LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Gabapentin Orion
(gabapentin)

This module reflects the scientific discussion for the approval of Gabapentin Orion. The procedure was finalised on 2022-04-29. 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 Gabapentin Orion, 100 mg, Capsule, hard.

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 is an extension, addition of 100 mg, a new strength, of the previously authorised product Gabapentin Orion, 300 mg and 400 mg, capsule, hard. marketed by Orion Corporation since 2018. Please note that a Public Assessment Report is not available for Gabapentin Orion, 300 mg and 400 mg.

The application for Gabapentin Orion, 100 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation, applies through the Swedish National Procedure.

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Neurontin, 100 mg, capsule, hard authorised in SE since 1994, with Pfizer AB as marketing authorisation holder.

The reference product used in the bioequivalence study is Neurontin, 400 mg, capsule, hard from DE with Pfizer Pharma PEE GmbH as marketing authorisation holder.

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

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

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 and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Gabapentin Orion is a generic product, 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 Gabapentin Orion from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing gabapentin 400 mg capsules with the reference product Neurontin 400 mg hard capsules.

Pharmacokinetic properties of the active substance
Gabapentin has an oral bioavailability of 60 % (from a 300 mg capsule). Following an oral dose of gabapentin maximal plasma concentrations occur within 2-3 hours. 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. The pharmacokinetics is non-linear with a decreased bioavailability with increasing dose leading to less than proportional increase in AUC with increasing dose. In the pharmacokinetic studies involving normal volunteers, linear kinetics was however observed at doses up to 600mg q8h. The terminal half-life is 5-7 hours.

Study 0996-18
Methods
This was a single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing gabapentin 400 mg capsules with Neurontin 400 mg hard 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 log-transformed data for AUC_{0-t} and C_{max}. The study was conducted between 17th April and 27th April 2019.

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=44.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**32985 ± 11434**	**3188± 1074**	**3.000 (0.667-6.000)**
Reference	**33861± 10419**	**3193±793**	**3.500 (1.333-6.000)**
***Ratio (90% CI)**	**95.0 (88.73 - 101.67)**	**96.0 (88.91 - 103.58)**	**-**
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%.

A biowaiver was sought for the 100 mg strength applied for.

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, gabapentin 400 mg capsules are considered bioequivalent with Neurontin 400 mg hard capsules.

Absence of studies with the strength applied for, 100 mg, is acceptable, as all conditions for biowaiver for additional strength(s), as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of gabapentin can be considered linear in the range relevant for strength biowaiver (100 to 400 mg).

The submitted BE study (study 0996-18) is not the one referred to in the application for the higher strengths (Gap-03/06) but a new study, performed in 2019 (ie after approval of the previous strengths). The applicant has clarified that a new BE study was performed since study Gap-03/06 was performed in 2006 and did not fulfil all current GL requirements (ISR not performed). The applicant has updated the clinical overview and module 2.7.1 in order to include information on both studies.

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 Gabapentin Orion 100 mg Capsules.

Safety specification

There are no safety concerns in the suggested RMP Part II: Module SVIII.

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.

Summary of the RMP
The submitted Risk Management Plan, version 1.1 signed 27-05-2021 is considered acceptable.
The RMPs for Gabapentin Orion 100 mg caps and the currently approved caps MAs (SE/H/2083/001-002/DC) will be combined to one common RMP document after the 100 mg caps MAA procedure via appropriate variation procedure, se section IV of this report for more information.

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 MPA;
- 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 Gabapentin Pfizer (DE/H/2852/001) concerning content and Buranagel (DE/H/5281/001/DC) concerning layout.

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

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Gabapentin Orion, is found adequate. There are no objections to approval of Gabapentin Orion, 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
The Applicant has submitted a signed commitment letter stating that a post approval variation to combine the RMP:s will be submitted within three months after End of Procedure.

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

N/A

VII. APPROVAL

Gabapentin Orion, 100 mg, Capsule, hard was approved in the national procedure on 2022-04-29

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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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