Public Assessment Report

Decentralised Procedure

Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion.

(Sodium valproate)

Procedure No: UK/H/5675/001/DC

UK Licence No: PL 24598/0047

Noridem Enterprises Ltd.
Lay Summary

Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion.
(sodium valproate, powder and solvent for solution for injection/infusion, 400mg)

This is a summary of the Public Assessment Report (PAR) for Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion (PL 24598/0047; UK/H/5675/001/DC). It explains how Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion.

For practical information about using Sodium Valproate 400mg Powder and Solvent for solution for injection/infusion, patients should read the package leaflet or contact their doctor or pharmacist.

The product will be referred to as Sodium Valproate throughout the remainder of this PAR.

What is Sodium Valproate and what is it used for?
Sodium Valproate is a ‘generic medicine’. This means that Sodium Valproate is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Epilim 400 mg Powder and Solvent for solution for injection/infusion (Aventis Pharma Limited, UK trading as Sanofi, UK).

Sodium Valproate is used to treat epilepsy (fits) in adults and children. The injection is given when it is not possible for the patient to have the medicine by mouth.

Sodium Valproate treatment must be started and supervised by a doctor specialised in the treatment of epilepsy or bipolar disorders.

Sodium Valproate must not be used by women who are trying to become pregnant or are pregnant as it can cause serious birth defects and developmental problems in the child, unless explicitly advised and agreed with the patient’s doctor to do so. All female patients who are capable of becoming pregnant will need to consider this risk and follow the advice provided in section 2 of the package leaflet. The patient’s doctor will discuss this with them.

How does Sodium Valproate work?
Sodium valproate (the active ingredient) belongs to a group of medicines called anti-convulsants or anti-epileptic agents. It works by helping to calm the brain down.

How is Sodium Valproate used?
The pharmaceutical form of this medicine is a powder and solvent for solution for injection/infusion. The route of administration of this medicine is as a slow injection or infusion into the patient’s vein.

Sodium Valproate is always given to the patient by a doctor or nurse.

The patient’s doctor will decide how much to give the patient depending on their illness. The amount of Sodium Valproate injection given to the patient (adult or child) will depend on the patient’s age or body weight.

If the patient has been taking sodium valproate by mouth, the patient’s doctor may decide to give them the same amount of Sodium Valproate injection by continuous or repeated infusion.
If the patient has not had Sodium Valproate injection before, the doctor will use the following doses:

**Adults (including the elderly)**
- The starting dose is usually between 400mg and 800mg (up to 10mg per kilogram of body weight)
- This is given as a slow intravenous injection over 3-5 minutes
This is followed by a continuous or repeated infusion, up to a maximum of 2500mg each day.

**Children**
- The usual dose is between 20mg and 30mg for each kilogram of body weight each day
- This may be increased to 40mg for each kilogram of body weight each day depending on the child’s illness

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Sodium Valproate have been shown in studies?**
No additional studies were needed as Sodium Valproate is a generic medicine that is given as an aqueous intravenous solution and contains the same active substance as the reference medicine, Epilim 400 mg Powder and Solvent for solution for injection/infusion (Aventis Pharma Limited, UK trading as Sanofi, UK).

**What are the possible side effects of Sodium Valproate?**
Because Sodium Valproate is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Sodium Valproate, see section 4 of the package leaflet available on the MHRA website.

**Why was Sodium Valproate approved?**
It was concluded that, in accordance with EU requirements, Sodium Valproate has been shown to have comparable quality and to be comparable to Epilim 400 mg Powder and Solvent for solution for injection/infusion. Therefore, the MHRA decided that, as for Epilim 400 mg Powder and Solvent for solution for injection/infusion, the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Sodium Valproate?**
A risk management plan (RMP) has been developed to ensure that Sodium Valproate is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Sodium Valproate including the appropriate precautions to be followed by healthcare professionals and patients.

This medicine is subject to additional monitoring (medicines under additional monitoring are called ‘black triangle’ medicines). This will allow quick identification of new safety information. The patient can help by reporting any side effects they may get. Please refer to the end of section 4 of the package leaflet for information on how to report side effects.
Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Sodium Valproate**

A Marketing Authorisation was granted in the UK on 27 April 2015.

The full PAR for Sodium Valproate follows this summary.

For more information about treatment with Sodium Valproate, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2015.
TABLE OF CONTENTS

I  Introduction  Page 6
II  Quality aspects  Page 7
III Non-clinical aspects  Page 9
IV Clinical aspects  Page 9
V  User consultation  Page 11
VI Overall conclusion, benefit/risk assessment and recommendation  Page 11
I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Noridem Enterprises Ltd a Marketing Authorisation for the medicinal product Sodium Valproate (PL 24598/0047; UK/H/5675/001/DC) on 27 April 2015. The product is prescription-only (POM) medicine indicated for the treatment of epileptic patients who would normally be maintained on sodium valproate and for whom oral therapy is temporarily not available.

This application was submitted using the Decentralised Procedure, with the UK as Reference Member State (RMS) and Germany as Concerned Member State (CMS). The applicant subsequently withdrew the application in Germany during the procedure, leaving no CMS. The application was submitted under Article 10(1) of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Epilim 400 mg Powder and Solvent for solution for injection/infusion which was first licenced to Elf Sanofi UK Limited (PL 00623/0038) on 5 May 1988. The reference product (PL 00623/0038) went through change of ownership procedures to Sanofi-Synthelabo Limited on 18 August 1993 (PL 11723/0022) and subsequently to the current licence holder, Aventis Pharma Limited, UK (trading as Sanofi, UK) on 27 November 2012 (PL 04425/0685).

Sodium valproate is an anticonvulsant. Sodium valproate increases the levels of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) at GABAA and GABAB receptors possibly by activating the synthetic enzyme glutamic acid decarboxylase and inhibiting the catabolic enzymes succinic semialdehyde dehydrogenase and GABA transaminase.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.
II QUALITY ASPECTS

II.1 Introduction
Each vial of freeze-dried powder contains 400 mg of the active substance sodium valproate.
Each ampoule of solvent contains 4ml of Water for Injections (WFI).
Each 1 ml of the reconstituted solution contains 95 mg of the active substance sodium valproate.

With the exception of WFI (in the ampoule of solvent), this product contains no other pharmaceutical excipients. The finished product is packed into:
- Lyophilised powder
  Clear glass type I vials with bromobutyl rubber type I closure with an aluminium secure cap with plastic flip-off cover.
- Solvent
  Clear glass type I ampoules.

Sodium Valproate is available in packs of 1 glass vial with 1 glass ampoule solvent, 4 glass vials with 4 glass ampoules solvent and 5 glass vials with 5 glass ampoules solvent.
Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Sodium valproate
Chemical name: Sodium 2-propylpentanoate

Structural formula:

![Structural formula image]

Molecular formula: $C_8H_{15}NaO_2$
Molecular weight: 166.20 g/mol
Appearance: A white or almost white, crystalline, hygroscopic powder.
Solubility: Very soluble in water and freely soluble in ethanol (96%).

Sodium valproate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, sodium valproate, are covered by European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious powder and solvent for solution for injection/infusion containing 95 mg of the active substance sodium valproate per each ml of reconstituted solution (each vial of freeze-dried powder contains 400 mg of the active substance.
sodium valproate and each ampoule of solvent contains 4ml of WFI) that was comparable to the originator product Epilim 400 mg Powder and Solvent for solution for injection/infusion (Aventis Pharma Limited, UK trading as Sanofi, UK). A satisfactory account of the pharmaceutical development has been provided.

The excipient, WFI, complies with the European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for this excipient. Suitable batch analysis data have been provided for WFI.

The excipient does not contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Manufacture of the product**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Stability of the Product**
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 36 months for the unopened vial of freeze-dried powder and the unopened ampoule of WFI with no special storage conditions.

Shelf-life and special precautions for storage and disposal for the reconstituted medicinal product are included in sections 6.3, 6.4 and 6.6 of the SmPC respectively. These are:

- For intravenous use, the reconstituted solution should be used immediately and any unused portion discarded.
- If the reconstituted solution is further diluted for use as an infusion solution, the dilute solution may be stored for up to 24 hours if kept at 2 to 8°C before use, discarding any remaining after 24 hours.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

**II.4 Discussion on chemical, pharmaceutical and biological aspects**
There are no objections to the approval of this application from a pharmaceutical viewpoint.
III  NON-CLINICAL ASPECTS

III.1  Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of sodium valproate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The MAH’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2  Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3  Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4  Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5  Ecotoxicity/environmental risk assessment (ERA)
Since Sodium Valproate 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.6  Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV  CLINICAL ASPECTS

IV.1  Introduction
As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), “bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.”

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of sodium valproate.

Based on the data provided, Sodium Valproate can be considered a generic of Epilim 400 mg Powder and Solvent for solution for injection/infusion (Aventis Pharma Limited, UK trading as Sanofi, UK).

IV.2  Pharmacokinetics
In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3  Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.
IV.4 **Clinical efficacy**
No new efficacy data were submitted and none were required for an application of this type.

IV.5 **Clinical safety**
No new safety data were submitted and none were required for this application.

IV.6 **Risk Management Plan (RMP)**
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

**Summary table of safety concerns:**

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
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<tbody>
<tr>
<td>- Liver dysfunction</td>
<td>- Recurrence of symptoms upon discontinuation / switching to another generic</td>
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<td>- Pancreatitis</td>
<td>- Use in renal insufficiency</td>
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<td>- Weight gain or loss</td>
<td>- Systemic Lupus Erythematosus</td>
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<td>- CNS disorders</td>
<td>- False positives in urine testing of diabetic patients</td>
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<td>- Hyperammonaemia</td>
<td>- Concomitant use of salicylates</td>
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<td>- Blood disorders</td>
<td>- Concomitant use of carbapenem agents</td>
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<td>- Reproductive system, breast disorders and abnormal pregnancy outcome</td>
<td>- Other drug interactions</td>
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<td>- Hypersensitivity</td>
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<td>- Serious skin reactions</td>
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<td>- Pleural effusion</td>
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<tr>
<td><strong>Important potential risks</strong></td>
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<td>- Use in breast feeding</td>
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<tr>
<td>- Suicidal ideation and behaviour</td>
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</table>
Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**Conditions for the marketing authorisation relating to the RMP:**
The Applicant was requested to note the Drug Utilisation Study as an annex 2 condition/outcome of the EU Article 31 Referral to the European Medicines Agency and to provide confirmation of their intention to collaborate with the brand leader or submit their own protocol for the study. A commitment has been provided.

**IV.7 Discussion on the clinical aspects**
No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application subject to the following commitment:

- **RMP:** The Applicant was requested to note the Drug Utilisation Study as an annex 2 condition/outcome of the EU Article 31 Referral to the European Medicines Agency and to provide confirmation of their intention to collaborate with the brand leader or submit their own protocol for the study. A commitment has been provided.

**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 PIL 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*.

**VI Overall conclusion, benefit/risk assessment and recommendation**
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sodium valproate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Sodium Valproate is presented below: