Bundesinstitut für Arzneimittel
und Medizinprodukte

Decentralised Procedure

RMS Public Assessment Report

Gabapentin Genericon 600/800 mg Filmtabletten
Gabapentin Symphar 600/800 mg Filmtabletten
Gabaneuril 600/800 mg Filmtabletten
Neurolept 600/800 mg Filmtabletten

Gabapentin

DE/H/1260/001-002/DC
DE/H/1313/001-002/DC
DE/H/1314/001-002/DC
DE/H/1315/001-002/DC

Applicants: Genericon Pharma Gesellschaft m.b.H
SymPhar Sp.z.o.o.
M.R.Pharma GmbH
Pliva Kraków Zaklady Farmaceutyczne S.A.

Reference Member State	DE
Date of this report:	26.02.2009

TABLE OF CONTENTS

ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product in the RMS	Gabapentin Genericon 600/800 mg Filmtabletten
INN (or common name) of the active substance(s):	Gabapentin
Pharmaco-therapeutic group (ATC Code):	N03AX12
Pharmaceutical form(s) and strength(s):	film-coated tablets, 600 mg, 800 mg
Reference Number for the Decentralised Procedure	DE/H/1260/001-002/DC
Reference Member State:	DE
Member States concerned:	AT
Applicant (name and address)	Genericon Pharma Gesellschaft m.b.H. Hafnerstrasse 211 8054 Graz Austria
Names and addresses of manufacturers responsible for batch release in the EEA	Zambon S.p.A. Via Della Chimica, 9 36100 Vicenza Italy Genericon Pharma Gesellschaft m.b.H. Hafnerstrasse 211 8054 Graz Austria

Proposed name of the medicinal product in the RMS	Gabapentin Symphar 600/800 mg Filmtabletten
INN (or common name) of the active substance(s):	Gabapentin
Pharmaco-therapeutic group (ATC Code):	N03AX12
Pharmaceutical form(s) and strength(s):	film-coated tablets, 600 mg, 800 mg
Reference Number for the Decentralised Procedure	DE/H/1313/001-002/DC
Reference Member State:	DE
Member States concerned:	PL
Applicant (name and address)	SymPhar Sp.z.o.o. ul. Wloska 1 00-777 Warschau Poland
Names and addresses of manufacturers responsible for batch release in the EEA	Zambon S.p.A. Via Della Chimica, 9 36100 Vicenza Italy SymPhar Sp.z.o.o. ul. Wloska 1 00-777 Warschau Poland

Proposed name of the medicinal product in the RMS	Gabaneuril 600/800 mg Filmtabletten
INN (or common name) of the active substance(s):	Gabapentin
Pharmaco-therapeutic group (ATC Code):	N03AX12
Pharmaceutical form(s) and strength(s):	film-coated tablets, 600 mg, 800 mg
Reference Number for the Decentralised Procedure	DE/H/1314/001-002/DC
Reference Member State:	DE
Member States concerned:	ES, FR, NL
Applicant (name and address)	M.R.Pharma GmbH Waldstraße 30 22889 Tangstedt Gemany
Names and addresses of manufacturers responsible for batch release in the EEA	Zambon S.p.A. Via Della Chimica, 9 36100 Vicenza Italy

Proposed name of the medicinal product in the RMS	Neurolept 600/800 mg Filmtabletten
INN (or common name) of the active substance(s):	Gabapentin
Pharmaco-therapeutic group (ATC Code):	N03AX12
Pharmaceutical form(s) and strength(s):	film-coated tablets, 600 mg, 800 mg
Reference Number for the Decentralised Procedure	DE/H/1315/001-002/DC
Reference Member State:	DE
Member States concerned:	IE, PL, UK
Applicant (name and address)	Pliva Kraków Zaklady Farmaceutyczne S.A. ul. Mogilska 80 PL-31-546 KRAKÓW Poland
Names and addresses of manufacturers responsible for batch release in the EEA	Zambon S.p.A. Via Della Chimica, 9 36100 Vicenza Italy Pliva Kraków Zaklady Farmaceutyczne S.A. ul. Mogilska 80 PL-31-546 KRAKÓW Poland AWD.pharma GmbH & Co. KG Wasastr. 50 D-01445 Radebeul Germany

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the RMS considers that the applications for

- Gabapentin Genericon 600 and 800 mg
- Gabapentin Symphar 600 and 800 mg
- Gabaneuril 600 and 800 mg
- Neurolept 600 and 800 mg

in the following indications

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 (see section 5.1).
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.

is approvable.

II. EXECUTIVE SUMMARY

II.1 Problem statement

These applications concern a decentralised procedure for marketing authorisation for gabapentin film-coated tablets 600 and 800 mg under the trade names Gabapentin Genericon 600 and 800 mg, Gabapentin Symphar 600 and 800 mg, Gabaneuril 600 and 800 mg and Neurolept 600 and 800 mg, respectively. The reference products in Germany are Neurontin 600 and 800 mg, respectively.

The applications are based on establishing essential similarity (Directive 2001/83/EC Article 10(1) generic application) with Neurontin 600 mg and 800 mg film-coated tablets (MAH: Parke-Davis/Pfizer, DE).

II.2 About the product

Gabapentin is structurally related to the neurotransmitter GABA (gamma amino butyric acid), but its mechanism of action is different from that of several other active substances that interact with GABAergic synapses. Gabapentin is an antiepileptic effective in the treatment of partial seizures with or without secondary generalisation and is used as adjunctive therapy in patients unresponsive to or intolerant of standard antiepileptic drugs. It is also used in the treatment of neuropathic pain. For treatment of epilepsy 900 – 3600 mg/day is advised.

II.3 General comments on the submitted dossier

All four procedures are referring to the same film-coated tablets. The application is supported by a clinical overview, and two bioequivalence studies in which the 600 mg and 800 mg tablets to be registered are compared with Neurontin 600 mg and 800 mg tablets (Parke-Davis/Pfizer, Germany; (see clinical evaluation).

The submitted documentation in relation to the proposed products is of sufficient high quality in view of the present European regulatory requirements. A quality overall summary, a non-clinical and clinical overview have been submitted. They represent an adequate summary of the dossier.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
The submitted bioequivalence studies are stated to be conducted in compliance with Good Clinical Practice and Good Laboratory Practice.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

An Active Drug Master File (ASMF) from the supplier of the active substance gabapentin was submitted.
The active substance gabapentin is described in USP 31.

The chemical-pharmaceutical documentation and Expert Report in relation to Gabapentin are of sufficient quality in view of the present European regulatory requirements.

The control tests and specifications for drug substance product are adequately drawn up.

Stability data are presented for 20 pilot and production scale batches of gabapentin (batch size between 113.8 and 342.0 kg) manufactured in January/Mart 1999, November/December 2001 and Mart/November/December 2003 at real time (25° C/60 % RH) up to 48 month and accelerated conditions (40° C/75 % RH)) for 6 month. Batches were packed in the same material as proposed for packaging.
For all the batches manufactured in 1999 and for one batch manufactured in 2001 the content of the individual unknown impurities exceed the current limits of 0.05 %. But there are no trend is observed, if the initial values exceed the limits too. No objection.
All other batches comply with the specifications and no significant changes were observed at real time (25° C/60 % RH) and accelerated conditions (40° C/75 % RH)).

A stress testing has been performed on one batch in order to know degradation products, degradation pathway of the substance and its intrinsic stability. This study has been used to confirm also the stability indicating character of the HPLC method used for the assay and chromatographic purity. The study has been performed in acid and alkaline media, oxidative medium at room temperature, thermal treatment and under UV irradiation. Gabapentin is degraded in the main degradation product (Lactam) in acid and alkaline media, is sensitive to oxidative and thermal treatment. The chromatograms are enclosed.

The proposed retest period of 2 years is justified.

Drug Product

Gabapentin 600mg and 800mg film-coated tablets are presented as white, capsule-shaped tablets. Formulations are dose-proportional.

The tablets are packed in blisters of PVC film and aluminium foil.

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.
Analytical data from three pilot scale batches (batch size 75,000 – 150,000 tablets) and three industrial scale batches (300,000 – 400,000 tablets) of 600 mg and 800 mg tablets were submitted.

The batch analysis results show that the finished products meet the specifications proposed.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.

Stability testing of the finished product was carried out both with three pilot scale batches (batch size 75,000 – 150,000 tablets) of 600 mg and 800 mg tablets under long term conditions (25° C/60 % RH) and intermediate (30°C/65% RH) for 36 month and under accelerated (40° C/75 % RH) conditions for six month and with three industrial scale batches (300,000 – 400,000 tablets) under long term and accelerated conditions for six month. The pilot scale batches were manufactured in November 2003and in April/June/July 2004 and the production scale batches in October 2006. All batches were stored in the packaging material proposed for marketing.

To date results of the pilot batches are available for 36 months under real time and intermediate conditions and for 6 months under accelerated conditions in blister packs. The obtained data show that the degradation product, related compound A, is out of the specification in the studies at 30°C/65% RH and in the tests at 40°C/75% RH excessive formation of the degradation product occurs.
On-going stability data of three industrial scale batches of each strength for 12 month at real time and intermediate conditions, and for six month at accelerated conditions has been presented. The data contradicts the observation of the pilot scale batches as the degradation product, related compound A, remains within the specification even after six months at accelerated conditions (at 40°C/75%RH).

On the basis of the presented results a shelf-life of 24 months is proposed for the product. The proposed shelf-life without any the storage precaution is regarded acceptable.

III.2 Non clinical aspects

Pharmacology

Gabapentin was developed as an anticonvulsive agent and is now also used for the treatment of neuropathic pain. It is a GABA analogue that is covalently bound to a lipophilic cyclohexane ring. However, it does not simply act as a GABA agonist and does not interfere with GABA re-uptake. Instead, it slightly enhances GABA levels in distinct brain regions and reduces the release of monoamine neurotransmitters. Recently, gabapentin has been shown to bind to the $\alpha_2\delta$-subunit of voltage sensitive calcium channels and may thus interfere with calcium entry in nerve terminals and thereby reduce neurotransmitter release. Gabapentin is not genotoxic. It is not teratogen but exerts some embryotoxic effects at higher doses; reversible variations of the urogenital system were observed in the offspring. In a bioassay for carcinogenicity in rats, a higher incidence of pancreatic acinus cell tumours was observed. The relevance of these tumours for a carcinogenic risk in humans is questionable due to the characteristics of these tumours and to the high doses needed for induction. From the pharmacological/toxicological point of view there are no objections to the grant of a Marketing Authorisation.

III.3 Clinical aspects

Pharmacokinetics

This application concerns two strengths (600/800 mg) of the active substance gabapentin.
For each strength a separate bioequivalence study was performed under fasting conditions.
The submitted documentation indicates, that the intended Gabapentin 600 mg and 800 mg film-coated tablets are bioequivalent with the DE reference product, Neurontin 600 mg and 800 mg film-coated tablets.

Clinical efficacy/safety

The clinical efficacy and safety of gabapentin are sufficiently known, gabapentin containing medicinal products have been marketed in many countries for many years and the proposed indications are in line in line with the commission decision dated August 4th 2006 regarding the article 30 referral for the innovator product Neurontin (EMEA/H/A-30/616).
Therefore, no formal clinical assessment was performed.

III.4 Pharmacovigilance system

DE/H/1260/001-002/DC
Pharmacovigilance System Genericon Pharma GmbH

Commitments have been given that the updated pharmacovigilance system of the company Genericon Pharma GmbH covering the outstanding issues will be submitted as soon as possible. The applicant also committed to submit a corresponding type I1 variation that will be finalised prior to the marketing of the product in Germany and Austria.

DE/H/1313/001-002/DC:
Pharmacovigilance System SymPhar Sp. zo. o.,

Provided that several commitments are fulfilled, the RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union 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.

DE/H/1314/001-002/DC:
Pharmacovigilance System M. R. Pharma GmbH

Commitments have been given that the updated pharmacovigilance system of the company M.R. Pharma GmbH covering the outstanding issues will be submitted as soon as possible. The applicant also committed to submit a type I1 variation that will be finalised prior to the marketing of the product in RMS and all CMS.

DE/H/1315/001-002/DC:
Pharmacovigilance System PLIVA Group
The RMS considers that the Pharmacovigilance system as described by the applicant fulfils the requirements as described in Volume 9A of the Rules Governing Medicinal Products in the European Union 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.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of the published data and is therefore recommended for approval.

Commitments have been given to provide the updated Pharmacovigilance-System of the companies M.R. Pharma GmbH and Genericon Pharma GmbH as soon as possible, however prior to the marketing of the product in RMS and all CMS.

The RMS endorses the proposed prescription status “Prescription Only”, because it is in line with the prescription status of the Dutch reference medicinal product.