COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Gabapentine 50 mg/ml Focus, oral solution

(loperamide hydrochloride)

NL License RVG: 125650

Date: 21 December 2020

This module reflects the scientific discussion for the approval of Gabapentine 50 mg/ml Focus, oral solution. The procedure was finalised on 5 June 2020. 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
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
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Gabapentine 50 mg/ml Focus, oral solution, from Focus Care Pharmaceuticals B.V.

The product is indicated:
Epilepsy

- as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged 6 years and above.
- 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

- 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 national procedure concerns a generic application claiming essential similarity with the innovator product Neurontin 300 mg hard capsules which has been registered in the Netherlands by Pfizer B.V. since 10 November 1999 through mutual recognition procedure (DE/H/0899/002).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Gabapentine Focus is a clear, colourless oral solution with a characteristic orange scent. Each ml solution contains 50 mg gabapentin.

The oral solution is packaged in a 150 ml, Type III, amber, glass bottle with a child-resistant and tamper-evident screw cap. Each pack contains one bottle, one 10 ml dosing syringe and one adapter.

The excipients are: purified water, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, propylene glycol, acesulfame potassium, carmellose sodium and orange flavour (benzyl alcohol, propylene glycol (E 1520), ethyl alcohol, triacetin (E 1518), ethyl butyrate, orange oil)

II.2 Drug Substance

The active substance is gabapentin, an established active substance described in the European British Pharmacopoeia (Ph.Eur.). It is a white to almost white crystalline powder and sparingly soluble in water. Gabapentin shows polymorphism and polymorphic form II is used.

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 European Pharmacopoeia.

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 in line with the CEP and considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 24 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 explained. Compatibility, stability and holding time studies were adequately performed.

Manufacturing process
The solution is manufactured by the dissolution of the components in purified water. The resulting final solution is filtered, filled in a bottle and capped. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot scaled batches. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches is preformed post authorisation.

Control of excipients
The excipients comply with the Ph.Eur, except for the orange flavour. The 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 (active substance and preservatives), pH, fill volume, assay (active substance and preservatives), related substances, uniformity of mass and microbiological examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life limits are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from two pilot scaled batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for two pilot scaled batches stored at 5°C (36 months) and 25°C/60%RH (6 months). The batches were stored in accordance with applicable European guidelines. The proposed shelf-life of 36 months and storage condition 'Store in a refrigerator. After first opening do not store above 25°C' can be granted. Stability data have been provided demonstrating that the product remains stable for one month following first opening of the container.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Gabapentin Focus 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 Gabapentin Focus is 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Neurontin which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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 MEB agrees 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 overview justifies why there is no need to generate additional clinical data. Therefore, the MEB agrees that no further clinical studies are required.

For this generic application, the MAH has submitted 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 50 mg/ml Focus, oral solution (Focus Care Pharmaceuticals B.V., NL) is compared with the pharmacokinetic profile of the reference product Neurontin 300 mg hard capsules (Pfizer Limited, UK).

The choice of the reference product in the bioequivalence studies is accepted. Gabapentin has non-linear pharmacokinetics at dosages of 400 mg and higher. Neurontin is available as 100 mg, 300 mg and 400 mg hard capsules and as 600 mg and 800 mg film-coated tablets. The EMA guideline states that for drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should be established both at the highest strength and at the lowest strength (or a strength in the linear range). If the non-linearity is not caused by limited solubility, but is due to saturation of uptake transporters and provided that conditions

a) the pharmaceutical products are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the compositions of the strengths are quantitatively proportional, and
d) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing

are fulfilled and the test and reference products do not contain any excipients that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength or a strength in the linear range.
Gabapentin Focus is an oral solution at a concentration of 50 mg gabapentin per ml. Thus, the amount dosed (900 to 3600 mg per day divided into 2 or 3 dosages) depends on the amount solution dosed. Therefore, the product fulfils point a to c.
The pharmacokinetics is dose proportional between 100 and 400 mg and less then dose proportional at a dose of >400 mg due to uptake transporter saturation (L-amino acid transport system). The use of the 300 mg strengths in the bioequivalence study is therefore in principle acceptable.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 19-44 years. Each subject received orally a single dose (300 mg) of one of the 2 gabapentin formulations. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33,2.67, 3, 3.33, 3.67, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable. The washout period of 7 days is sufficient (more than five times the terminal half-life of gabapentin).

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

One subject was voluntary withdrawn before dosing in Period I and one subject did not report for check-in at period II. Therefore, 26 subjects completed the study and were eligible for pharmacokinetic analysis.

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

Treatment N=26	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	28829	29115	2590	3.0 (1.67-5.0)
Reference	30085	30408	2841	3.5 (1.33-5.0)
***Ratio (90% CI)**	0.95 (0.88-1.03)	0.85 (0.88-1.02)	0.91 (0.84-0.99)	--

$AUC_{0-\infty}$ 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 hours				
C_{max} maximum plasma concentration				
t_{max} time for maximum concentration				

**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 50 mg/ml Focus is considered bioequivalent with Neurontin 300 mg hard capsules.

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 Focus.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Hypersensitivity reactions including drug rash with eosinophilia and systemic symptoms (DRESS) - Abuse and dependence - Dizziness, somnolence, loss of consciousness, syncope and potential for accidental injury - Visual disturbance (e.g. diplopia, amblyopia)
Important potential risks	- Suicidal ideation/behaviour - Pancreatic cancer
Missing information	- Long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children - Use in pregnant and lactating women

The MEB agrees 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. No new clinical studies were conducted. 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 reference product Neurontin. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gabapentine 50 mg/ml Focus, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Neurontin 300 mg hard 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.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Gabapentine 50 mg/ml Focus, oral solution was authorised in the Netherlands on 5 June 2020.

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