**IPAR**

**Public Assessment Report for a**
**Medicinal Product for Human Use**

Scientific Discussion

Lamotrigine SyriMed 5mg/ml Oral Suspension
Lamotrigine
PA22697/018/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

**CONTENTS**

## I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Lamotrigine SyriMed 5mg/ml Oral Suspension, from Syri Pharma Limited on 2nd September 2022 for:

**Epilepsy**
*Adults and adolescents aged 13 years and above*

- Adjunctive or monotherapy treatment of partial seizures and generalised seizures, including tonic-clonic seizures.
- Seizures associated with Lennox-Gastaut syndrome. <Invented Name> is given as adjunctive therapy but may be the initial antiepileptic drug (AED) to start with in Lennox-Gastaut syndrome.

*Children and adolescents aged 2 to 12 years*

- Adjunctive treatment of partial seizures and generalised seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut syndrome.
- Monotherapy of typical absence seizures.

**Bipolar disorder**

*Adults aged 18 years and above*

- Prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes (see section 5.1).

Lamotrigine is not indicated for the acute treatment of manic or depressive episodes.

This application for a marketing authorisation was submitted in accordance with Article 10 (1) of Directive 2001/83/EC and is referred to as a 'generic' application.

The application was submitted as a decentralised procedure with Ireland as reference member state (RMS) and UK (NI) as concerned member states (CMS).
Lamotrigine is a prescription only medicine.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

| | |
|---|---|
| Name of the product | Lamotrigine SyriMed 5mg/ml Oral Suspension |
| Name(s) of the active substance(s) (INN) | Lamotrigine |
| Pharmacotherapeutic classification (ATC code) | N03AX09 |
| Pharmaceutical form and strength(s) | 25/5mg Oral suspension |
| Marketing Authorisation Number(s) in Ireland (PA) | PA22697/018/001 |
| Marketing Authorisation Holder | Syri Pharma Limited t/a Thame Laboratories |
| MRP/DCP No. | IE/H/1110/001/DC |
| Reference Member State | IE |
| Concerned Member State | DE XI |

## II. QUALITY ASPECTS

### II.1. Introduction

This application is for Lamotrigine SyriMed 5mg/ml Oral Solution.

### II.2 Drug substance

The active substance is Lamotrigine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

**II.3 Medicinal product**

P.1 Composition

*Composition of the medicinal product (lamotrigine 5mg/ml).*

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for Liquid preparations for oral use (oral suspension), and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

**II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects**

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Lamotrigine SyriMed 5mg/ml Oral Solution.

## III. NON-CLINICAL ASPECTS

### III.1 Introduction

This active substance is a generic formulation of Lamictal 25mg tablets on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

Pharmacodynamic, pharmacokinetic and toxicological properties of Lamotrigine are well known. As Lamotrigine is a widely used, well-known active substance, the applicant has not provided additional nonclinical studies and further studies are not required.

### III.2 Ecotoxicity/environmental risk assessment

Since Lamotrigine SyriMed 5mg/ml Oral Suspension is intended for generic substitution, an increased exposure to the environment is not anticipated. The absence of ERA studies has been justified.

### III.3 Discussion on the non-clinical aspects

Overview based on literature review is appropriate for generics, to avoid the need for repetitive tests on animals and humans. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

## IV. CLINICAL ASPECTS

*For generic applications (Article 10.1, 10.3, 10.4, 10.c),the following statements can be used:*

Lamotrigine is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Lamictal marketed by MAH.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Lamotrigine 25mg/5ml Oral Suspension of Syri Limited is compared with the pharmacokinetic profile of the reference product Lamictal (Lamotrigine) 25mg Tablets of GlaxoSmithKline. The choice of reference product is appropriate

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasting conditions. The study was conducted under standardised conditions. Sampling for drug blood levels were carried out a appropriate time intervals and for sufficient duration to characterise the pharmacokinetics of the test and reference product. Lamotrigine 25mg/5ml Oral Suspension of Syri Limited, was compared to the reference product Lamictal (Lamotrigine) 25mg Tablets of GlaxoSmithKline. The results of the study are shown in Table 1.

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

| **Treatment** | **$AUC_{0-72}$** ng*hr/ml | **$AUC_{0-\infty}$** xg/ml/h | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 12380.732 ± 3308.064 | | 414 ± 63.276 | 1.052 ± 0.765 |
| **Reference** | 12234.192 ± 3642.178 | | 399.741 ± 83.117 | 1.378 ± 1.056 |
| ***Ratio (90% CI)** | 101.8746 (99.5378, 104.2663) | | 104.3252 (98.9216, 110.024) | |
| **CV (%)** | 4.3458% | | 9.9803% | |
| **$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t. | | | | |

| | | | | |
|---|---|---|---|---|
| $AUC_{0-72h}$ canbe 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<br>**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.<br>$AUC_{0-\infty}$ does not need to be reported when$AUC_{0-72h}$ is reported instead of $AUC_{0-t}$<br>**$C_{max}$** Maximum plasma concentration<br>**$t_{max}$** Time until Cmax is reached | | | | |

**ln-transformed values*

Mean concentration time profiles for untransformed and ln transformed data are shown in the following figures.

Based on the pharmacokinetic parameters of the active substance, the reference tablet Lamictal (Lamotrigine) 25mg Tablets marketed by GlaxoSmithKline and test suspension Lamotrigine 25mg/5ml Oral Suspension are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

**IV.2 Pharmacokinetics**

Lamotrigine is rapidly and completely absorbed from the gut with no significant first-pass metabolism. Peak plasma concentrations occur approximately 2.5 hours after oral administration of lamotrigine. Time to maximum concentration is slightly delayed after food but the extent of absorption is unaffected. There is considerable inter-individual variation in steady state maximum concentrations but within an individual, concentrations rarely vary.

Distribution

Binding to plasma proteins is about 55%; it is very unlikely that displacement from plasma proteins would result in toxicity.

The volume of distribution is 0.92 to 1.22 L/kg.

Biotransformation

UDP-glucuronyl transferases have been identified as the enzymes responsible for metabolism of lamotrigine.

Lamotrigine induces its own metabolism to a modest extent depending on dose. However, there is no evidence that lamotrigine affects the pharmacokinetics of other AEDs and data suggest that interactions between lamotrigine and medicinal products metabolised by cytochrome P450 enzymes are unlikely to occur.

Elimination

The apparent plasma clearance in healthy subjects is approximately 30 mL/min. Clearance of lamotrigine is primarily metabolic with subsequent elimination of glucuronide-conjugated material in urine. Less than 10% is excreted unchanged in the urine. Only about 2% of lamotrigine-related material is excreted in faeces. Clearance and half-life are independent of dose. The apparent plasma half-life in healthy subjects is estimated to be approximately 33 hours (range 14 to 103 hours). In a study of subjects with Gilbert's Syndrome, mean apparent clearance was reduced by 32% compared with normal controls but the values are within the range for the general population.

The half-life of lamotrigine is greatly affected by concomitant medicinal products. Mean half-life is reduced to approximately 14 hours when given with glucuronidation-inducing medicinal products such as carbamazepine and phenytoin and is increased to a mean of approximately 70 hours when co-administered with valproate alone.

Linearity
The pharmacokinetics of lamotrigine are linear up to 450 mg, the highest single dose tested.

Special patient populations
*Children*
Clearance adjusted for body weight is higher in children than in adults with the highest values in children under five years. The half-life of lamotrigine is generally shorter in children than in adults with a mean value of approximately 7 hours when given with enzyme-inducing medicinal products such as carbamazepine and phenytoin and increasing to mean values of 45 to 50 hours when co-administered with valproate alone (see section 4.2).

*Infants aged 2 to 26 months*
In 143 paediatric patients aged 2 to 26 months, weighing 3 to 16 kg, clearance was reduced compared to older children with the same body weight, receiving similar oral doses per kg body weight as children older than 2 years. The mean half-life was estimated at 23 hours in infants younger than 26 months on enzyme-inducing therapy, 136 hours when co-administered with valproate and 38 hours in subjects treated without enzyme inducers/inhibitors. The inter-individual variability for oral clearance was high in the group of paediatric patients of 2 to 26 months (47%). The predicted serum concentration levels in children of 2 to 26 months were in general in the same range as those in older children, though higher $C_{max}$ levels are likely to be observed in some children with a body weight below 10 kg.

*Elderly*
Results of a population pharmacokinetic analysis including both young and elderly patients with epilepsy, enrolled in the same trials, indicated that the clearance of lamotrigine did not change to a clinically relevant extent. After single doses apparent clearance decreased by 12% from 35 mL/min at age 20 to 31 mL/min at 70 years. The decrease after 48 weeks of treatment was 10% from 41 to 37 mL/min between the young and elderly groups. In addition, pharmacokinetics of lamotrigine was studied in 12 healthy elderly subjects following a 150 mg single dose. The mean clearance in the elderly (0.39mL/min/kg) lies within the range of the mean clearance values (0.31 to 0.65mL/min/kg) obtained in nine studies with non-elderly adults after single doses of 30 to 450mg.

*Renal impairment*
Twelve volunteers with chronic renal failure, and another six individuals undergoing haemodialysis were each given a single 100mg dose of lamotrigine. Mean clearances were 0.42mL/min/kg (chronic renal failure), 0.33mL/min/kg (between haemodialysis) and 1.57mL/min/kg (during haemodialysis), compared with 0.58mL/min/kg in healthy volunteers. Mean plasma half-lives were 42.9hours (chronic renal failure), 57.4hours (between haemodialysis) and 13.0hours (during haemodialysis), compared with 26.2hours in healthy volunteers. On average, approximately 20% (range = 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated during a 4-hour haemodialysis session. For this patient population, initial doses of lamotrigine should be based on the patient's concomitant medicinal products; reduced maintenance doses may be effective for patients with significant renal functional impairment.

*Hepatic impairment*
A single dose pharmacokinetic study was performed in 24 subjects with various degrees of hepatic impairment and 12 healthy subjects as controls. The median apparent clearance of lamotrigine was 0.31, 0.24 or 0.10mL/min/kg in patients with Grade A, B, or C (Child-Pugh Classification) hepatic impairment, respectively, compared with 0.34mL/min/kg in the healthy controls. Initial, escalation and maintenance doses should generally be reduced in patients with moderate or severe hepatic impairment.

**IV.3 Pharmacodynamics**

The results of pharmacological studies suggest that lamotrigine is a use- and voltage-dependent blocker of voltage gated sodium channels. It inhibits sustained repetitive firing of neurones and inhibits release of glutamate (the neurotransmitter which plays a key role in the generation of epileptic seizures). These effects are likely to contribute to the anticonvulsant properties of lamotrigine.

In contrast, the mechanisms by which lamotrigine exerts its therapeutic action in bipolar disorder have not been established, although interaction with voltage gated sodium channels is likely to be important.

**IV.4 Clinical Efficacy**

The efficacy of lamotrigine is well characterised

**IV.5 Clinical Safety**

The safety of lamotrigine is well characterised

Risk Management Plan
The risk management plan proposed by the applicant, including the proposed pharmacovigilance activities and risk minimisation measures is considered acceptable. The approved summary of safety concerns is outlined in the table below:

| | |
|---|---|
| **Important identified risks** | • Hypersensitivity syndrome<br>• Severe skin reactions<br>• Clinical worsening and suicide risk<br>• Interaction with hormonal contraceptives<br>• Use in patients with renal impairment<br>• Hepatic impairment<br>• Rebound seizures after abrupt withdrawal<br>• Interaction with concomitant drugs<br>• Teratogenicity<br>• Use in breastfeeding<br>• Overdose |
| **Important potential risks** | • Medication error leading to over or under dosage |
| **Missing information** | • Use in children and adolescents under 18 years suffering from bipolar disorder<br>• Interaction studies for children population<br>• Development in children<br>• Effects on ability to drive and use machines |

Routine risk minimisation measures and routine pharmacovigilance activities are proposed to address the safety concerns outlined above and this is considered acceptable.

The Applicant should submit Periodic Safety Update Reports (PSUR) Periodic Safety Update Reports (PSUR) in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

**IV.6 Discussion on the clinical aspects**

Bioequivalence of Lamotrigine SyriMed 5mg/ml Oral Suspension has been demonstrated with the reference product Lamictal 25ml tablets.

**V. OVERALL CONCLUSIONS**

*For generic applications (Article 10.1, 10.3, 10.4), the following statements can be used:*
Lamotrigine SyriMed 5mg/ml Oral Suspension is a generic form of Lamictal. Lamictal is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Lamotrigine SyriMed 5mg/ml Oral Suspension demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

**VI. REVISION DATE**

01.09.2027