Public Assessment Report

Gabapentin Thame 50mg/ml Oral Solution

(Gabapentin)

UK Licence Number: PL 39307/0068

Syri Limited t/a Thame Laboratories
LAY SUMMARY

Gabapentin Thame 50mg/ml Oral Solution

(gabapentin, oral solution, 50 mg/ml)

This is a summary of the Public Assessment Report (PAR) for Gabapentin Thame 50mg/ml Oral Solution (PL 39307/0068). It explains how Gabapentin Thame 50mg/ml Oral Solution 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 Gabapentin Thame 50mg/ml Oral Solution.

The product will be referred to as Gabapentin Oral Solution throughout the remainder of this public assessment report (PAR).

For practical information about using Gabapentin Oral Solution, patients should read the package leaflet or contact their doctor or pharmacist.

What is Gabapentin Oral Solution and what is it used for?
Gabapentin Oral Solution is a ‘generic medicine’. This means that Gabapentin Oral Solution is similar to a ‘reference medicine’ already authorised in the European Union (EU) but is available as a different strength (50 mg/ml) and different pharmaceutical form (oral solution).

The reference medicine for Gabapentin Oral Solution is Neurontin 300mg Hard Capsules (Pfizer Limited, UK).

Gabapentin Oral Solution is used to treat:
- Various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not). The patient’s doctor will prescribe this medicine for the patient to help treat their epilepsy when their current treatment is not fully controlling their condition. The patient should take Gabapentin Oral Solution in addition to their current treatment unless told otherwise. This medicine can also be used on its own to treat adults and children over 12 years of age.

- Peripheral neuropathic pain (long lasting pain caused by damage to the nerves). A variety of different diseases can cause peripheral neuropathic pain (primarily occurring in the legs and/or arms), such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles etc.

How does Gabapentin Oral Solution work?
The active substance in this medicine is called gabapentin, which belongs to a group of medicines used to treat epilepsy and peripheral neuropathic pain (long lasting pain caused by damage to the nerves). Gabapentin works by stabilising electrical activity in the brain.

How is Gabapentin Oral Solution used?
The pharmaceutical form of this medicine is an oral solution and the route of administration is oral (by mouth). The patient should always take this medicine exactly as their doctor has told them using the oral syringe provided to measure the correct dose. The patient should check with their doctor or pharmacist if they are not sure. The patient’s doctor will determine what dose is appropriate for them.
The usual doses are:
For epilepsy:

Adults and adolescents:
The recommended starting dose is generally between 300 mg and 900 mg a day (6 to 18 ml) this will be increased gradually by the patient’s doctor, up to a maximum dose of 3600 mg a day (72 ml). Take this medicine in 3 separate doses: once in the morning, once in the afternoon, and once in the evening.

Children aged 6 years old and above
The doctor will decide the dose, depending on the child’s weight. The treatment is started with a low starting dose which is gradually increased over a period of about three days.

The recommended dose is 25 to 35 mg for each kilogram of body weight a day. It is usually given in three separate doses: once in the morning, once in the afternoon and once in the evening.

For peripheral neuropathic pain:

Adults
The recommended starting dose is generally between 300 mg and 900 mg a day (6 to 18 ml). This will be increased gradually by the patient’s doctor. The maximum dose is 3600 mg a day (72 ml). Take the medicine in three separate doses: once in the morning, once in the afternoon and once in the evening.

If the patient has kidney problems or is receiving haemodialysis
The patient’s doctor may prescribe a different dosing schedule and/or dose if they have problems with their kidneys or are undergoing haemodialysis.

If the patient is an elderly patient (over 65 years of age)
The patient should take the normal dose of Gabapentin Oral Solution unless they have problems with their kidneys. The patient’s doctor may prescribe a different dosing schedule and/or dose if they have problems with their kidneys.

If the patient has the impression that the effect of this medicine is too strong or too weak, they should talk to their doctor or pharmacist as soon as possible.

Please read section 3 of the package leaflet for detailed dosing recommendations including use of the oral syringe, the route of administration, and the duration of treatment.

For further information on how Gabapentin Oral Solution is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

What benefits of Gabapentin Oral Solution been shown in studies?
Because Gabapentin Oral Solution is a hybrid generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine Neurontin 300mg Hard Capsules (Pfizer Limited, UK) when administered at the same dose (300mg; 6 ml of oral solution versus 1 hard capsule). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of Gabapentin Oral Solution?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects (may affect more than 1 in 10 people) are viral infection, feeling drowsy, dizziness, lack of coordination, feeling tired and fever.
Common side effects (may affect up to 1 in 10 people) are:

- pneumonia, respiratory infections, urinary tract infection, inflammation of the ear or other infections
- low white blood cell counts
- anorexia, increased appetite
- anger towards others, confusion, mood changes, depression, anxiety, nervousness, difficulty with thinking
- convulsions, jerky movements, difficulty with speaking, loss of memory, tremor, difficulty sleeping, headache, sensitive skin, decreased sensation (numbness), difficulty with coordination, unusual eye movement, increased, decreased or absent reflexes
- blurred vision, double vision
- vertigo
- high blood pressure, flushing or dilation of blood vessels
- difficulty breathing, bronchitis, sore throat, cough, dry nose
- vomiting (being sick), nausea (feeling sick), problems with teeth, inflamed gums, diarrhoea, stomach pain, indigestion, constipation, dry mouth or throat, flatulence
- facial swelling, bruises, rash, itch, acne
- joint pain, muscle pain, back pain, twitching
- difficulties with erection (impotence)
- swelling in the legs and arms, difficulty with walking, weakness, pain, feeling unwell, flu-like symptoms
- decrease in white blood cells, increase in weight
- accidental injury, fracture, abrasion.

Additionally, in clinical studies in children, aggressive behaviour and jerky movements were reported commonly.

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

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

Why was Gabapentin Oral Solution approved?
The MHRA decided that the benefits of this medicinal product are greater than its risks and recommended that it be approved for use.

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

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Gabapentin Oral Solution
A Marketing Authorisation was granted in the UK on 18 June 2018.

The full PAR for Gabapentin Oral Solution follows this summary.

For more information about treatment with Gabapentin Oral Solution read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2018.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Introduction</td>
<td>6</td>
</tr>
<tr>
<td>II Quality aspects</td>
<td>8</td>
</tr>
<tr>
<td>III Non-clinical aspects</td>
<td>10</td>
</tr>
<tr>
<td>IV Clinical aspects</td>
<td>11</td>
</tr>
<tr>
<td>V User consultation</td>
<td>12</td>
</tr>
<tr>
<td>VI Overall conclusion, benefit/risk assessment and recommendation</td>
<td>12</td>
</tr>
<tr>
<td>Table of content of the PAR update</td>
<td>15</td>
</tr>
</tbody>
</table>
I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Syri Limited t/a Thame Laboratories, a marketing authorisation for the medicinal product Gabapentin Thame 50mg/ml Oral Solution (PL 39307/0068). The product is a prescription-only medicine (POM) indicated for:

Epilepsy:
- as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above.
- as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above.

Treatment of peripheral neuropathic pain:
- the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid medicinal product. The reference medicinal product for this application is Neurontin 300 mg Hard Capsules which was first authorised to the marketing authorisation holder (MAH) Parke Davis & Company Limited (PL 00018/0203) on 05 February 1993 and subsequently underwent several changes of ownership procedures of which the most recent was to the current MAH, Pfizer Limited (PL 00057/0536) on 01 November 2005.

Gabapentin is marketed in Europe in the form of capsules and oral solution. The originator product is Neurontin (gabapentin) 300 mg capsules (Pfizer Limited). For Gabapentin 50 mg/ml oral solution there is no innovator available in EU.

The Applicant has developed a generic oral solution that is bioequivalent to the originator’s product Neurontin (gabapentin) 300 mg capsules.

Gabapentin readily enters the brain and prevents seizures in a number of animal models of epilepsy. Gabapentin binds with high affinity to the α2δ (alpha-2-delta) subunit of voltage-gated calcium channels and it is proposed that binding to the α2δ subunit may be involved in gabapentin’s anti-seizure effects in animals. Broad panel screening does not suggest any other drug targets other than α2δ.

Two bioequivalence studies were conducted. The first study was not acceptable as it used a formulation of test product which differed significantly from that of the final proposed formulation. A further bioequivalence study was therefore conducted and was instead used to support this application. The applicant has stated that the bioequivalence studies were conducted in accordance with Good Clinical Practice (GCP) guidelines.

With the exception of the bioequivalence studies, no new non-clinical or clinical data were submitted, which is acceptable given that this is a hybrid application, which refers to an originator product that has been in clinical use for over 10 years.

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

No new or unexpected safety concerns were identified during the review of information provided by the Marketing Authorisation Holder and it was, therefore, judged that, similarly to the reference product, the benefits of taking Gabapentin Oral Solution outweigh the risks and a Marketing Authorisation was granted.
II QUALITY ASPECTS

II.1 Introduction
Each ml contains 50 mg gabapentin as the active ingredient. Other ingredients consist of the pharmaceutical excipients asaccharose potassium (E950), saccharin sodium (E954), propylene glycol (E1520), methyl parahydroxybenzoate (E218), ethyl parahydroxybenzoate (E214), carmellose sodium (E466), and purified water.

Gabapentin Thame 50mg/ml Oral Solution is packaged in amber (Type III) glass bottles containing 150 ml of oral solution, closed with a tamper evident, child resistant white plastic cap consisting of a polypropylene inner, polyethylene outer and an expanded polyethylene (EPE) liner. Each bottle is placed in a carton with a 10 ml oral syringe with 0.5 ml graduation and a syringe adaptor.

This medicinal product is available in a single 150 ml bottle pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Gabapentin
Chemical name: [1-(Aminomethyl)cyclohexyl]acetic acid. OR 1-(Aminomethyl)cyclohexaneacetic acid OR Cyclohexaneacetic acid, 1-(aminomethyl)-

Structure:

![Structure of Gabapentin](image)

Molecular formula: C₉H₁₇NO₂
Molecular weight: 171.24
Description: White or almost white, crystalline powder.

The active substance is the subject of an active substance master file (ASMF).

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analyses data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

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 safe, efficacious oral solution containing 50 mg per ml of solution that is a hybrid generic version of the reference product Neurontin 300mg Hard Capsules (Pfizer Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients used contain material of animal or human origin.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at pilot scale batch size and has shown satisfactory results. A satisfactory process validation protocol for commercial scale batches has been provided.

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 the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 12 months for the unopened bottle with the storage conditions “Do not store above 25°C” and “Do not refrigerate or freeze”. The in-use shelf life of the product is 30 days after first opening.

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 gabapentin 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 applicant’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.

The safety of the excipients and the content relative to the acceptable daily intake (ADI) as specified by the European Union and WHO was presented. The maximum daily intakes were calculated for the different patient populations i.e. adults, adolescents and children and found to be below WHO recommended ADI values and as such considered acceptable. In addition, carmellose sodium (carboxymethylcellulose sodium) is used in a wide range of pharmaceutical formulations and has low oral, dermal and inhalation toxicity. It is non-irritating to the eyes and skin, and nonsensitising to the skin. No significant acute toxicological effects are expected.

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.

Impurities
Impurity limits have been suitably justified.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Gabapentin Oral Solution is intended for generic substitution, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
There are no objections to the approval of this application from a non-clinical viewpoint.
IV CLINICAL ASPECTS
IV.1 Introduction
The clinical pharmacology of gabapentin is well-known. With the exception of data from the bioequivalence study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

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 gabapentin.

Based on the data provided, Gabapentin Oral Solution can be considered bioequivalent to Neurontin 300mg Hard Capsules (Pfizer Limited, UK).

IV.2 Pharmacokinetics
In support of this application, the applicant submitted the following two bioequivalence studies:

STUDY 1
This was a randomized, Open label, Balanced, Two-treatment, Two period, Two sequence, single-dose, Crossover, bioequivalence study of Gabapentin 300mg/6ml oral solution of Syri Limited t/a Thame Laboratories, UK with Neurontin 300mg hard capsules of Pfizer Limited, United Kingdom in Normal, healthy, adult human subjects under fasting conditions.

This study utilised an earlier formulation of test product which was found to have stability issues, this earlier formulation differed significantly to that of final proposed formulation of Gabapentin Thame 50mg/ml Oral Solution. This study could therefore, not be accepted to support bioequivalence between the test and reference product, therefore a further bioequivalence study was conducted and is presented below:

STUDY 2
This was a randomized, open label, balanced, two treatments, two periods, two sequence, single dose, crossover bioequivalence study of the applicant’s test product Gabapentin Thame 50 mg/ml oral solution (Thame Laboratories Limited) versus the reference product is Neurontin 300mg Hard Capsules (Pfizer Limited, UK) in healthy, adult, male human subjects under fasting conditions.

Subjects were administered a single oral dose of 6 ml of oral solution of the test product (300 mg) or 1 x 300 mg hard capsule of the reference product under fasting conditions.

Blood samples were collected for plasma levels before dosing and up to and including 48 hours after each administration. The washout period between treatment phases was 7 days. The pharmacokinetic results are presented below:

Table: Bioequivalence of Test and Reference products for gabapentin:

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (T)</th>
<th>Reference (R)</th>
<th>T/R</th>
<th>Lower Limit</th>
<th>Upper Limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀₋inf</td>
<td>26573.4362</td>
<td>25668.6150</td>
<td>103.5250</td>
<td>96.8432</td>
<td>110.6679</td>
</tr>
<tr>
<td>AUC₀₄</td>
<td>24684.3538</td>
<td>23828.9609</td>
<td>103.5897</td>
<td>96.8153</td>
<td>110.8382</td>
</tr>
<tr>
<td>Cₘₐₓ</td>
<td>2541.2723</td>
<td>2541.1632</td>
<td>100.0043</td>
<td>93.4055</td>
<td>107.0693</td>
</tr>
</tbody>
</table>

*Geometric mean was taken as the antilog (exponential) of the least squares mean of the ln-transformed data.
Conclusion
The 90% confidence intervals of the test/reference ratio for AUC and $C_{\text{max}}$ values for gabapentin lie within the acceptable limits of 80.00% to 125.00%, in line with the ‘Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product is bioequivalent to the reference product Neurontin 300mg Hard Capsules (Pfizer Limited, UK) under fasting conditions.

**IV.3 Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for applications of this type.

**IV.4 Clinical efficacy**
No new efficacy data were submitted and none were required for applications of this type.

**IV.5 Clinical safety**
With the exception of the safety data collected during the bioequivalence studies, no new data on safety have been submitted and none are required for applications of this type. No new or unexpected adverse events were observed during the bioequivalence studies.

**IV.6 Risk Management Plan (RMP)**
The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**IV.7 Discussion on the clinical aspects**
The grant of a marketing authorisation is recommended for this application from a clinical viewpoint.

**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 gabapentin is considered to have demonstrated the therapeutic value of the compound. This product is bioequivalent to the reference product and its benefit-risk balance is, therefore, considered to be similar and 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 this medicine is presented below:
Annex 1

**Table of content of the PAR update**
Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
</table>