LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Gabapentin Orion
(gabapentin)

SE/H/2083/01-02/E/01

This module reflects the scientific discussion for the approval of Gabapentin Orion. The Public Assessment Report was written in 05-2018 by the previous RMS DK after initial procedure DK/H/2722/001-002/DC and is attached at the end of this document. RMS transfer from DK to SE was completed 2020-05-06. For information on changes after this date please refer to the module 'Update'.

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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)

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Gabapentin Orion hard capsules 300 mg and 400 mg, from Orion Corporation.

The product is indicated for:

> Epilepsy
> Gabapentin Orion is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above.
>
> Gabapentin Orion is indicated 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
> Gabapentin Orion 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Neurontin (MA numbers in the reference member state (RMS) state: 32061 and 32062) which has been registered in RMS by Pfizer ApS since 2001.

The concerned member state (CMS) involved in this procedure was Finland and Sweden.

The applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Neurontin hard capsules 400 mg, registered in United Kingdom. This generic product can be used instead of its reference product.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Gabapentin Orion hard capsules 300 mg and 400 mg contains as active substance 300 mg and 400 mg of gabapentin, respectively.

Gabapentin Orion hard capsules 300 mg have a yellow cap and yellow body. They are imprinted with ‘D’ and ‘03’, and the length of the capsules is 20 mm.
Gabapentin Orion hard capsules 400 mg have an orange cap and orange body. They are imprinted with ‘D’ and ‘04’, and the length of the capsules is 22 mm.

Gabapentin Orion hard capsules 300 mg are packed in PVC/PVdC-Aluminium blisters in pack sizes of 10, 20, 30, 50, 60, 90, 100 and 200 capsules, and in HDPE containers with PP closure and silica gel desiccant in pack sizes of 100, 200 and 1,000 capsules.

Gabapentin Orion hard capsules 400 mg are packed in PVC/PVdC-Aluminium blisters in pack sizes of 10, 20, 30, 50, 60, 90, 100, 200 and 300 capsules, and in HDPE containers with PP closure and silica gel desiccant in pack sizes of 100, 200, 300 and 500 capsules.
Not all pack-sizes may be marketed.

The excipients are:

Capsule content
Maize starch
Talc

Capsule shell
Gelatin
Titanium dioxide (E 171)
Sodium laurilsulfate
Iron oxide yellow (E 172)
Iron oxide red (E 172) (400 mg capsules only)

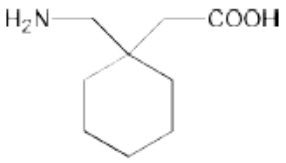
Printing Ink
Shellac
Iron oxide black (E 172).

Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, gabapentin, is described in the European Pharmacopoeia. It is a white or almost white, crystalline powder. It is sparingly soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in methylene chloride. It dissolves in dilute acids and dilute solutions of alkali hydroxides. It is not optically active. It shows polymorphism and form II is manufactured by the active substance manufacturers.

Structure of gabapentin:



The active substance is sourced from two external suppliers. The CEP procedure is used for the active substance. The re-test periods are according to the CEPs.

Information relating to the finished product manufacturer's control of active substance has been presented. The specification complies with the CEPs/Ph. Eur. monograph and additional tests for benzene, particle size, bulk density and microbial contamination. The IR identification test

is shown suitable for controlling the polymorphic form (form-II). Certificates of analysis issued by the finished product manufacturer have been provided.

II.3 Medicinal Product

The product is formulated as a hard capsule for oral dosing in two strengths, 300 mg and 400 mg gabapentin.

The development of the product has been adequately described, the choice of excipients is justified and their functions explained. All excipient are of Ph. Eur. quality with exception of the iron oxides (yellow, red and black) for which the E-number has been specified.

The manufacturing process has been described in sufficient detail and satisfactory validation results have been provided on production scale level. Stability studies have been performed on the lubricated blend and filled capsules in bulk. The results justify the proposed holding times/bulk storage.

The product specifications cover appropriate parameters for hard capsules and is acceptable. The limit for the impurity gabapentin lactam of 0.4% exceeds the qualification threshold of 0.15%, but sufficient documentation for its qualification has been presented. An acceptable risk assessment on elemental impurities have also been provided. Details and validations of all relevant analytical procedures are presented.

Batch analysis has been performed on several batches of each strength. The batch analysis results show that the finished product meets the proposed specifications.

Stability studies have been conducted in accordance with the ICH stability guidelines. Up to 36 months long-term, 12 months intermediate and 6 months accelerated data is presented together with photostability data and in-use stability data for the HDPE container. The proposed shelf-life of 3 years can be accepted. The storage condition should be “store below 30°C”. Setting an in-use shelf-life is considered unnecessary, as the product appears unaffected by opening the container.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Gabapentin Orion, 300 mg and 400 mg, hard capsules are of sufficient quality in view of the present European regulatory requirements.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of gabapentin are well known. As gabapentin is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 30 publications up to year 2006. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. The overview has been revised in August, 2015 and it is assumed that the presented non-clinical overview is up to date with regard to gabapentin’s pre-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Gabapentin Orion hard capsules 300 mg and 400 mg are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

From a non-clincial point of view the benefit/risk ratio of the product is considered positive.

IV. CLINICAL ASPECTS

IV.1 Introduction

Gabapentin is a well-known active substance with established efficacy and tolerability. As gabapentin is a widely used, well-known active substance, the applicant has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 33 publications up to 2012. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Gabapentin Orion 40 mg hard capsules is compared with the pharmacokinetic profile of the reference product Neurontin 400 mg hard capsules by Parke Davis sourced from the UK market.

Biowaiver

The bioequivalence study was carried out on Gabapentin Orion 400 mg hard capsules. Based on the study results for Gabapentin Orion 400 mg hard capsules, a biowaiver is requested for Gabapentin Orion 300 mg hard capsules. The conditions of the strength biowaiver are considered fulfilled.

Bioequivalence study

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted on 36 healthy Asian male subjects (33 completed) under fasting conditions with a wash out period of 07 days between the two administrations. 400 mg was administered in each period.

Calculation of the pharmacokinetic variables has been performed. The primary variables were AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}.

The test product is considered as bioequivalent to the reference product if the 90% CI (Confidence Intervals) of the geometric mean ratios of Ln-transformed parameters from Gabapentin for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ should fall within the acceptance range of 80.00-125.00%

The results are presented in the table below:

Treatment	AUC_{0-t} µg/ml/h	$AUC_{0-\infty}$ µg/ml/h	C_{max} µg/ml	t_{max} h	$T_{1/2}$ h
Test	31902.06 (±10223.632)	32684.94 (±10296.567)	3099.40 (±932.207)	3.00 (1.33-8.00)	6.08
Reference	33407.04 (±13671.960)	34231.39 (±13815.283)	3277.86 (±1249.424)	3.25 (1.33-5.00)	6.12
***Ratio (90% CI)**	97.43 (91.68 - 103.55)	97.40 (91.87-103.27)	96.25 (89.47 - 103.54)		
CV (%)	14.66		17.64		

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} **Time until Cmax is reached**

**ln-transformed values*

For the primary parameters, the 90% confidence interval for the ratio of the test and reference products were within the acceptance interval of 80.00-125.00%.

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Gabapentin Orion hard capsules 400 mg is considered bioequivalent with Neurontin hard capsules 400 mg with regard to rate and extent of absorption under fasting conditions.

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

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 Gabapentin Orion.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	• Abuse and dependence • Concomitant use with opioids • Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
Important potential risks	• Suicidality • Pancreatitis
Missing information	• Long term effects on learning, in growth, endocrine function, puberty and childbearing potential in children • Use during pregnancy and lactation

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

IV.4 Discussion on the clinical aspects

No new studies have been performed. This is considered acceptable as abridged applications, like this procedure, avoid the need for repetitive tests on animals and humans. Reference to the safety and efficacy of the reference product is acceptable as bioequivalence with the reference product has been demonstrated.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Neurontin, DE/H/0899/002-003/MR. The format and lay-out are bridged to the Orion Corporation house style leaflet which has been user tested in several procedures. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gabapentin Orion 300 mg and 400 mg hard capsules have a proven chemical-pharmaceutical quality and is a generic form of Neurontin. 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.

The MAH presented a risk management plan summarising the safety concerns. There are no additional pharmacovigilance or risk minimisation measures.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gabapentin Orion with the reference product, and have therefore granted a marketing authorisation. The decentralised

procedure was finalised on 29-11-2017. Gabapentin Orion was authorised in Denmark on 03-01-2018.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

The date for the first renewal will be: 29-11-2022.

There were no post-approval commitments made during the procedure.