

Public Assessment Report

Gabapentin M&A Pharmachem 400 mg Capsules
Gabapentin M&A Pharmachem 300 mg Capsules
Gabapentin M&A Pharmachem 100 mg Capsules

(Gabapentin)

PL 04077/0210

PL 04077/0211

PL 04077/0212

M & A Pharmachem Ltd

LAY SUMMARY

Gabapentin M&A Pharmachem 400 mg Capsules

Gabapentin M&A Pharmachem 300 mg Capsules

Gabapentin M&A Pharmachem 100 mg Capsules

(Gabapentin)

This is a summary of the public assessment report (PAR) for applications for Gabapentin M&A Pharmachem 400 mg, 300 mg and 100 mg Capsules (PL 04077/0210-0212). These products will be referred to as Gabapentin Capsules in the remainder of the report.

This summary explains how Gabapentin Capsules were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use Gabapentin Capsules.

For practical information about Gabapentin Capsules, patients should read the package leaflets or contact their doctor or pharmacist.

What are Gabapentin Capsules and what are they used for?

Gabapentin Capsules are 'generic medicines'. This means that Gabapentin Capsules are similar to 'reference medicines' already authorised in the European Union (EU) called Neurontin 100 mg, 300 mg and 400 mg Hard Capsules (Pfizer Limited; PL 00057/0853, 0536 and 0537).

Gabapentin Capsules are used to:

- Treat epilepsy. Gabapentin can be used in addition to current treatment when epilepsy has not been fully controlled in children over 6 years and adults. It can also be used on its own to treat children over 12 years and adults.
- Relieve peripheral neuropathic pain (long lasting pain caused by damage to nerves) caused by diseases such as diabetes or shingles.

How are Gabapentin Capsules used?

Gabapentin Capsules are taken by mouth. A single capsule should be swallowed with plenty of water and can be taken with or without food.

Dose for neuropathic pain:

- Adults (over 18 years of age):
The dose is usually built up gradually, starting at 300 mg on the first day, followed by 600 mg on the second day and 900 mg on the third day. The dose may then be increased to a maximum of 3600 mg each day, given in 3 divided doses – in the morning, at midday and in the evening.
- The dose for the elderly and those with kidney problems may be reduced.

Dose for epilepsy:

- **Adults and children over 12 years:**
The starting dose is usually between 300 mg and 900 mg each day. The dose is then built up gradually each day in 3 divided doses – in the

morning, at midday and in the evening. The maximum daily dose is 3600 mg.

- **Children 6-12 years of age:**
The dose to be given to a child will be decided by a doctor and is calculated using the child's weight. The treatment is started using a low dose, which is gradually increased over a period of approximately 3 days. It is usually given in 3 divided doses each day, by taking the capsules in the morning, at midday and in the evening.
- The dose for the elderly and those with kidney problems may be reduced.

Gabapentin Capsules should not be given to children under 6 years.

These medicinal products can only be obtained on prescription from a doctor.

For further information on how Gabapentin Capsules are used, refer to the Summaries of Product Characteristics or package leaflets available on the MHRA website.

How do Gabapentin Capsules work?

Gabapentin Capsules contain the active substance, gabapentin, which belongs to a group of medicines known as anti-epileptics. These medicinal products prevent seizure from happening.

How have Gabapentin Capsules been studied?

Because Gabapentin Capsules are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the European Union (EU) reference product, Neurontin[®] 100 mg, 300 mg and 400 mg, rapid release capsules (Parke-Davis Ltd, Spain), which is equivalent to Neurontin 100 mg, 300 mg and 400 mg Hard Capsules in the UK (Pfizer Limited). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Gabapentin Capsules?

As Gabapentin Capsules are generic medicines that are bioequivalent to Neurontin[®] 100 mg, 300 mg and 400 mg, rapid release capsules (Parke-Davis Ltd, Spain), their benefits and risks are taken as being the same as those for Neurontin[®] 100 mg, 300 mg and 400 mg, rapid release capsules (Parke-Davis Ltd, Spain).

Why are Gabapentin Capsules approved?

It was concluded that, in accordance with EU requirements, Gabapentin Capsules have been shown to have comparable quality and to be bioequivalent to Neurontin[®] 100 mg, 300 mg and 400 mg, rapid release capsules (Parke-Davis Ltd, Spain). Therefore, the view was that, as for Neurontin[®] 100 mg, 300 mg and 400 mg, rapid release capsules (Parke-Davis Ltd, Spain) the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Gabapentin Capsules?

A satisfactory pharmacovigilance system has been provided to ensure that Gabapentin Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Gabapentin Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Gabapentin Capsules

Marketing Authorisations were granted in the UK on 19th February 2007.

For more information about taking Gabapentin Capsules, read the Patient Information Leaflet (PIL), or contact your doctor or pharmacist.

The full PAR for Gabapentin Capsules follows this summary.

This summary was last updated in April 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products Gabapentin 400 mg Capsules (PL 04077/0210), Gabapentin 300 mg Capsules (PL 04077/0211) and Gabapentin 100 mg Capsules (PL 04077/0212) on 19th February 2007. The products are prescription only medicines (POM).

The applications were submitted as abridged applications according to Article 10.1 of Directive 2001/83/EC, as amended. The applicant has cross-referred to Neurontin 100 mg, 300 mg and 400 mg Capsules, originally authorised to Parke Davis & Company Limited (PL 00018/0202-0204) on 5th February 1993. These reference licenses underwent change of ownership procedures to Warner Lambert's (UK) Limited (PL 00019/0172-0174) on 31st of December 1997 and then to the current Marketing Authorisation Holder, Pfizer Limited (PL 00057/0853, 0536 and 0537), on 1st November 2005. The reference product used in bioequivalence study was Neurontin 400 mg capsules (S-5) from Spain.

Gabapentin is indicated for neuropathic pain and epilepsy. For use in neuropathic pain, in adults over 18 years of age, a starting dose of 300 mg once daily to a maximum of 3600 mg daily in 3 divided doses is proposed. For use in epilepsy, in adults and children over 12 years of age, a starting dose of 300 mg once daily to a maximum of 3600 mg daily in 3 divided doses is proposed. The maximum time period should not exceed 12 hours, in a three times daily schedule. Gabapentin may be given orally with or without food.

II QUALITY ASPECTS

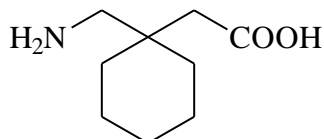
DRUG SUBSTANCE

General Information

Nomenclature

rINN/USAN/BAN: Gabapentin
Chemical name: 1-(aminomethyl)cyclohexaneacetic acid

Chemical structure:



Molecular Formula: $C_{19}H_{17}NO_2$

Molecular weight: 171.24 g/mol

Physical form: White or almost white powder.

Gabapentin is freely soluble in water, 0.1N HCl, 0.1N NaOH and glacial acetic acid.

A European drug master file (DMF) together with a satisfactory letter of access was provided for the active substance.

A satisfactory drug substance specification was provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Gabapentin is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analyses data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated supporting a retest period of 24 months, store at less than 25°C.

DRUG PRODUCT

Other Ingredients

Capsule contents: lactose monohydrate, maize starch, talc.

Capsule shells: gelatin, titanium dioxide, sunset yellow (E110).

Printing ink: shellac glaze, black iron oxide, soya lecithin, antifoam DC150

Talc, maize starch and lactose monohydrate all comply and are tested to Ph.Eur monograph requirements. The qualitative and quantitative compositions of hard gelatin shells are also given. Ingredients used comply with suitable Ph.Eur/NF grade. The coloring agent black iron oxide complies with EEC purity requirements.

Specifications given for capsules are satisfactory. Typical C of A's for excipients and hard gelatin capsules are provided and are satisfactory. Lactose grade used is Granulac 200. The specification provided includes particle size controls and is satisfactory.

Lactose and gelatin are the only materials of animal/human origin. Satisfactory declarations are provided. The milk used is sourced from healthy animals under the same conditions as milk collected for human consumption and calf rennet used for the production of the raw material whey is in accordance with the Public statement EMEA/CPMP/571/02 of Feb 27 02. Only gelatin with EDQM Certificates of Suitability is used.

Dissolution and impurity profiles

Dissolution and impurity profiles for all strengths of drug product were found to be similar to those for the reference products.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches of each strength. The results are satisfactory.

Finished product specifications

The finished product specifications are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. The test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The capsules are packaged in polyvinylchloride (PVC)-polyvinylidenechloride (PVdC)/aluminium blister strips in packs of 90 or 100 capsules. Specifications and routine tests are provided and are satisfactory. Typical Certificate of Analysis from the dosage form manufacturer and supplier are provided for PVC/PVDC and aluminium foil. The supplier of the PVC/PVDC film has declared that the material complies with the current European regulations concerning packaging materials in contact with food and drugs. The lacquer used complies with relevant guidelines for contact with food materials.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 3 years has been set, which is satisfactory. Storage conditions are "Do not store above 25°C", "Store in the original packaging".

ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

The grant of Marketing Authorisations is recommended.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of gabapentin are well-known. Therefore, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

There are no objections to the approval of Gabapentin Capsules from a non-clinical point of view.

IV CLINICAL ASPECTS CLINICAL PHARMACOLOGY

Gabapentin is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) but its mechanism of action is different from that of several drugs that interact with GABA synapses. The identification and function of the gabapentin binding site remains to be elucidated and the relevance of its various actions to the anticonvulsant effect to be established. Analgesic activity has been shown in animal models of inflammatory and neuropathic pain.

Bioequivalence

The applicant has submitted an open-label, single dose, randomised, two-period cross-over study which compared the test product, gabapentin 400 mg rapid release capsules (M & A Pharmachen Ltd) with reference product, Neurontin[®] 400 mg rapid release capsules (Parke-Davis Ltd, Spain). The study was performed in 24 healthy subjects by Anapharm Inc., Quebec, Canada and consisted of two treatment phases of 36 hours each, separated by a washout period of 7 days.

The test product was compared to the reference product with respect to the pharmacokinetic variables C_{max} , $C_{max}/AUC(0-\infty)$, $t_{1/2,z}$, $AUC(0-t_{last})$ and $AUC(0-\infty)$ using an analysis of variance with sequence, subject (sequence), product and period effects after a logarithmic transformation of the data. Parametric point estimates and 90% confidence intervals for the 'test/reference' mean ratios of those variables were calculated and presented graphically. In addition, a non-parametric point estimate and 90% confidence interval for the 'test-reference' were calculated. T_{max} was analysed by the Wilcoxon's test. Bioequivalence of the test and reference products was assessed on the basis of the confidence intervals for the primary variables $AUC(0-\infty)$ and C_{max} in relation to the bioequivalence range of 80% to 125%.

The main pharmacokinetic findings, using Neurontin[®] 400 mg Capsules (Parke-Davis, Spain) as reference product, are summarised in the table 1 below.

Table 1. Summary of the main Pharmacokinetic Parameters (N=24)

Parameters	Test (Gabapentin (A)) Mean \pm SD CV (%)	Reference (Neurontin (B))	
		Mean \pm SD	CV (%)
$AUC_{(0-t)}$ (ng.h/mL)	38302.24 \pm 8280.23 21.62	38053.43 \pm 9787.89	25.72
$AUC_{(0-inf)}$ (ng.hr/ml)	39426.04 \pm 8334.00 21.14	39097.60 \pm 9930.54	25.40
C_{max} (ng/mL)	4202.01 \pm 1025.25 24.40	4404.49 \pm 1240.46	28.16
Residual area (%)	2.95 \pm 1.55 52.52	2.74 \pm 1.30	47.39
T_{max}^* (h)	2.75 \pm 0.75 -	2.63 \pm 1.31	-

K_{el}	(h⁻¹)	0.1239	+ 0.0153	12.36	0.1216	+ 0.0209	17.17
t_{1/2 el}	(h)	5.68	+ 0.74	13.08	5.86	+ 1.00	17.13

*For T_{max}, medians and IQR are presented instead of means and SD.

Gabapentin (A) vs Neurontin (B)

	AUC_(0-t)	AUC_(0-inf)	C_{max}
Ratio¹	101.48%	101.71%	96.07%
90% Geometric C.I.²	93.26% to 110.42%	93.52% to 110.62%	85.85% to 107.51%
Intra-Subject CV	17.17%	17.06%	22.99%

¹ Calculated using least-squares means according to the formula: $e^{(\text{Gabapentin (A)} - \text{Neurontin (B)}) \times 100}$.

² 90% Geometric Confidence Interval using In-transformed data

The results of the study show that the 90% Confidence Intervals for the log-transformed parameters AUC_(0-t) and AUC_(0-∞) for Gabapentin were all within the 80-125% acceptable range. These results therefore demonstrate that the test product, gabapentin 400 mg capsules marketed by M & A Pharmachen Ltd is bioequivalent to the reference product, Neurontin[®] 400 mg rapid release capsules (Parke-Davis Ltd, Spain).

The essentially linear pharmacokinetics of Gabapentin, particularly at this dose range, makes it likely that the lower-doses of Gabapentin formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

A total of 42 adverse events were reported – 23 following treatment A and 17 following treatment B. These included headache, dizziness, drowsiness, nausea, localised pain etc. All were of mild to moderate intensity and were assessed as probably or possibly related to study medication. No serious adverse event was reported.

Assessor's Comment

The study design, analytical methodology and statistical evaluation of the presented bioequivalent trial are in accordance with the recommendations of the relevant CPMP guidelines: 'Investigation of bioavailability and bioequivalence.' Therefore, the bioequivalence of the generic product with the referenced innovator product, marketed by Parke-Davis Ltd has been proven.

EFFICACY

No new efficacy data are presented for these applications and none are required. However the applicant has provided a critical and extensive review of clinical trials published in the literature regarding the efficacy and safety of Gabapentin in patients with neuropathic pain and epilepsy.

SAFETY

No new safety data are provided or needed. But the applicant has provided a brief safety review of Gabapentin. No new safety issues have been identified.

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory.

CONCLUSIONS

The applicant has demonstrated bioequivalence. The grant of Marketing Authorisations is recommended.

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, as amended. The language used for the purpose of user testing the package leaflet was English.

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 AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION***Quality***

The important quality characteristics of Gabapentin Capsules are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Non-Clinical

No new non-clinical data were submitted and none are required for applications of this type.

Clinical

Bioequivalence has been demonstrated between the applicant's Gabapentin 400 mg Capsules and Neurontin 400[®] mg capsules. The essentially linear pharmacokinetics of Gabapentin, particularly at this dose range, makes it likely that the lower-doses of Gabapentin formulations also are bioequivalent to the corresponding marketed brand formulations although bioequivalence has not been assessed explicitly.

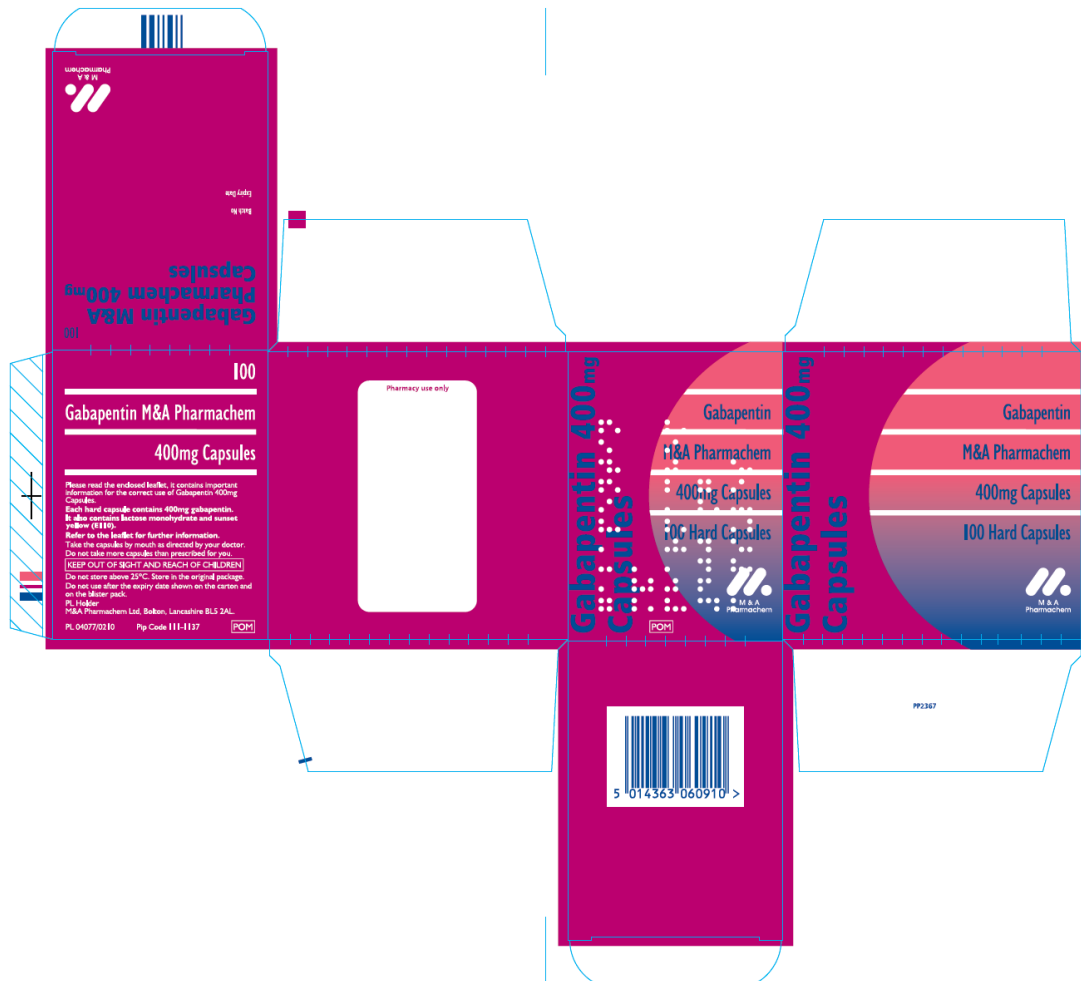
Benefit Risk Assessment

The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the innovator products are interchangeable. The benefit risk is, therefore, considered to be positive.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING









PP2368

Table of content of the PAR update

Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists some non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

Date submitted	Application type	Scope	Outcome
20 th February 2015	Type IB	To update the SmPC, sections 4.2, 4.4, 4.8 & 4.9 in line with the Brand Leader (Neurontin, Pfizer Limited) and in line with the quality review document (QRD) template. As a consequence, the patient information leaflet (PIL) has been updated.	Approved on 6 th March 2015

Annex 1

Reference: PL 04077/0210-0027; PL 04077/0211-0027; PL 04077/0212-0026

Product: Gabapentin M&A Pharmachem 400, 300 and 100 mg Capsules

MAH: M&A Pharmachem Ltd

Active Ingredient: Gabapentin

Reason:

To update the SmPC, sections 4.2, 4.4, 4.8 & 4.9 in line with the Brand Leader (Neurontin, Pfizer Limited) and in line with the quality review document (QRD) template. As a consequence, the patient information leaflet (PIL) has been updated.

Supporting evidence

The applicant has submitted updated sections of the SmPCs and the leaflet.

Evaluation

The amended sections of the SmPCs and the leaflet mock-up are satisfactory.

Conclusion

The variation was approved on 6th March 2015 and the updated SmPC fragments and the PIL have been incorporated into these Marketing Authorisations. The proposed changes are acceptable.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) - Updated

Following approval of the variation on 6th March 2015 the SmPCs were updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.

PATIENT INFORMATION LEAFLET (PIL) - Updated

Following approval of the variation on 6th March 2015 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.