Public Assessment Report

Scientific discussion

Gabapentine Glenmark 100 mg, 300 mg and 400 mg hard capsules

(gabapentin)

NL/H/3976/001-003/DC

Date: 22 March 2018

This module reflects the scientific discussion for the approval of Gabapentine Glenmark 100 mg, 300 mg and 400 mg hard capsules. The procedure was finalised on 22 December 2017. 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 Member States have granted a marketing authorisation for Gabapentine Glenmark 100 mg, 300 mg and 400 mg hard capsules from Glenmark Pharmaceuticals Europe Limited.

The product is indicated for:
Epilepsy
Gabapentin 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 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 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 innovator products Neurontin 100 mg, 300 mg and 400 mg capsules (NL License RVG 22481, 22482 and 22483) which have been registered in The Netherlands by Pfizer B.V. since 10 November 1999 through mutual recognition procedure DE/H/0899/001.

The concerned member states (CMS) involved in this procedure were Germany, Denmark (only the 300 mg and 400 mg strengths), Spain, Romania and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Gabapentine Glenmark 100 mg is a size ‘3’ hard gelatin capsule with a white opaque cap and a white opaque Body, imprinted with Glenmark logo “G” on the cap and ‘456’ on the body with black ink, filled with a white to off-white powder. Each hard capsule contains as active substance 100 mg of gabapentin.

Gabapentine Glenmark 300 mg is a size ‘1’ hard gelatin capsule with a light yellow to yellow cap and a light yellow to yellow body, imprinted with Glenmark logo “G” on the cap and ‘457’ on the body with black ink, filled with a white to off-white powder. Each hard capsule contains as active substance 300 mg of gabapentin.

Gabapentine Glenmark 400 mg is a size ‘0’ hard gelatin capsule with a light orange to orange cap and a light orange to orange body, imprinted with Glenmark logo “G” on the cap and ‘458’ on the body with black ink, filled with a white to off-white powder. Each capsule contains as active substance 400 mg of gabapentin.

The hard capsules are packed in clear PVC/PVdC- Alu blisters and white opaque HDPE bottles.

The excipients are:
Capsule content - lactose monohydrate, maize starch and talc
Capsule shell – gelatin, titanium dioxide (E171), sodium lauryl sulphate, yellow iron oxide (E172) (only 300 mg and 400 mg strengths) and red iron oxide (E172) (only 400 mg strength)
Printing ink – shellac and black iron oxide (E172)

II.2 Drug Substance

The active substance is gabapentin, an established active substance described in the European Pharmacopoeia (Ph.Eur.) and the United States Pharmacopeia (USP). It is a white or almost white, crystalline powder. Gabapentin is sparingly soluble in water, slightly soluble in ethanol (96%), practically insoluble in methylene chloride. Polymorphic form II is used for the drug product.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and includes additional tests and limits as stated on the CEP. In addition, the applicant has adopted additional limits for residual solvent toluene, particle size, polymorphic form, microbiogical quality, and bulk density. Batch analytical data demonstrating compliance with this specification have been provided for an adequate amount of batches.

Stability of drug substance
The active substance is stable for 3 years 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. The MAH has clearly identified the test and reference product used in the bioequivalence study. The test and reference products were used in comparative dissolution study in support of the bioequivalence study. The study was performed with the 400 mg strengths. The results show similar and fast dissolution profiles for both products and support similarity. In addition, the applicant has presented comparative dissolution data to support the biowaiver for the other capsule strengths. The data presented shows that the results are comparable in all media tested.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines and includes sifting, pre-lubrication, lubrication, capsule filling and packaging. Process validation data on the product have been presented for three batches per strength in accordance with the relevant European guidelines.

Control of excipients
All excipients, except the excipients for the capsule shell, comply with the monograph of the Ph. Eur. The hard gelatine capsule shells comply with In-house specifications. These 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, average fill weight, dissolution, uniformity of dosage units, related compounds, assay, water content and microbial enumeration tests and tests for specified microorganisms. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches per strength stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months), in accordance with applicable European guidelines. One batch per capsule strength, packed in blister, was included in the photostability study. No significant change or trends have been observed. Hence, no restriction in order to protect from light is considered necessary. On basis of the data submitted, a shelf life was granted of 24 months, without additional storage conditions is considered acceptable. Stability data have been provided demonstrating that the product remains stable for 50 days following first opening of the container.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
The excipient lactose monohydrate is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Gabapentine Glenmark 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 Gabapentine Glenmark 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 member states agreed 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a 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 Glenmark (Glenmark Pharmaceuticals Europe Limited, UK) is compared with the pharmacokinetic profile of the reference product Neurontin 400 mg hard capsules (Pfizer B.V., NL).

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A bio-waiver for the lower 2 strengths of 100 mg and 300 mg on the basis of the bioequivalence study conducted on the 400 mg strength has been granted since the following conditions are fulfilled:

- Gabapentin shows linear PK up to the 400 mg dose
- All the strengths are manufactured by the same manufacturing process
- The qualitative composition of the strengths is the same
- The proposed formulation of 100 mg, 300 mg and 400 mg are dose proportional
- The dissolution profiles of Glenmark's 400 mg (bio strength, which has been shown to be bio-equivalent to Neurontin 400 mg Hard Capsules) and 100 mg and 300 mg are comparable at different pH values

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy female subjects, aged 18-41 years. Each subject received a single dose (400 mg) of one of the 2 gabapentin formulations. The hard capsule was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 7.00, 8.00, 10.00, 12.00, 18.00, 24.00, 30.00, 36.00 and 48.00 hours after administration of the products.

The design of the study is acceptable. The sampling times and the wash-out period are considered sufficiently long considering the elimination half life of gabapentin of 5-7 hrs. One single dose study with the highest strength is considered acceptable to investigate bioequivalence for immediate release product with linear pharmacokinetics. In addition, fasting conditions are also considered appropriate since gabapentin can be taken regardless of the food intake.

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

All 32 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=32	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	28878 ± 8543	29282 ± 8554	2763 ± 676	3.5 (0.75 – 6.00)
Reference	30900 ± 8374	31312 ± 8396	2857 ± 742	3.5 (1.00 – 6.00)
***Ratio (90% CI)**	0.93 (0.86 – 1.01)	0.93 (0.86 – 1.01)	0.97 (0.90 – 1.05)	--

$AUC_{0-\infty}$ 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 studies:
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 Glenmark is considered bioequivalent with Neurontin.

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 Glenmark.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Abuse and dependence - Concomitant use with opioids - Drug rash with eosinophilia and systemic symptoms (DRESS) - Respiratory depression
Important potential risks	- Pancreatitis - Suicidality
Missing information	- Use during pregnancy and lactation - Long term effects on learning, in growth, endocrine function, puberty and childbearing potential in children

The member states agreed 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

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Gabapentine Glenmark 100 mg, 300 mg and 400 mg hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Neurontin 100, 300 and 400 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.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Gabapentine Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 December 2017.

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
NL/H/3976/IB/001/G	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack; - Change within the range of the currently approved pack sizes - Change outside the range of the currently approved pack sizes	-	03-05-2018	Approved	-