Public Assessment Report

Scientific discussion

Siranalen 75 mg, 150 mg and 300 mg, hard capsules

(pregabalin)

NL/H/3234/001-003/DC

Date: 8 January 2018

This module reflects the scientific discussion for the approval of Siranalen 75 mg, 150 mg and 300 mg, hard capsules. The procedure was finalised on 25 May 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

AED	Antiepileptic drugs
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CPMP	Committee for Proprietary Medicinal Products
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MHRA/CHM	Commission on Human Medicines of the Medicines and Healthcare products Regulatory Agency
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 Siranalen 75 mg, 150 mg and 300 mg, hard capsules from Medochemie Limited.

The product is indicated for:

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

- Generalised Anxiety Disorder
  Siranalen is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

- Neuropathic pain
  Siranalen 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 was 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 75 mg, 150 mg and 300 mg hard capsules, which has been registered 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 Bulgaria (only the 75 mg strength), Cyprus, Czech Republic (only 75 mg and 150 mg strengths), Greece, Croatia, Lithuania (only 75 mg and 150 mg strengths), Latvia (only 75 mg and 150 mg strengths), Malta, Romania and the Slovak Republic.

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

The MAH obtained scientific advice from the RMS regarding the dossier requirements in March 2014.

II. QUALITY ASPECTS

II.1 Introduction

Siranalen is a hard capsule. Each capsule contains 75 mg, 150 mg or 300 mg of pregabalin:

Siranalen 75 mg hard capsules are blue-white hard gelatine capsules size “4” filled with off white powder.

Siranalen 150 mg hard capsules are white-white hard gelatine capsules size “2” filled with off white powder.

Siranalen 300 mg hard capsules are maroon-white hard gelatine capsules size “0” filled with off white powder.

The hard capsules are packed in PVC/Al blisters and PVC/PVDC/Al blisters.

The excipients are:
Capsule content - maize starch, lactose monohydrate and talc
Capsule body - gelatine and titanium dioxide (E171)
Capsule cap of 75 mg - gelatine, titanium dioxide (E171) and patent blue V (E131)
Capsule cap of 150 mg - gelatine and titanium dioxide (E171)

Capsule cap of 300 mg – gelatine, titanium dioxide (E171), erythrosine (E 127), carmoisine (E122) and brilliant blue FCF (E133)

The capsule contents of the 75 mg, 150 mg and 300 mg strengths are dose proportional.

II.2 Drug Substance

The active substance is pregabalin, an established active substance which is not described in the European Pharmacopoeia (Ph.Eur.) or in another pharmacopoeia. A draft monograph has been published in Pharmeuropa 26.3. 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 manufactured. The drug substance shows isomerism. The drug substance corresponds to the S-enantiomer. A test for the R-isomer is included in the drug substance specification.

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 Ph.Eur.

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

Quality control of drug substance
The drug substance specification has been established in-house, based on the specification of the drug substance manufacturer, with additional requirements for particle size. The specification is acceptable. Absence of a test for microbiological purity has been justified. In-house methods were adequately described and validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for 3 full scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable throughout the tested period. A retest period of 36 months without any specific storage condition is justified.

The MAH states however a retest period of 24 months without any specific storage condition. This can also be accepted.

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 and particle size.

Dissolution profiles of all strengths are compared with their respective reference product in 0.06M HCl, acetate buffer pH 4.5 and phosphate buffer pH 6.8. All profiles show dissolution of more than 85% after 15 minutes.

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. Two manufacturing sites have been stated. Process validation data on the product have been presented for one production scaled batch from each manufacturing site in accordance with the relevant European

guidelines. All predefined acceptance criteria were met. All batches complied with the release specification.

Control of excipients
Excipients of the capsule fill are tested according to the Ph.Eur. The colourants comply with relevant Commission Regulations/Directives. An acceptable in-house specification is presented for the capsule shells. 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 weight, uniformity of dosage units, disintegration, water content, identification of the active substance, dissolution rate, related compounds, assay and microbial limit tests. The latter is not routinely performed. The release and shelf life specifications are identical except for water content. This is acceptable. The dissolution requirement reflects the dissolution rate observed in pharmaceutical development, batch analysis and stability data. Analytical methods were adequately described and validated.
Batch analysis data showing compliance with the proposed release specification were provided for three batches of 75 mg, two batches of 150 mg and three batches of 300 mg of manufacturer-I and three batches of 75 mg, one batch of 150 mg and one batch of 300 mg of manufacturer-II.

Stability of drug product
Stability data on the product was provided for a variety of pilot scaled batches and one production batch of each strength. Batches are tested at 25°C/60% RH (up to 24 months), 30°C/75% RH (up to 24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. No clear changes are observed in the currently available stability data. Some batches show initially slight increase in water content, but remain stable later on. Water content levels are slightly higher in the batches stored at intermediate storage conditions. No further changes or trends are seen for the other parameters at the different storage conditions. The photostability data demonstrate that the drug product is not sensitive to light. Polymorphic form was already demonstrated to remain stable upon storage. Considering the data on production scaled batches and pilot scaled batches, a shelf life was granted of 30 months without specific storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The product contains lactose monohydrate and gelatine. Scientific data and/or certificates of suitability issued by the EDQM 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 member states consider that Siranalen 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 Siranalen 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 comprehensive justification based on the requirements described in the guideline on Investigation of Bioequivalence and scientific advice given by the MEB regarding the possibility of obtaining a biowaiver for this medicinal product.

IV.2 Pharmacokinetics

Biowaiver
A Biopharmaceutics Classification System (BCS) based biowaiver has been requested for all strengths. 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

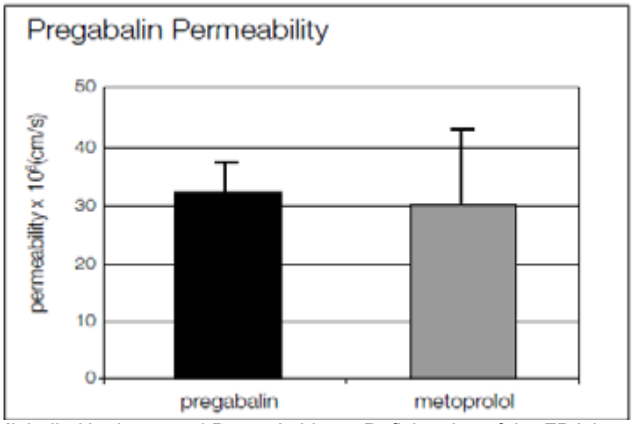
The BCS based biowaiver is applicable to Class 1 highly soluble drugs with known human absorption formulated as oral, immediate release formulations with the same pharmaceutical form as an innovator product. To fulfil the requirements for such a biowaiver, the MAH provided comprehensive documentation on solubility, permeability and dissolution of the product. The MAH also showed that the composition of the generic and innovator product is similar. In addition, a supportive discussion was provided on the therapeutic index of the product. Hence a BCS based biowaiver is applicable only for drugs which are not considered to have a narrow therapeutic index.

Solubility
A solubility test was performed in 3 pH media (0.1N HCl, Citro-phosphate buffer pH 4.5, Citro-phosphate buffer pH 6.8). For each medium a total of 6 samples were used and for each sample a total of 3 solubility runs were performed, resulting in 18 runs for each medium. The pH values of each solution initially and after addition of the required quantities of pregabalin are also determined in order to meet the solubility criteria for BCS.

The results of the solubility study show that pregabalin gets dissolved in a quantity more than the recommendation for a BCS based biowaiver, i.e. 1.2 mg/ml calculated as a ratio of the higher strength of the dosage form (300 mg) in 250 mg of media as recommended by the Committee for Proprietary Medicinal Products (CPMP) guideline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr). The solution is clear in all media, indicating that pregabalin exhibits high solubility in all 3 media. Together with provided data from literature, pregabalin can therefore be classified as a highly soluble drug product.

Permeability
Exploratory preclinical data, using an in situ rat intestinal (jejunal) perfusion model, showed that effective permeability of pregabalin was comparable to that of the highly permeable metoprolol (32x 10-6 ± 5.33 cm/s versus 30.2x 10-6 ± 12.8 cm/s), suggesting that pregabalin is a highly permeable compound.
Results for permeability of pregabalin compared to the permeability of metoprolol are presented below (Table 2).

Figure 2. Permeability of pregabalin[2].



[2]Michelle Hottinger and Bryan A. Liang, Deficiencies of the FDA in Evaluating Generic Formulations: Addressing Narrow Therapeutic Index Drugs, American Journal of Law & Medicine, 38 (2012): 667-689

Even if active transport is believed to be involved in the absorption of pregabalin, dose proportionality within the therapeutic dose range indicated no saturation of the absorption process.
In humans, pregabalin oral bioavailability is estimated to be ≥90% and is independent of dose.

Based on the above information, it is concluded that pregabalin meets the BCS criteria for a highly permeable compound.

In vitro dissolution
Dissolution profile of scale-up batches and production scale batches are compared with dissolution profile of reference products and it was observed that all strengths of pregabalin hard capsules (Siranalen and Lyrica) are showing drug release of more than 85% in 15 minutes in all media (0.06N HCl, 0.1N HCl, Citro-phosphate buffer pH 4.5, Citro-phosphate buffer pH 6.8), confirming very rapid release of the drug substance from the drug product.

Qualitative and quantitative composition
The qualitative and quantitative composition of the capsule content of the test and reference products are identical.
The excipients used in the generic formulation are well-established and are not expected to bring any additional toxicity or to affect the availability of the active from the pharmaceutical form. In addition, the amount of each excipient is within the normal range.

Therapeutic index
Based on the advice from the Commission on Human Medicines of the Medicines and Healthcare products Regulatory Agency (MHRA/CHM) from 2013 with regards to switching between formulations of antiepileptic drugs (AEDs), AEDs can be classified into 3 categories of risk. The classification is based primarily on their therapeutic index, pharmaceutical aspects (in particular solubility) and the rate and extent of drug absorption (relates to drug permeability). According to this classification pregabalin is a category 3 drug, for which no specific measures are normally required and which can be prescribed generically and without specifying a specific manufacturer's product. Pregabalin is therefore not considered to be a narrow therapeutic index drug.

Safety profile
In support, a literature review on pregabalin safety profile has been performed through which it was shown that the safety profile of pregabalin is good when it is used according to the product information. Pregabalin is excreted almost entirely unchanged in the urine and exhibits low inter-individual pharmacokinetic variability. It has a relatively wide dose range and when taken in overdose no adverse events have been recorded at doses 25x the maximum recommended dosage. It is renally cleared and has not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions.

Conclusion
The following conclusions can be drawn from the submitted argumentation:

- The solubility of pregabalin is higher than 1.2 mg/ml and can therefore be classified as a highly soluble drug.
- The permeability is comparable with metoprolol and the bioavailability in human is more than 90%. On basis of these data pregabalin can be classified as a highly permeable drug.
- All dissolution tests showed that pregabalin dissolves within 15 minutes for more than 85% from the reference products as well as from the various Siranalen strengths.
- The qualitative composition is similar to the innovator product.
- Pregabalin is not considered a drug having a narrow therapeutic index.

Based on the available data pregabalin is considered to be BCS class 1 (high solubility and high permeability). The justification for BCS-based biowaiver is accepted.

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 Siranalen.

Summary table of safety concerns as approved in RMP:

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. No bioequivalence study was performed to support the application. Instead a BCS-based biowaiver was requested and granted. 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

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; with the exception of administrative data and design/lay-out, the proposed PL is identical to the PL of reference product Lyrica.

To support the changes made to the PL compared to the originator package leaflet (administrative data, design, layout) a full Readability Test performed on the PL for Entacapone, Encapia 200 mg film-coated tablets, in 2011 has been submitted. The PL for entacapone has been successfully user tested and the results indicated that the PL is well structured and organised, easy to understand and written in a comprehensive manner. The test showed that the patients/users are able to act upon the information that it contains. Bridging is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Siranalen 75 mg, 150 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.

For this generic application, 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 Siranalen with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 May 2016.

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
NL/H/3234/IA/002/G	B.III.1.a.1: Variation to introduce a new CEP from the already approved manufacturer for the drug substance. B.I.b1.d: Deleting residual solvents drug substance specifications. B.III.2.a1: Variation for change in the MAH's drug substance specifications to comply with the available EP monograph of pregabalin.	--	21-11-2017	Approval	--
NL/H/3234/IB/003/G	A variation to update the SmPC and PL of the aforementioned products so as to be in accordance with the SmPC and PL of Lyrica. More specifically to introduce the updates recommended for Lyrica by Commission Implementation Decision C(2004)2720. The MAH also submitted the updated labelling as to introduce the safety features according to the latest QRD, as per the recommendation laid down in CMDh/345/ 2016. In addition, the labelling has been updated with regards to section 3. The excipient carrmoisine E122 has been listed in section 3 for the strength of 300 mg.	SmPC and PL	14-12-2017	Approval	--