GABAPENTIN 100 MG CAPSULES
GABAPENTIN 300 MG CAPSULES
GABAPENTIN 400 MG CAPSULES
PL 39891/0001-3
UKPAR

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GABAPENTIN 300 MG CAPSULES
GABAPENTIN 400 MG CAPSULES
PL 39891/0001-3

LAY SUMMARY

The MHRA granted Double-e Pharma Limited Marketing Authorisations (licences) for the medicinal products Gabapentin 100 mg, 300 mg and 400 mg capsules (PL 39891/0001-3) on 07 August 2013.

These prescription-only medicines (POM) are used to treat various forms of epilepsy (seizures that are initially limited to certain parts of the brain, whether the seizure spreads to other parts of the brain or not) and peripheral neuropathic pain (long lasting pain that primarily occurs in the legs and/or arms, caused by damage to the nerves). A variety of different diseases can cause peripheral neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, pins and needles and numbness.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Gabapentin 100 mg, 300 mg and 400 mg capsules outweigh the risks; hence Marketing Authorisations have been granted.
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**INTRODUCTION**

The MHRA granted Double-e Pharma Limited Marketing Authorisations (licences) for the medicinal products Gabapentin 100 mg, 300 mg and 400 mg capsules (PL 39891/0001-3) on 07 August 2013.

These are prescription-only medicines (POM) indicated for use in epilepsy in the treatment of partial seizures with and without secondary generalisation. Gabapentin can be used as adjunctive therapy in adults and children aged 6 years and above and as monotherapy in adults and adolescents aged 12 years and above. Gabapentin is also indicated for the treatment of peripheral neuropathic pain, such as painful diabetic neuropathy and post-herpetic neuralgia in adults.

The applications were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of the originator products Neurontin 100 mg, 300 mg and 400 mg Hard Capsules (PL 00018/0202-0204; Parke-Davis and Company Limited), which were initially granted licences in the UK on 05 February 1993. The current Marketing Authorisation Holder of the reference products is Pfizer Limited (PL 00057/0853, 0536-0537), following a change of ownership that was concluded on 01 November 2005.

These products contain the active ingredient gabapentin. Gabapentin is an orally active anticonvulsant agent that is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid). Despite its structural similarity to GABA, its mechanism of action is different from that of several other active substances that interact with GABA synapses, including valproate, barbiturates, benzodiazepines, GABA transaminase inhibitors, GABA uptake inhibitors, GABA agonists, and GABA prodrugs. The binding site for gabapentin has been identified as the alpha2-delta subunit of voltage-gated calcium channels. *In vitro* studies with radiolabelled gabapentin have characterised a novel peptide binding site in rat brain tissues that may be related to its anticonvulsant and analgesic properties.

With the exception of a bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that these applications were based on the products being generic medicinal products of originator products that have been licensed for over 10 years.

A bioequivalence study was performed, which compared the pharmacokinetics of the applicant’s Gabapentin 400 mg capsules with those of Neurontin 400 mg Hard Capsules (Parke-Davis and Company Ltd, UK). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP)

The MHRA has been assured that acceptable standards of GMP are in place for this product type at all sites responsible for the manufacture and assembly of these products.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Gabapentin
INN: Gabapentin
Chemical name: 1-(Aminomethyl)cyclohexaneacetic acid
Structure:

\[
\begin{align*}
&\text{CH}_2\text{COOH} \\
&\text{CH}_2\text{NH}_2
\end{align*}
\]

Molecular formula: C9H17NO2
Molecular weight: 171.24
Physical form: White or almost white crystalline powder
Solubility: Freely soluble in water and slightly soluble in ethanol.

An Active Substance Master File (ASMF) has been provided by each of the two proposed active substance manufacturers, covering the manufacture and control of the active substance gabapentin.

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.
**DRUG PRODUCT**

**Other ingredients**
Other ingredients consist of the pharmaceutical excipients, as follows:

- Capsule core: lactose monohydrate, maize starch and talc.
- Capsule shell: gelatin and titanium dioxide (E171). In addition, the 300 mg capsules contain yellow iron oxide (E172) and the 400 mg capsules contain red and yellow iron oxide (E172).
- Printing ink: shellac, black iron oxide (E172) and propylene glycol.

The printing ink complies with suitable in-house standards. The yellow and red iron oxides within the capsule shell comply with their respective United States Pharmacopeia – National Formulary monographs and are also in compliance with current European guidelines concerning the use of colourants. All other excipients used comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate and gelatin, none of the excipients used contain material of animal or human origin.

Suitable European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificates of Suitability have been provided by the suppliers of gelatin, showing that it is in compliance with current European regulations concerning the minimisation of transmission of TSE/BSE. The lactose monohydrate is produced from milk sourced from healthy animals, under the same conditions as milk collected for human consumption.

**Pharmaceutical development**

The objective of the pharmaceutical development programme was to produce safe, tolerable capsules that could be considered generic medicinal products of the originator products Neurontin 100 mg, 300 mg and 400 mg Hard Capsules (Pfizer Ltd). The applicant has provided a suitable product development rationale and data.

Comparative *in vitro* dissolution profiles have been provided for the applicant’s products versus the reference products.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished products.

Process validation has been carried out on production-scale batches of each finished. The results are satisfactory. The protocol for validation of the maximum capsule filling batch size, of each strength, has been provided and is satisfactory.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided that comply with the release specifications. Certificates of analysis have been provided for any working standards used.

**Container Closure System**

The finished products are packaged in polyvinylchloride/aluminium blisters in a pack size of 100 capsules.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided.
Stability
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 3 years, with the storage conditions of “Do not store above 30°C”.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPCs, PIL and labels are pharmaceutically acceptable.

A package leaflet for the products has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that the package leaflet contains.

MAA forms
The MAA forms are pharmaceutically satisfactory.

Expert report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

NON-CLINICAL ASSESSMENT

As the pharmacodynamic, pharmacokinetic and toxicological properties of gabapentin are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product’s pharmacology and toxicology.

A suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with products currently marketed, the environmental burden is not expected to increase. Thus, the justification for non-submission of an Environmental Risk Assessment is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
In support of these applications, the Marketing Authorisation Holder has submitted the following bioequivalence study:

A single-dose, randomised, open-label, two-treatment, two-period, crossover bioequivalence study to compare the pharmacokinetic profile of the applicant’s Gabapentin 400 mg capsules with Neurontin 400 mg Hard Capsules (Parke-Davis and Company Ltd) in healthy male and female subjects, under fasting conditions.

Study participants were given each treatment after an overnight fast of at least 10 hours. Blood samples were collected for the measurement of pharmacokinetic parameters pre-dose and up to 36 hours post dose. Each treatment regimen was separated by a 7-day washout period.

The main pharmacokinetic results are presented in the table below:

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>UNIT</th>
<th>NEURONTIN* (REFERENCE)</th>
<th>GABAPENTIN (TEST)</th>
<th>MEAN RATIO</th>
<th>90% CONFIDENCE INTERVAL</th>
<th>INTRA INDIVIDUAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>GEOMETRIC</td>
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<tr>
<td></td>
<td></td>
<td>MEAN</td>
<td>SD</td>
<td>Range</td>
<td>MEAN</td>
<td>SD</td>
</tr>
<tr>
<td>Cmax</td>
<td>(ng/ml)</td>
<td>3387</td>
<td>1.38</td>
<td>1244 - 5869</td>
<td>3993</td>
<td>1.34</td>
</tr>
<tr>
<td>Tmax</td>
<td>(h)</td>
<td>3.25</td>
<td>1.50 - 5.00</td>
<td>3.50</td>
<td>1.00 - 6.00</td>
<td>0.25</td>
</tr>
<tr>
<td>AUC(0 - 12)</td>
<td>(ng·h/ml)</td>
<td>32418</td>
<td>1.32</td>
<td>16526 - 55778</td>
<td>33468</td>
<td>1.32</td>
</tr>
<tr>
<td>AUC(0 - 24)</td>
<td>(ng·h/ml)</td>
<td>33029</td>
<td>1.32</td>
<td>17562 - 56363</td>
<td>34062</td>
<td>1.31</td>
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<tr>
<td>Cmax/AUC(0 - 24)</td>
<td>(h)</td>
<td>0.10</td>
<td>1.15</td>
<td>0.07 - 0.13</td>
<td>0.10</td>
<td>1.18</td>
</tr>
<tr>
<td>t½</td>
<td>(h)</td>
<td>6.57</td>
<td>1.21</td>
<td>4.22 - 8.89</td>
<td>6.51</td>
<td>1.18</td>
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<tr>
<td>MTmax</td>
<td>(h)</td>
<td>5.81</td>
<td>1.12</td>
<td>7.75 - 13.0</td>
<td>9.02</td>
<td>1.10</td>
</tr>
</tbody>
</table>

Compared with the reference product, the 90% confidence intervals for the test product are within 80.00-125.00% for AUC and Cmax. Gabapentin 400 mg capsules can, therefore, be considered to be bioequivalent with Neurontin 400 mg Hard Capsules.

As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 400 mg strength can be extrapolated to the 100 mg and 300 mg strength capsules.

Efficacy
No new data on efficacy have been submitted and none are required for this type of application.

Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted and none were required. No new or unexpected safety issues were raised by the bioequivalence data.
PHARMACOVIGILANCE SYSTEM
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for this product

EXPERT REPORT
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)
These are consistent with the SmPCs for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)
This is consistent with that for the reference products and is satisfactory.

LABELLING
This is satisfactory

APPLICATION FORMS (MAA)
These are satisfactory.

CONCLUSION
The grant of marketing authorisations is recommended for these applications.
OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

QUALITY
The important quality characteristics of Gabapentin 100 mg, 300 mg and 400 mg 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 product and Neurontin 400 mg Hard Capsules (Parke-Davis and Company Ltd, UK). As these products meet the bio-waiver criteria specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**), the results and conclusions of the bioequivalence study on the 400 mg strength can be extrapolated to the 100 mg and 300 mg capsules.

No new or unexpected safety concerns arose from these applications.

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products.

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant’s products and the reference products. Extensive clinical experience with gabapentin is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.
**STEPS TAKEN FOR ASSESSMENT**

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<thead>
<tr>
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<th>Description</th>
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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 14 July 2011.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 15 July 2011.</td>
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<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information on 27 January 2012, 15 June 2012, 11 September 2012, 11 January 2013 and 16 July 2013.</td>
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<td>5</td>
<td>The applications were approved on 07 August 2013.</td>
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## STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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<th>Scope</th>
<th>Outcome</th>
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GABAPENTIN 100 MG CAPSULES
GABAPENTIN 300 MG CAPSULES
GABAPENTIN 400 MG CAPSULES
PL 39891/0001-3
Summary of Product Characteristics and Patient Information Leaflet
The current approved versions of the SmPCs and PIL are available on the MHRA website.

Labelling

Carton for 100 mg strength:
Blister for 100 mg strength:
Carton for 300 mg strength:
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<th>Gabapentin 300 mg capsules</th>
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<td>Gabapentin 300 mg capsules</td>
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Blister for 300 mg strength:
Carton for 400 mg strength:
Blister for 400 mg strength: