▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Sodium Valproate Seacross 100 mg/ml solution for injection/infusion
Sodium valproate
PA22766/012/001

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 Sodium Valproate Seacross 100 mg/ml solution for injection/infusion, from Seacross Pharma (Europe) Limited, indicated in patients with epilepsy who have been treated satisfactorily with oral doses of sodium valproate containing medicinal products and in whom further oral administration is temporarily not possible or for emergency situations in which a rapid loading dose is necessary, for the treatment of:
- generalised seizures in the form of absences, myoclonic seizures and tonic-clonic seizures,
- focal and secondary generalised seizures.

This decentralised application is a hybrid application according to Article 10(3) of Directive 2001/83/EC, concerning a proposed 'hybrid generic medicine' version of sodium valproate. In this Assessment Report, the name Sodium Valproate Seacross is used.

The European Reference Medicinal Product is Epilim (400mg powder and solvent for solution for injection/infusion) first registered in Ireland by Sanofi-Aventis Pharma Limited T/A SANOFI (PA0540/150/013) on 15th of December 1998.

With Ireland as the RMS, Seacross Pharmaceuticals Limited is applying for Marketing Authorisation for Sodium Valproate Seacross 100mg/ml solution for injection/infusion in the following CMSs; Germany, Italy, Netherlands, Portugal, Spain and France.

Subject to medical prescription which may not be renewed.

The product is also subject to conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC see section V.

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	Sodium Valproate Seacross 100 mg/ml solution for injection/infusion
Name(s) of the active substance(s) (INN)	Sodium valproate
Pharmacotherapeutic classification (ATC code)	N03AG01
Pharmaceutical form and strength(s)	solution for injection/infusion; 100 mg/ml
Marketing Authorisation Number(s) in Ireland (PA)	PA22766/012/001
Marketing Authorisation Holder	Seacross Pharma (Europe) Limited
MRP/DCP No.	**IE/H/1258/001/DC**
Reference Member State	IE
Concerned Member State	DE, ES, FR, IT, NL, PT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Sodium Valproate Seacross 100 mg/ml for solution for injection/infusion.

II.2 Drug substance

The active substance is Sodium Valproate, 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

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 guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur..

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for parenteral preparations, 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 have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 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. requirements.

P.8 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 Sodium Valproate Seacross 100 mg/ml solution for injection/infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Epilim 400mg Powder and Solvent for solution for injection/infusion 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.

The pharmacodynamic, pharmacokinetic and toxicological properties of sodium valproate are well known.

III.2 Ecotoxicity/environmental risk assessment
Since Sodium Valproate Seacross 100 mg/ml solution for injection/infusion 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.3 Discussion on the non-clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of sodium valproate are well known. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As sodium valproate is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Sodium valproate is a well-known active substance with established efficacy and tolerability.

This decentralised application is a hybrid application according to Article 10(3) of Directive 2001/83/EC, concerning a proposed 'hybrid generic medicine' version of sodium valproate. In this Assessment Report, the name Sodium Valproate Seacross is used.

The European Reference Medicinal Product is Epilim (400mg powder and solvent for solution for injection/infusion) first registered in Ireland by Sanofi-Aventis Pharma Limited T/A SANOFI (PA0540/150/013) on 15th of December 1998.

For this application, the applicant was not required to perform bioequivalence studies in compliance with the CHMP guideline on the Investigation of Bioequivalence (CPMP/PWP/EWP/1401/98 Rev 1/Corr**) regarding parenteral solutions as the product is an aqueous solution for injection.

SmPC
The SmPC is generally in line with the reference product and has been updated to accommodate slight variations between the reference product in IE and those in the CMS. The texts have also been updated to reflect the most recent QRD guidance.

IV.2 Pharmacokinetics

Distribution:
The percentage of free (unbound) drug is usually between 6 – 15% of the total plasma levels. An increased incidence of adverse effects may occur with plasma levels above the effective therapeutic range.

The pharmacological (or therapeutic) effects of valproate may not be clearly correlated with the total or free (unbound) plasma valproic acid levels.

Metabolism:
Valproate, a two-chain fatty acid, is metabolized almost entirely by the liver through at least five pathways, mainly by mitochondrial β-oxidation and glucuronidation. Less than 3% of the in administered dose is excreted unchanged in urine.

The major pathway of valproate biotransformation is glucuronidation (~ 40%), mainly via UGT1A6, UGT1A9 and UGT2B7.

Plasma protein binding of valproate ranges from 80% to 94%. The relationship between dose and total valproate concentration is non-linear; concentration does not increase proportionally with the dose but, rather, increases to a lesser extent due to saturable protein binding. The kinetics of the unbound drug are linear. Age, total drug concentration, and levels of albumin and fatty acids can influence binding to plasma proteins. In infants with a mean age of 10.7 months receiving monotherapy, the percentage of unbound valproic acid increased with total plasma drug concentration.

Elimination:
Plasma clearance of valproic acid ranges from 4.3 to 10.5 mL/ minute in adult healthy volunteers and is independent of hepatic blood flow. The elimination half-life ranges from 9 to 18 hours.

Valproate elimination is markedly decreased in newborns, because of reduced clearance (perhaps due to a delay in the development of glucuronosyl transferase and other enzyme systems) as well as an increased volume of distribution (in part due to decreased plasma protein binding). Half-life is increased in newborns, varying considerably from 17 to 40 hours. In children aged 2–10 years plasma clearance values are 50% higher than those in adults. In children over the age of 10 years, pharmacokinetic parameters approximate those of adults.

The half-life of valproate is usually reported to be within the range 8 – 20 hours.
In patients with severe renal insufficiency, it may be necessary to alter dosage in accordance with free plasma valproic acid levels.

IV.3 Pharmacodynamics

Sodium valproate is the sodium salt form of valproic acid with anti-epileptic activity. Sodium valproate is converted into its active form, valproate ion, in blood. Although the mechanism of action remains to be elucidated, sodium valproate increases concentrations of gamma-aminobutyric acid (GABA) in the brain, probably due to inhibition of the enzymes responsible for the catabolism of GABA. This potentiates the synaptic actions of GABA. Sodium valproate sodium may also affect potassium channels, thereby creating a direct membrane-stabilizing effect.

IV.4 Clinical Efficacy

The clinical efficacy of sodium valproate has been well established. The overview provided is considered adequate.

IV.5 Clinical Safety

The clinical safety of sodium valproate has been well established. The overview provided is considered adequate.

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 Sodium Valproate Seacross 100mg/ml Solution for Injection/Infusion. The submitted Risk Management Plan, version 0.9 signed 25 May 2024 is considered acceptable.

Summary of safety concerns	
Important identified risks	• Teratogenicity
Important potential risks	• Risks to unborn children via third generation and paternal exposure. • Neurodevelopmental disorders in children born to fathers treated with valproate before conception
Missing information	None

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risks		
Teratogenicity	Routine risk minimisation measures:	None

	Labelled in Sections 4.2; 4.3; 4.4; 4.6 and 4.8 of the SmPC and in Sections 2 and 4 of PL. Visual warning corresponding to warning text and associated pictogram on the outer packaging (details to be agreed at national level) Visual warning symbol (pictogram) on the primary packaging (details to be agreed at national level). Smaller pack sizes to encourage monthly prescribing. Additional risk minimisation measures: Pregnancy prevention programme (PPP): · Healthcare professional Guide for female and male patients; · Patient Guide for female patients.	
Important potential risks		
Risks to unborn children via third generation and paternal exposure	Routine risk minimisation measures: None Additional risk minimisation measures: None	None
Neurodevelopmental disorders in children born to fathers treated with valproate before conception	Routine risk minimisation measures: SmPC: Labelled in Sections 4.2, 4.4 and 4.6. PIL: Section 2 and 3 Additional risk minimisation measures: · Guide for healthcare professionals for female and male patients; · Patient Guide for male patients;	None
Missing information		
None	None	None

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted 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. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

Acceptable

V. OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The benefit/risk profile of this product is acceptable.

List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

Additional risk minimisation measures (including educational material)
The educational material should contain the following key elements:

Guide for Healthcare Professionals for female and male patients

- The HCP guide should reflect all pregnancy prevention program (PPP) conditions as outlined in the summary of product characteristics (SmPC).
- The role of the different HCPs for implementation of the PPP and educational materials aimed at patients should be provided (as outlined below).
- Information on congenital malformations and developmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- Information on congenital malformations and neuro-developmental disorders including the magnitude of these risks for children of mothers exposed to valproate during pregnancy.
- Information on **male infertility and testicular toxicity in animals.**
- A dedicated section on use of valproate in male patients.
- Valproate may be initiated in **female children** only if there is no suitable alternative treatment.
- Recommendations for prescribers when valproate is prescribed to **female children**, in particular the need to
    - explain the risks of congenital malformations and neurodevelopmental disorders to the parent/caregivers (and children depending on their age)
    - explain to the parents/caregivers of female girls the importance of contacting the specialist once a female child using valproate experiences menarche
    - reassess the need for valproate therapy at least annually and consider alternative treatment options in female children who experienced menarche
    - make efforts to switch the female children to alternative treatment before they reach adulthood.

- Valproate may be initiated in **girls and women of childbearing potential** only if the conditions of valproate pregnancy prevention program (as outlined in the SmPC) are fulfilled.
- The need to clearly explain to the patient/caregivers the risks of valproate and required actions (in line with valproate PPP) to minimise these risks to all WCBP using valproate and to ensure that the information is well understood.
- The need to use and document the annual risk acknowledgement form, at initiation and during each annual review of valproate treatment by a specialist.
- The need to provide patient educational tools to each WCBP using valproate.
- Guidance on the contraception methods (in line with the SmPC recommendations on contraception).
- Recommendations on switching or discontinuing valproate.
- Recommendations on pregnancy planning.
- Recommendations if valproate is the only suitable treatment for a patient who is (planning to become) pregnant.
- Dedicated section on use of valproate in male patients
- *{To be agreed at a national level, prior to marketing:}* A link to the dedicated website, indicating to patients where additional online information about valproate use in WCBP can be found.

Key information to be included for the role of different HCPs in the HCP guide

a. Valproate should be initiated by specialist.
b. The patient guide should be provided to the patients by the prescriber.
c. The Annual risk acknowledgment form should be used by the specialist at initiation of valproate treatment and during annual treatment reviews.

d. The patient card should be provided by the pharmacists.
e. Optional for countries where valproate may be unpacked in pharmacies: Avoid unpacking valproate and in the situations where this cannot be avoided, always provide a copy of a package leaflet, patient card and the outer box if available.

The additional details regarding the role of the HCPs (including all relevant HCPs such as GPs, gynecologists, paediatricians, midwifes, pharmacists, etc.) in the implementation of the PPP and educational materials should be assessed on national level taking into account the differences in health care systems in individual Member States.

Patient Guides

Female guide

- The Patient Guide should provide comprehensive information on the risks to the unborn child due to in utero exposure to valproate and related substances.
- It should provide details of the pregnancy prevention programme conditions.
- It should include required actions in terms of both pregnancy and pregnancy planning.
- It should include information on the need for effective contraception.
- It should be tailored to different situations in the lifetime of a woman and be age-appropriate:
    - The first prescription,
    - Women continuing valproate treatment and not planning a family,
    - Women of childbearing potential continuing valproate treatment and considering planning a family,
    - Pregnant women (unplanned pregnancy) taking valproate.
- It should include information on the annual risk acknowledgement form and the patient card.
- It should state that it should be read in conjunction with the package leaflet.

Male Guide

- The patient guide should explain the available evidence, uncertainties about the risk, and detail considerations for valproate use in male patients.

VI. REVISION DATE

30.08.2029