LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Shaktatin
(gabapentin)

SE/H/2446/01/DC

This module reflects the scientific discussion for the approval of Shaktatin. The procedure was finalised on 2025-02-26. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Shaktatin, 50 mg/ml, oral solution.

The active substance is gabapentin. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Shaktatin, 50 mg/ml, oral solution, is a hybrid article 10(3) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and NO as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Neurontin, 300 mg, hard capsule authorised in the UK since 1993, with Pfizer Ltd. as marketing authorisation holder.

The reference product used in the bioequivalence study is Neurontin, 300 mg, hard capsule from the UK with Pfizer Ltd. as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
The drug product Gabapentin 50 mg/mL Oral Solution has a different strength and a different pharmaceutical form than the reference product, Neurontin 300 mg hard capsule. However, the therapeutic indications, the posology and the recommended maximum daily dose is in line with the reference product. From a non-clinical perspective, the differences between Gabapentin 50 mg/mL Oral Solution and the reference product are acceptable.

Pharmacodynamic, pharmacokinetic and toxicological properties of gabapentin are well known. As gabapentin is a widely used, well-known active substance, no further studies are required, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Impurities in the drug product
The proposed specification of the lactam impurity (Impurity A) is not more than 0.15% at release and 0.40% at shelf life. Given that the maximum daily dose of gabapentin is 3600 mg, the qualification threshold as outlined in ICH Q3B(R2) is 0.15%. Although some further toxicological justification would have been informative, the negative *in silico* prediction for mutagenicity provides support for the proposed specification.

Excipients
A discussion on the safety of the excipients in the drug product is included in the non-clinical overview.

For the excipients with an acceptable daily intake limit (ADI), levels of excipients do not exceed the limits specified by the European Union and WHO. Thus, no safety concerns are expected when using Gabapentin 50 mg/mL Oral solution at clinically relevant doses.

Environmental Risk Assessment (ERA)
Since Shaktatin is intended for a generic substitution, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Approval of Shaktatin can be recommended from the non-clinical perspective.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Shaktatin (gabapentin) with the reference product Neurontin capsules.

<u>Pharmacokinetic properties of the active substance</u>
Absorption: Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Absolute bioavailability of a 300 mg capsule is approximately 60%.

Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics. Therefore, there are no restrictions with respect to food in the SmPC of the originator.

Linearity: Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose.

Elimination: The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

<u>Study ARL/17/218</u>
Methods

This was a single-dose, two-way crossover study conducted in 28 healthy volunteers, comparing Gabapentin, 50 mg/ml, oral solution with Neurontin, 300 mg, capsules under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 48 hours post-dose. Plasma concentrations of gabapentin were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 2017-10-04 and 2017-10-14.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for gabapentin, n=26.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**25783 ± 8050**	**2651 ± 743**	**2.67 (0.75-4.00)**
Reference	**24607 ± 6268**	**2630 ± 655**	**2.33 (0.75-4.02)**
***Ratio (90% CI)**	**103.59 (96.82-110.84)**	**100.00 (93.41-107.07)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

For AUC_{0-t} and C_{max} the 90 % confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00 %.

Discussion and overall conclusion
The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Shaktatin (gabapentin) is considered bioequivalent with Neurontin capsules.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

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 Shaktatin.

Part II Safety specification

Summary of safety concerns	
Important identified risks	• Suicidal ideation and behaviour • Abuse and dependence • Withdrawal symptoms • Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Important potential risks	• Risk of birth defects
Missing information	• Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children • Use during pregnancy and lactation

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

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP has been updated to reflect the above safety concerns and is now endorsed.

Conclusion RMP assessment
The MAH satisfactorily responded to the questions raised during the procedure and updated the RMP accordingly.
The submitted Risk Management Plan, version 0.2 signed 12-12-2024 is considered acceptable.

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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to GabaLiquid GeriaSan 50 mg/ml Lösung zum Einnehmen for content and Dexamcol 1 mg/ml + 5 mg/ml colírio, solução for the layout.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

This hybrid application concerns gabapentin in the formulation of oral solution 50 mg/ml. The oral solution may be useful in the treatment of children and others who have difficulties in swallowing solid dosage forms.

The quality of the hybrid product, Shaktatin, is found adequate. There are no objections to approval of Shaktatin, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

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

N/A

VII. APPROVAL

The decentralised procedure for Shaktatin, 50 mg/ml, oral solution was positively finalised on 2025-02-26.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se