COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gabapentine Strides 100 mg, 300 mg, and 400 mg, hard capsules (gabapentin)

NL/H/4662/001-003/DC

Date: 22 April 2025

This module reflects the scientific discussion for the approval of Gabapentine Strides 100 mg, 300 mg, and 400 mg, hard capsules. The procedure was finalised on 1 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
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 Gabapentine Strides 100 mg, 300 mg, and 400 mg, hard capsules, from Strides Pharma (Cyprus) Limited.

The product is indicated for:
Epilepsy
Gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above.
Gabapentin is indicated as monotherapy in the treatment of partial seizures with and without secondary generalisation in adults and adolescents aged 12 years and above.

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

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Neurontin 100 mg, 300 mg and 400 mg , harde capsules (NL RVG 22481, 22482 and 22483) which have been registered in Germany by Pfizer Limited since 10 November 1999 (original product). In the Netherlands, Neurontin has been registered by the procedure DE/H/0899/001.

The concerned member states (CMS) involved in this procedure were France, Germany, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Gabapentine Strides are hard capsules containing 100 mg, 300 mg, or 400 mg gabapentin as active substance. The three capsule strengths are easily distinguishable from each other based on colour.

Gabapentin Strides 100 mg hard capsules have an opaque white cap and opaque white body imprinted with 'S617/100 mg' on the cap with edible blue ink and '  ' on the body with edible green ink. The capsules are filled with a white to off white powder and their size is 15.80 mm ± 0.4 mm.

Gabapentin Strides 300 mg hard capsules have an opaque yellow cap and opaque yellow body imprinted with 'S618/300 mg' on the cap with edible blue ink and 'S' on the body with edible green ink. The capsules are filled with a white to off white powder and their size is 19.30 mm ± 0.4 mm.

Gabapentin Strides 400 mg hard capsules have an opaque blue cap and opaque blue body imprinted with 'S619/400 mg' on the cap with edible white ink and 'S' on the body with edible white ink. The capsules are filled with a white to off white powder and their size is 21.40 mm ± 0.4 mm.

The excipients are: mannitol (E421), maize starch, talc (E553b) and magnesium stearate (E470b).

Capsule shell - gelatin (E441), titanium dioxide (E171), iron oxide yellow (E172, 300 mg capsule), brilliant blue FCF aluminium lake (E133, 400 mg capsule).

Printing ink cap - shellac (E904) (in blue ink), indigo carmine aluminium lake (E132) (in blue ink), titanium dioxide (E171) (in white ink), ammonia and propylene glycol.

Printing ink body - shellac (E904), iron oxide yellow (E172) (in green ink), brilliant blue FCF aluminium lake (E133) (in green ink), titanium dioxide (E171) (in white ink), ammonia and propylene glycol.

The three capsule strengths are dose proportional.

The hard capsules are packed in high-density polyethylene (HDPE) bottle pack with a white opaque child resistant closure or white opaque HDPE liner cap.

II.2 Drug Substance

The active substance is gabapentin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Gabapentin is a white or almost white, crystalline powder, sparingly soluble in water, slightly soluble in ethanol (96 percent), practically insoluble in methylene chloride. It dissolves in dilute acids and dilute solutions of alkali hydroxides. The substance exhibits polymorphism and does not exhibit optical rotation. For this product, polymorphic form II is consistently produced. The stability data presented by the MAH is sufficient to support that no control of the polymorphic form is necessary in the drug substance (nor in the drug product).

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 active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional tests and limits as stated on the CEP. In addition, the MAH has adopted limits for residual solvents, bulk density, particle size, and foreign matter. Batch analytical data demonstrating compliance with this specification have been provided for six batches.

Stability of drug substance
The active substance is stable for 36 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 adequately explained. Suitability of the product for the paediatric population has been discussed, including the (level of) excipients. The MAH has adequately discussed the development of the dissolution method.
The MAH has identified the test and reference product used in the bioequivalence study. The test and reference products were used in comparative dissolution study in support of the bioequivalence study. The results were found similar, all results showed dissolution over 85% in 15 minutes. In addition, the MAH has presented comparative dissolution data to support the biowaiver of strength for the lower strengths. The biowaivers of strength can be granted as the products showed dissolution over 85% in 15 minutes

Manufacturing process
The main steps of the manufacturing process are sifting, blending, (pre-)lubrication, capsule filling, polishing and packing. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients (mannitol, corn (maize) starch, talc, and magnesium stearate) are controlled as per current Ph. Eur. For the capsule shell (gelatin) an in-house specification is applied. 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, identification, disintegration time, water content, uniformity of dosage units, dissolution, assay, related substances and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The elemental risk assessment is included. The

predicted level of elemental impurities in the drug product is compared to the control threshold. The predicted concentrations of elemental impurities are less than control threshold except Lead and Cadmium (only in 100 mg). Lead and cadmium limits are well within the permitted daily exposure (PDE) and will not exceed the PDE. The risk assessment is considered to be sufficient.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from full scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches per strength stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable European guidelines. Photostability studies were conducted as per guidance and the product is not photosensitive. On basis of the data submitted, a shelf life was granted of 3 years. No specific storage conditions needed to be included in the SmPC or on the label.

In-use stability data have been provided demonstrating that the product remains stable for 100 days following first opening of the container when stored in the approved HDPE container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM for the excipient gelatin 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 Gabapentine Strides 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 Gabapentine Strides is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Neurontin which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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

Gabapentin is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Gabapentine Strides 400 mg, hard capsules (Strides Pharma (Cyprus) Limited, Cyprus) was compared with the pharmacokinetic profile of the reference product Neurontin 400 mg, harde capsules (Pfizer Limited, United Kingdom).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Dissolution data have been provided at pH 1.2, 4.5 and 6.8. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver
The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Gabapentin shows non-linear pharmacokinetics over the 100 mg - 900 mg dose range. However, over the narrowed dose range of 100 mg - 400 mg linear pharmacokinetics can be

assumed, as supported by the UK PAR on Gabapentin Kent and NL PAR on Gabapentin Glenmark.

In conclusion, for the 100 mg and 300 mg capsule strengths a waiver for additional strength with the 400 mg capsule strength as reference, is following the criteria in accordance with the EMA Bioequivalence guideline, and is acceptable.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, two way crossover, open label, balanced bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (400 mg) of one of the two gabapentin formulations. The capsule was orally administered with 150 mL water after an overnight fast for eight hours. After dosing, the subjects fasted for the next four hours. There were two dosing periods, separated by a washout period of twelve days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 0.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 10, 16, 24 and 36 hours after administration of the products.

The design of the study is acceptable.

Gabapentin may be taken without reference to food intake. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects did not report to the facility at check-in for period II. Another subject experienced adverse events (fever and cough; relationship with drug unlikely) before check in at period II and was withdrawn from the study. 33 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of gabapentin, 400 mg under fasted conditions.

Treatment N=33	**AUC_{0-t} (µg.h/mL)**	**$AUC_{0-\infty}$ (µg.h/mL)**	**C_{max} (µg/mL)**	**t_{max} (h)**
Test	48.1 ± 14.8	50.1 ± 14.5	4.4 ± 1.1	3.25 (0.5 – 6.0)
Reference	49.8 ± 15.5	51.8 ± 15.8	4.7 ± 1.3	3.0 (1.0 – 6.0)
***Ratio (90% CI)**	0.97 0.88 – 1.06	-	0.94 0.86 - 1.02	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to t = 36 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Gabapentine Strides is considered bioequivalent with Neurontin, 400 mg.

The results of the bioequivalence study with the 400 mg formulation can be extrapolated to the lower strengths, 100 mg and 300 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Gabapentine Strides.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	Abuse and dependence
Important potential risks	Suicidal ideation and behaviour Risk of birth defects
Missing information	Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children

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 Neurontin. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. 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 Gabapentin 600 and 800 mg film-coated tablets, NL/H/4661/001-002/DC (no marketing authorisation in the Netherlands). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gabapentine Strides 100 mg, 300mg and 400 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Neurontin 100 mg, 300 mg and 400 mg, harde capsules. Neurontin is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

In the Board meeting of 21 November 2019, the following was discussed:
Quality
Earlier in the procedure it was established that there were several packaging sizes for which no adequate stability studies and in-use studies had been submitted. The packaging sizes in question have now been withdrawn.
Furthermore, a Qualified Person (QP) declaration for a specific release manufacturer was missing. This has now been provided.

Conclusion
The Board is positive about this medicine. The objections formulated earlier in the procedure have been resolved.

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 Gabapentine Strides with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 December 2019.

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/4662/001-003/IA/001/G	Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for importation and/or batch release. Not including batch control/testing. Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	Yes No	04-03-2021	Approved	N/A
NL/H/4662/001-003/IB/002	Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes.	Yes	09-04-2021	Approved	N/A
NL/H/4662/001-003/E/001	Repeat use.	No	18-07-2022	Approved	N/A
NL/H/4662/001-003/IB/003	Change in the specification parameters and/or limits of the finished product. Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue.	No	30-01-2023	Approved	N/A
NL/H/4662/001-003/IA/006	Change in test procedure for the finished product. Minor changes to an approved test procedure.	No	28-02-2023	Approved	N/A
NL/H/4662/001-003/IB/007	Change in the shelf-life or storage conditions of the finished product. Extension of the shelf life of the finished product.	Yes	27-03-2023	Approved	N/A

	As packaged for sale (supported by real time data).				
NL/H/4662/001 -002/IB/005	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance. Other variation.	No	10-05-2023	Approved	N/A
NL/H/4662/001 /IB/004	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products. Other variation.	Yes	19-05-2023	Approved	N/A
NL/H/4662/001 -003/IB/008/G	Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules, etc.) in a pack. Change outside the range of the currently approved pack sizes. Change in immediate packaging of the finished product. Change in type of container or addition of a new container. Solid, semi-solid and non-sterile liquid pharmaceutical forms.	Yes Yes	24-06-2023	Approved	N/A
NL/H/4662/001 -003/IA/009	Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacturer responsible for importation and/or batch release. Including batch control/testing.	Yes	28-08-2023	Approved	N/A
NL/H/4662/001 -003/IB/010	Change in the manufacturing process of the finished product , including an intermediate used in the manufacture of the finished product. Other variation.	No	02-11-2023	Approved	N/A
NL/H/4662/001 -003/IB/011/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure	Yes	10-01-2024	Approved	N/A

	concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPC. Other variation. Change in ATC Code / ATC Vet Code.				
NL/H/4662/001-003/IA/012/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient. European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. Updated certificate from an already approved manufacturer. Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient. European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient. Updated certificate from an already approved manufacturer. Change in the specification parameters and/or limits of an active substance, starting material / intermediate /	No No No	29-03-2024	Approved	N/A

	reagent used in the manufacturing process of the active substance. Tightening of specification limits.				
NL/H/4662/001-003/IB/014	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product. Implementation of change(s) for which no new additional data are submitted by the MAH.	Yes	27-06-2024	Approved	N/A
NL/H/4662/001-003/IB/013	Change in the specification parameters and/or limits of the finished product. Addition of a new specification parameter to the specification with its corresponding test method.	No	09-10-2024	Approved	N/A
NL/H/4662/001-003/IA/015	Change to importer, batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	No	19-12-2024	Approved	N/A
NL/H/4662/001-003/IA/016/G	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient. European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient. Deletion of certificates (in case multiple certificates exist per material). Submission of a new or updated Ph. Eur. certificate	No	24-02-2025	Approved	N/A

	of suitability or deletion of Ph. Eur. certificate of suitability: - For an active substance - For a starting material/reagent/intermediate used in the manufacturing process of the active substance - For an excipient. European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient. Updated certificate from an already approved manufacturer.				