LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Neurisol
(gabapentin)

SE/H/2518/01/DC

This module reflects the scientific discussion for the approval of Neurisol. The procedure was finalised on 2024-12-18. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Neurisol, 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 Neurisol, 50 mg/ml, Oral solution, is a Hybrid Art. 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 DK, FI, IS, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Neurontin, 300 mg Capsule, hard authorised in Sweden since 1994, with Upjohn EESV as marketing authorisation holder.

The reference product used in the bioequivalence study is Neurontin, 300 mg Capsule, hard from United Kingdom with Upjohn UK Limited as marketing authorisation holder.

European Reference Product (ERP)

A European Reference Product is used in CMS Iceland: Neurontin, 300 mg Capsule, hard authorised in Sweden since1994, with Upjohn EESV as marketing authorisation holder.

The justification to use this product is based on RMS's own files. The ERP information was circulated during the validation period.

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
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.

Environmental Risk Assessment (ERA)
Since Neurisol is intended for substitution of products already on the market, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Neurisol from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study comparing Neurisol with the reference product Neurontin.

Pharmacokinetic properties of the active substance
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%.

The pharmacokinetics of gabapentin is not affected by food, and 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.

Bioequivalence Study 172-15
Methods
This was a single-dose, two-way crossover study conducted in 28 healthy volunteers (26 completed), comparing Neurisol, 50 mg/ml, oral solution with Neurontin, 300 mg, hard capsules at a dose of 300 mg 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 log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 5th September 2015 and 1st October 2015.

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	**28829 ± 7766**	**2590 ± 610**	**3.00 (1.67-5.00)**
Reference	**30085 ± 6529**	**2841 ± 649**	**3.50 (1.33-6.00)**
***Ratio (90% CI)**	**94.96 (87.90-102.58)**	**91.11 (83.51-99.41)**	**-**

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 method was adequately validated.

Based on the submitted single-dose bioequivalence study, Neurisol oral solution 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 Neurisol.

Safety specification

Summary of safety concerns	
Important identified risks	• Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) • Suicidal ideation and behaviour • Abuse and Dependence • Withdrawal symptoms
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.

Part V 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 is endorsed.

Conclusion RMP assessment

The applicant has satisfactorily responded to the questions raised in the first round of assessment and updated the RMP accordingly.

The submitted Risk Management Plan, version 0.2 signed 19 June 24 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 oral solution (DE/H/4632/001/DC) for content and Neupedix (Alprostatil) 500 micrograms solution for infusion (AT/H/1362/001/DC).

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of Neurisol, is found adequate. There are no objections to approval of Neurisol, 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

Post approval commitments

Description	Due date
The applicant commits to perform a validation in accordance with ICH Q2 for the determination of the total N-nitroso content analytical method that is included in the release and shelf-life specification of the product. Relevant validation data and method information will be submitted through a post approval variation application no later than 6 months from the end of the procedure.	2025-06-18

VII. APPROVAL

The decentralised procedure for Neurisol, 50 mg/ml, Oral solution was positively finalised on 2024-12-18.

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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)

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