential similarity with the reference product Lyrica hard capsules, which has been registered in Europe by Pfizer ApS since 2004.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Each hard capsule contains 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg or 300 mg of pregabalin, respectively.

The 25 mg capsules are white cap and body, imprinted with "25" on the body with black ink. The length of the capsule cap is 6.97mm-7.97mm and the length of the capsule body is 11.8mm-12.84mm.

The 50 mg capsules are white cap and body, imprinted with "50" on the body with black ink. The length of the capsule cap is 7.73mm-8.73mm and the length of the capsule body is 12.98mm-13.98mm.

The 75 mg capsules are swedish orange cap and white body, imprinted with "75" on the body with black ink. The length of the capsule cap is 7.73mm-8.73mm and the length of the capsule body is 12.98mm-13.98mm.

The 100 mg capsules are swedish orange cap and body, imprinted with "100" on the body with black ink. The length of the capsule cap is 8.67mm-9.67mm and the length of the capsule body is 14.84mm-15.84mm.

The 150 mg capsules are white cap and body, imprinted with "150" on the body with black ink. The length of the capsule cap is 9.3mm-10.51mm and the length of the capsule body is 16.1mm-17.22mm.

The 200 mg capsules are red cap and body, imprinted with "200" on the body with black ink. The length of the capsule cap is 10.68mm-11.68mm and the length of the capsule body is 18.1mm-19.22mm.

The 225 mg elongated capsules are red cap and white body, imprinted with "225" on the body with black ink. The length of the capsule cap is 11.53mm-12.45mm and the length of the capsule body is 20.3mm-21.44mm.

The 300 mg capsules are swedish orange cap and white body, imprinted with "300" on the body with black ink. The length of the capsule cap is 11.40mm-12.20mm and the length of the capsule body is 19.80mm-20.70mm.

The capsules are packed in PVC/Aluminium foil blisters in a cardboard box in pack sizes of 7 (50 mg and 100 mg only), 14 and 56 hard capsules. However, not all pack sizes may be marketed.

The capsule content is: Pregelatinized starch; mannitol and talc.
The capsule shell is composed of: Gelatin; titanium dioxide (E171); red iron oxide (E172) (75 mg, 100 mg and 300 mg only); red iron oxide (E172) and yellow iron oxide (E172) (200 mg and 225 mg only).

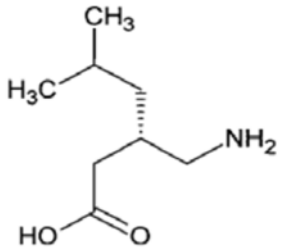
The printing ink contains: Shellac; black iron oxide (E172) and propylene glycol (E1520).

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, pregabalin, is not described in the European Pharmacopoeia. It is a white or almost white crystalline powder. It is soluble in 1M sodium hydroxide and sparingly soluble in water. It is optically active.

Structural formula:



Molecular formula: $C_8H_{17}NO_2$
Molecular weight: 159.23

The documentation on the active substance is provided as an ASMF. The proposed starting materials of the synthesis is acceptable after re-definition of the starting materials was performed.

The active substance is not described in any pharmacopoeia and the specifications have been set based on in-house requirements. The proposed specifications are acceptable.

Based on the stability data presented, an appropriate re-test period has been set.

The finished product manufacturer’s specification on the drug substance is in line with the ASM’s specification and is found acceptable.

II.3 Medicinal Product

The finished product is conventional hard capsules to be marketed in PVC/alu blisters. The strengths applied for are 25, 50, 75, 100, 150, 200, 225 and 300 mg. All strengths are dose proportional.

The development of the product has been adequately described, the choice of excipients is justified and their functions explained.

Satisfactory validation of the manufacturing process has been carried out on 3 pilot scale batches of each strength. A process validation scheme is provided in the dossier for further process evaluation on production scale batches.

The finished product specifications cover appropriate parameters for this dosage form. The proposed limit for total impurities at shelf-life is considered acceptable. Satisfactory validations of the analytical methods have been presented. Batch analysis results presented show that the finished products meet the specifications proposed.

Stability data are provided for 3 pilot scale batches of the strengths 25, 200 and 300 mg packed in PVC-alu blisters and HDPE bottles under long term, intermediate and accelerated conditions. The proposed shelf-life of 36 months with no special precautions for storage is supported by the data. In-use stability studies have been carried out on the lowest (25 mg) and highest (300 mg) strengths and the finished product has been shown to be stable under the intended use.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of pregabalin are well known. As pregabalin is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers several publications up to year 2013. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Pregabalin “Pharmathen” 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pregabalin is a well-known active substance with established efficacy and tolerability. As pregabalin is a widely used, well-known active substance, the MAH has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers several publications up to year 2013. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application the MAH has submitted as report one bioequivalence study with Lyrica 300 mg hard capsules, Pfizer, from the Greek market as the reference product and Pregabalin "Pharmathen" 300 mg hard capsules as the test product.

Biowaiver
The bioequivalence study was conducted using the highest strength 300 mg. The additional strengths applied for comply with the criteria cf. Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr*) section 4.1.6 in order to accept biowaiver. Pregabalin has shown linearity over dose range (150-600 mg) and as recommended by the guideline, the bioequivalence study was conducted using the highest strength (300 mg). Similar dissolution profiles are demonstrated between the biobatch and additional strengths in different media.

Bioequivalence study
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 8 days between the two administrations. 300 mg was administered in each period.

28 healthy subjects participated in the study. 20 subjects completed the study.

Primary variables for the evaluation of bioequivalence were AUC_{0-t} and C_{max}.

Bioequivalence of Test Product-T vs. Reference Product-R was concluded, if the 90% confidence interval fell within the acceptance range 80.00-125.00% for ln-transformed pharmacokinetic parameters AUC_{0-t} and C_{max} for pregabalin.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), N=20

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h	$T_{1/2}$ h
Test	72017.680 ± 10261.9937	73648.441 ± 10744.1533	8940.756 ± 1337.1236	1.500 (0.750 - 3.017)	6.162 ± 0.7980
Reference	72164.704 ± 10735.0412	73706.875 ± 11220.3492	8764.800 ± 1855.7685	1.500 (0.750 - 4.000)	6.065 ± 0.7312
*Ratio (90% CI)	99.9 97.26 – 102.65	100.1 97.50 – 102.67	103.3 95.35 – 111.92	-	-
CV (%)	14.2	14.8	12.6	-	-

AUC_{0-t}	Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

ln-transformed values

90% CI for AUC_{0-t} and C_{max} are within the criteria (80.00-125.00%) to demonstrate bioequivalence between the test product and reference product under fasting conditions.

Pharmacokinetic conclusion
Based on the submitted bioequivalence study Pregabalin "Pharmathen" 300 mg hard capsules is considered bioequivalent with Lyrica 300 mg hard capsules under fasting conditions.

The results of the bioequivalence study can be extrapolated to the other strengths as relevant criteria for waiving are fulfilled in accordance with current guidance.

The RMS 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 Pregabalin "Pharmathen".

The following summary list of safety concerns with no additional pharmacovigilance measures or risk minimisation measures has been agreed:

Table 2. Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Weight gain • Peripheral oedema and oedema-related events • Hypersensitivity and allergic reactions • Dizziness, somnolence, loss of consciousness, syncope, and potential for accidental injury • Vision-related effects • Discontinuation events • Congestive heart failure • Euphoria • Drug interactions (lorazepam, ethanol and CNS depressants) • Abuse, misuse and drug dependence
Important potential risks	• Haemangiosarcoma • Suicidality • Off label use in paediatric population
Missing information	• Use in pregnancy and lactation • Withdrawal of concomitant antiepileptic medicinal products

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Pregabalin “Pharmathen” 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, 200 mg, 225 mg and 300 mg hard capsules has a proven chemical-pharmaceutical quality and is a generic form 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 MAH has presented a risk management plan summarising the safety concerns. There are no additional pharmacovigilance or risk minimisation measures.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Pregabalin “Pharmathen” with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised on 18 May 2016.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 14 July 2020.

There were no post-approval commitments made during the procedure.