ANNEX I

LIST OF THE NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION, MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

Member State	Marketing Authorisation Holder	Applicant	Invented Name	Strength	Pharmaceutical Form	Route of administration
Austria	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Hauptstraße 1 1210 Wien, Austria		Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Hauptstraße 1 1210 Wien, Austria		Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Corporation Austria Gesellschaft m.b.H Floridsdorfer Hauptstraße 1 1210 Wien, Austria		Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Corporation Austria Gesellschaft m.b.H. Floridsdorfer Haupstraße 1 1210 Wien, Austria		Neurontin	800 mg	Film-coated tablets	Oral use
Belgium	Pfizer S.A. Boulevard de la Plaine, 17 B-1050 Bruxelles Belgium		Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer S.A. Boulevard de la Plaine, 17 B-1050 Bruxelles Belgium		Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer S.A. Boulevard de la Plaine, 17 B-1050 Bruxelles Belgium		Neurontin	400 mg	Capsules, hard	Oral use

	Pfizer S.A. Boulevard de la Plaine, 17 B-1050 Bruxelles Belgium	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer S.A. Boulevard de la Plaine, 17 B-1050 Bruxelles Belgium	Neurontin	800 mg	Film-coated tablets	Oral use
Czech Republic	PFIZER SPOL S R.O., Stroupežnického17, 15000 Praha 5	Neurontin	100 mg	Capsules, hard	Oral use
	PFIZER SPOL S R.O., Stroupežnického17, 15000 Praha 5	Neurontin	300 mg	Capsules, hard	Oral use
	PFIZER SPOL S R.O., Stroupežnického17, 15000 Praha 5	Neurontin	400 mg	Capsules, hard	Oral use
	PFIZER SPOL S R.O., Stroupežnického17, 15000 Praha 5	Neurontin	600 mg	Film-coated tablets	Oral use
	PFIZER SPOL S R.O., Stroupežnického17, 15000 Praha 5	Neurontin	800 mg	Film-coated tablets	Oral use
Cyprus	Pfizer Hellas A.E. 243, Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	300 mg	Capsules, hard	Oral use

	Pfizer Hellas A.E. 243, Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	400 mg	Capsules, hard	Oral use
Denmark	Pfizer Aps. Lautrupvang 8 2750 Ballerup	Gabapentin “Pfizer”	300 mg	Capsules, hard	Oral use
	Pfizer Aps. Lautrupvang 8 2750 Ballerup	Gabapentin “Pfizer”	400 mg	Capsules, hard	Oral use
	Pfizer Aps. Lautrupvang 8 2750 Ballerup	Gabapentin “Pfizer”	600 mg	Film-coated tablets	Oral use
	Pfizer Aps. Lautrupvang 8 2750 Ballerup	Gabapentin “Pfizer”	800 mg	Film-coated tablets	Oral use
Estonia	Pfizer Europe MA EEIG Ramsgate Road, Sandwich Kent, CT 13 9NJ UK	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Europe MA EEIG Ramsgate Road, Sandwich Kent, CT 13 9NJ UK	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Europe MA EEIG	Neurontin	400 mg	Capsules, hard	Oral use

	Ramsgate Road, Sandwich Kent, CT 13 9NJ UK	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Europe MA EEIG Ramsgate Road, Sandwich Kent, CT 13 9NJ UK	Neurontin	800 mg	Film-coated tablets	Oral use
	Pfizer Europe MA EEIG Ramsgate Road, Sandwich Kent, CT 13 9NJ UK				
Finland	Pfizer Oy, Tietokuja 4 00330 Helsinki Finland	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Oy, Tietokuja 4 00330 Helsinki Finland	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Oy, Tietokuja 4 00330 Helsinki Finland	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Oy, Tietokuja 4 00330 Helsinki Finland	Neurontin	800 mg	Film-coated tablets	Oral use

France	Pfizer 3-25 avenue du Docteur Lannelongue F-75668 Paris Cedex 14	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer 3-25 avenue du Docteur Lannelongue F-75668 Paris Cedex 14	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer 3-25 avenue du Docteur Lannelongue F-75668 Paris Cedex 14	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer 3-25 avenue du Docteur Lannelongue F-75668 Paris Cedex 14	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer 3-25 avenue du Docteur Lannelongue F-75668 Paris Cedex 14	Neurontin	800 mg	Film-coated tablets	Oral use
Germany	Parke-Davis GmbH Pfizerstrasse 1 76139 Karlsruhe	Neurontin	100 mg	Capsules, hard	Oral use
	Parke-Davis GmbH Pfizerstrasse 1 76139 Karlsruhe	Neurontin	300 mg	Capsules, hard	Oral use
	Parke-Davis GmbH Pfizerstrasse 1 76139 Karlsruhe	Neurontin	400 mg	Capsules, hard	Oral use

	Parke-Davis GmbH Pfizerstrasse 1 76139 Karlsruhe	Neurontin	600 mg	Film-coated tablets	Oral use
	Parke-Davis GmbH Pfizerstrasse 1 76139 Karlsruhe	Neurontin	800 mg	Film-coated tablets	Oral use
Greece	PFIZER HELLAS 243 Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	100 mg	Capsules, hard	Oral use
	PFIZER HELLAS 243 Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	300 mg	Capsules, hard	Oral use
	PFIZER HELLAS 243 Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	400 mg	Capsules, hard	Oral use
	PFIZER HELLAS 243 Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	600 mg	Film-coated tablets	Oral use
	PFIZER HELLAS 243 Messoghion Ave., Neo Psychiko 154 51 Greece	Neurontin	800 mg	Film-coated tablets	Oral use
Iceland	Pfizer Aps Lautrupvang 8	Neurontin	100 mg	Capsules, hard	Oral use

	2750 Ballerup Denmark				
	Pfizer Aps Lautrupvang 8 2750 Ballerup Denmark	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Aps Lautrupvang 8 2750 Ballerup Denmark	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Aps Lautrupvang 8 2750 Ballerup Denmark	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Aps Lautrupvang 8 2750 Ballerup Denmark	Neurontin	800 mg	Film-coated tablets	Oral use
Ireland	Pfizer Healthcare Ireland 9 Riverwalk, National Digital Pk, Citywest Business Campus, Dublin 24, Ireland c/o Pfizer Ltd. Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Healthcare Ireland	Neurontin	300 mg	Capsules, hard	Oral use

9 Riverwalk, National Digital Pk, Citywest Business Campus, Dublin 24, Ireland c/o Pfizer Ltd. Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS				
Pfizer Healthcare Ireland 9 Riverwalk, National Digital Pk, Citywest Business Campus, Dublin 24, Ireland c/o Pfizer Ltd. Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	400 mg	Capsules, hard	Oral use
Pfizer Healthcare Ireland 9 Riverwalk, National Digital Pk, Citywest Business Campus, Dublin 24, Ireland c/o Pfizer Ltd. Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	600 mg	Film-coated tablets	Oral use
Pfizer Healthcare Ireland 9 Riverwalk, National Digital Pk, Citywest Business Campus, Dublin 24, Ireland c/o Pfizer Ltd. Walton Oaks Dorking Road	Neurontin	800 mg	Film-coated tablets	Oral use

	Tadworth, Surrey KT20 7NS				
Hungary	Pfizer Kft. 1123 Budapest, Alkotás u. 53. MOM Park “F” épület	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Kft. 1123 Budapest, Alkotás u. 53. MOM Park “F” épület	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Kft. 1123 Budapest, Alkotás u. 53. MOM Park “F” épület	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Kft. 1123 Budapest, Alkotás u. 53. MOM Park “F” épület	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Kft. 1123 Budapest, Alkotás u. 53. MOM Park “F” épület	Neurontin	800 mg	Film-coated tablets	Oral use
Italy	Pfizer Italia S.r.l. Via Valbondione, 113 00188 Roma	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Italia S.r.l. Via Valbondione, 113 00188 Roma	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Italia S.r.l. Via Valbondione, 113 00188 Roma	Neurontin	400 mg	Capsules, hard	Oral use

Latvia	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	800 mg	Film-coated tablets	Oral use
Lithuania	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent	Neurontin	300 mg	Capsules, hard	Oral use

	CT13 9NJ, UK				
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Limited. Ramsgate Road Sandwich, Kent CT13 9NJ, UK	Neurontin	800 mg	Film-coated tablets	Oral use
Luxembourg	Pfizer S.A.. Boulevard de la Plaine 17 B-1050 Bruxelles Belgium	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer S.A.. Boulevard de la Plaine 17 B-1050 Bruxelles Belgium	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer S.A.. Boulevard de la Plaine 17 B-1050 Bruxelles Belgium	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer S.A.. Boulevard de la Plaine 17 B-1050	Neurontin	600 mg	Film-coated tablets	Oral use

	Bruxelles Belgium				
	Pfizer S.A.. Boulevard de la Plaine 17 B-1050 Bruxelles Belgium	Neurontin	800 mg	Film-coated tablets	Oral use
Malta	Pfizer Hellas A.E., Alketou 5, 11633 Athens Greece	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Hellas A.E., Alketou 5, 11633 Athens Greece	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer Hellas A.E., Alketou 5, 11633 Athens Greece	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Hellas A.E., Alketou 5, 11633 Athens Greece	Neurontin	600 mg	Film-coated tablets	Oral use
Norway	Pfizer AS Postboks 3 NO-1324 Lysaker	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer AS Postboks 3 NO-1324 Lysaker	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer AS Postboks 3 NO-1324 Lysaker	Neurontin	400 mg	Capsules, hard	Oral use

	Pfizer AS Postboks 3 NO-1324 Lysaker	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer AS Postboks 3 NO-1324 Lysaker	Neurontin	800 mg	Film-coated tablets	Oral use
Poland	Parke-Davis GmbH Pfizerstr 1, 76139 Karlsruhe, Germany	Neurontin	100 mg	Capsules, hard	Oral use
	Parke-Davis GmbH Pfizerstr 1, 76139 Karlsruhe, Germany	Neurontin	300 mg	Capsules, hard	Oral use
	Parke-Davis GmbH Pfizerstr 1, 76139 Karlsruhe, Germany	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Polska Sp. z o.o. Ul. Rzymowskiego 28 02-697 Warszawa	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Polska Sp. z o.o. Ul. Rzymowskiego 28 02-697 Warszawa	Neurontin	800 mg	Film-coated tablets	Oral use
Portugal	Laboratórios Pfizer, Lda. Lagoas Park - Edifício nº 10 102740-271Porto Salvo	Neurontin	100 mg	Capsules, hard	Oral use
	Laboratórios Pfizer, Lda. Lagoas Park - Edifício nº 10 102740-271Porto Salvo	Neurontin	300 mg	Capsules, hard	Oral use

	Laboratórios Pfizer, Lda. Lagoas Park - Edifício nº 10 102740-271Porto Salvo	Neurontin	400 mg	Capsules, hard	Oral use
	Laboratórios Pfizer, Lda. Lagoas Park - Edifício nº 10 102740-271Porto Salvo	Neurontin	600 mg	Film-coated tablets	Oral use
	Laboratórios Pfizer, Lda. Lagoas Park - Edifício nº 10 102740-271Porto Salvo	Neurontin	800 mg	Film-coated tablets	Oral use
The Netherlands	Pfizer BV Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer BV Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer BV Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer BV Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer BV Rivium Westlaan 142 2909 LD Capelle a/d IJssel	Neurontin	800 mg	Film-coated tablets	Oral use
Slovenia	Pfizer Luxembourg SARL 283, route d'Arlon L-8011 Strassen Luxembourg	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Luxembourg SARL	Neurontin	300 mg	Capsules, hard	Oral use

	283, route d'Arlon L-8011 Strassen Luxembourg				
	Pfizer Luxembourg SARL 283, route d'Arlon L-8011 Strassen Luxembourg	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Luxembourg SARL 283, route d'Arlon L-8011 Strassen Luxembourg	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Luxembourg SARL 283, route d'Arlon L-8011 Strassen Luxembourg	Neurontin	800 mg	Film-coated tablets	Oral use
The Slovak Republic	Pfizer Limited Ramsgate Road, Sandwich Kent, CT13 9NJ, UK **Contact address:** Pfizer Luxembourg SARL, branch office Dubravska cesta 2, 841 04 Bratislava, Slovak Republic	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer Limited Ramsgate Road, Sandwich Kent, CT13 9NJ, UK **Contact address:** Pfizer Luxembourg SARL, branch office Dubravska cesta 2, 841 04 Bratislava, Slovak Republic	Neurontin	300 mg	Capsules, hard	Oral use

	Pfizer Limited Ramsgate Road, Sandwich Kent, CT13 9NJ, UK **Contact address:** Pfizer Luxembourg SARL, branch office Dubravska cesta 2, 841 04 Bratislava, Slovak Republic	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer Limited Ramsgate Road, Sandwich Kent, CT13 9NJ, UK **Contact address:** Pfizer Luxembourg SARL, branch office Dubravska cesta 2, 841 04 Bratislava, Slovak Republic	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer Limited Ramsgate Road, Sandwich Kent, CT13 9NJ, UK **Contact address:** Pfizer Luxembourg SARL, branch office Dubravska cesta 2, 841 04 Bratislava, Slovak Republic	Neurontin	800 mg	Film-coated tablets	Oral use
Spain	PARKE DAVIS, S.L. Avda. de Europa, 20 B. Parque Empresarial La Moraleja	Neurontin	300 mg	Capsules, hard	Oral use

	28108 Alcobendas				
	PARKE DAVIS, S.L. Avda. de Europa, 20 B. Parque Empresarial La Moraleja 28108 Alcobendas	Neurontin	400 mg	Capsules, hard	Oral use
	PARKE DAVIS, S.L. Avda. de Europa, 20 B. Parque Empresarial La Moraleja 28108 Alcobendas	Neurontin	600 mg	Film-coated tablets	Oral use
	PARKE DAVIS, S.L. Avda. de Europa, 20 B. Parque Empresarial La Moraleja 28108 Alcobendas	Neurontin	800 mg	Film-coated tablets	Oral use
Sweden	Pfizer AB 91 90 Sollentuna	Neurontin	100 mg	Capsules, hard	Oral use
	Pfizer AB 91 90 Sollentuna	Neurontin	300 mg	Capsules, hard	Oral use
	Pfizer AB 91 90 Sollentuna	Neurontin	400 mg	Capsules, hard	Oral use
	Pfizer AB 91 90 Sollentuna	Neurontin	600 mg	Film-coated tablets	Oral use
	Pfizer AB 91 90 Sollentuna	Neurontin	800 mg	Film-coated tablets	Oral use
United Kingdom	Pfizer Ltd. Ramsgate Road Sandwich Kent, CT13 9NJ, UK C/o Walton Oaks	Neurontin	100 mg	Capsules, hard	Oral use

Dorking Road Tadworth, Surrey KT20 7NS				
Pfizer Ltd. Ramsgate Road Sandwich Kent, CT13 9NJ, UK C/o Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	300 mg	Capsules, hard	Oral use
Pfizer Ltd. Ramsgate Road Sandwich Kent, CT13 9NJ, UK C/o Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	400 mg	Capsules, hard	Oral use
Pfizer Ltd. Ramsgate Road Sandwich Kent, CT13 9NJ, UK C/o Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	600 mg	Film-coated tablets	Oral use
Pfizer Ltd. Ramsgate Road Sandwich Kent, CT13 9NJ, UK C/o Walton Oaks Dorking Road Tadworth, Surrey KT20 7NS	Neurontin	800 mg	Film-coated tablets	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF NEURONTIN AND ASSOCIATED NAMES (see Annex I)

- Quality issues

No significant issues relating to quality were identified and the pharmaceutical particulars of the product information were completed, except for the sections to be completed nationally.

- Non-clinical issues

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but the precise mechanism of action of gabapentin is not yet known.

No significant issues were identified during the procedure.

- Efficacy issues

The therapeutic indication of gabapentin as adjunctive epilepsy therapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above is well established. The CHMP agreed that the indication should not be restricted to patients refractory to standard medication.

Regarding the indication in pain, the review of the previously available information and the review of the results of the newly conducted multicenter, placebo-controlled clinical study supports the use of Neurontin for the treatment of post-herpetic neuralgia and painful diabetic peripheral neuropathy. In addition, the clinical data support of the starting dose, the titration schedule, and the maximum total daily dosage of 3600 mg administered in three doses.
Therefore, the MAH proposal of a harmonised wording was endorsed; as follows: *"Gabapentin is indicated for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults."*

Regarding epilepsy, the indication as adjunctive therapy in children aged 3 years and above as well as the indication as monotherapy were debated.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). In spite of these modest results, taking into consideration the adequate safety profile and the medical need in this paediatric population, the CHMP agreed to the following indication:
"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)." An update of efficacy data in children has been made in section 5.1.

In addition, the MAH confirmed the intention, in a letter of commitment, to submit across EU a paediatric liquid formulation in order to provide a dosage form more suitable for use in children.

Regarding the indication in epilepsy as monotherapy, based on the published studies, the CHMP considered that, although not statistically significant for all studies, the results were sufficiently consistent to support the clinical efficacy and safety of gabapentin as monotherapy.

Therefore, the following indication was agreed by the CHMP:
"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."
The posology is to be adjusted individually depending on response and tolerability.

- Safety issues

Based on the available information and a literature search, no major safety issue seems to be associated with the administration of gabapentin. However, several amendments to the SPC were introduced.

The most common undesirable effects observed in clinical trials consisted of somnolence, dizziness, ataxia, fatigue, fever and viral infection. Somnolence, peripheral oedema and asthenia may be more frequent in the elderly. Furthermore, attempts to withdraw concomitant anti-epileptics in treatment refractory patients on more than one anti-epileptic, in order to reach gabapentin monotherapy is not recommended as a low success rate is expected, as with other anti-epileptics. Finally, in children, aggressive behaviour and hyperkinesias were reported commonly.

The absence of adequate long term studies (more than 36 weeks) in children to assess growth, learning, intelligence, and development in children and adolescents, is mentioned in section 4.4.

Benefit/Risk considerations

Based on the documentation submitted by the MAH and the scientific discussion within the Committee, the CHMP considered that the benefit/risk ratio of neurontin and associated names is favourable relating to:

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).
The MAH confirmed the intention, in a letter of commitment, to submit across EU a paediatric liquid formulation in order to provide a dosage form more suitable for use in children.

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.

All divergent opinions have been resolved.

Grounds for amendments of the Summaries of Products Characteristics, labelling and Package leaflet

Whereas,

- the scope of the referral was the harmonisation of the Summary of Product Characteristics, labelling and package leaflet
- the Summary of Products Characteristic, labelling and package leaflet proposed by the Marketing Authorisation Holders has been assessed based on the documentation submitted and the scientific discussion within the Committee,

the CHMP has recommended amendments of the Summary of Products Characteristic, Labelling and Package Leaflet, as set out in Annexe III of the CHMP opinion for Neurontin and associated names (see Annexe I of the opinion).

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neurontin and associated names 100 mg hard capsule
Neurontin and associated names 300 mg hard capsule
Neurontin and associated names 400 mg hard capsule
Neurontin and associated names 600 mg film-coated tablet
Neurontin and associated names 800 mg film-coated tablet

[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mg hard capsule contains 100 mg of gabapentin.

Each 300 mg hard capsule contains 300 mg of gabapentin.

Each 400 mg hard capsule contains 400 mg of gabapentin.

Each 600 mg film-coated tablet contains 600 mg of gabapentin.

Each 800 mg film-coated tablet contains 800 mg of gabapentin.

Excipients:

Each 100 mg hard capsule contains 13 mg lactose (as monohydrate).

Each 300 mg hard capsule contains 41 mg lactose (as monohydrate).

Each 400 mg hard capsule contains 54 mg lactose (as monohydrate).

For a full list of excipients, see section 6.1.

[To be completed nationally]

3. PHARMACEUTICAL FORM

Capsule, hard

Film-coated tablet

[Description to be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

For oral use.

Gabapentin can be given with or without food and should be swallowed whole with sufficient fluid-intake (e.g. a glass of water).

For all indications a titration scheme for the initiation of therapy is described in Table 1, which is recommended for adults and adolescents aged 12 years and above. Dosing instructions for children under 12 years of age are provided under a separate sub-heading later in this section.

Table 1		
DOSING CHART – INITIAL TITRATION		
Day 1	Day 2	Day 3
300 mg once a day	300 mg two times a day	300 mg three times a day

Epilepsy

Epilepsy typically requires long-term therapy. Dosage is determined by the treating physician according to individual tolerance and efficacy. When in the judgment of the clinician there is a need for dose reduction, discontinuation, or substitution with an alternative medication, this should be done gradually over a minimum of one week.

Adults and adolescents:

In clinical trials, the effective dosing range was 900 to 3600 mg/day. Therapy may be initiated by titrating the dose as described in Table 1 or by administering 300 mg three times a day (TID) on Day 1. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks. Dosages up to 4800 mg/day have been well tolerated in long-term open-label clinical studies. The total daily dose should be divided in three single doses, the maximum time interval between the doses should not exceed 12 hours to prevent breakthrough convulsions.

Children aged 6 years and above:

The starting dose should range from 10 to 15 mg/kg/day and the effective dose is reached by upward titration over a period of approximately three days. The effective dose of gabapentin in children aged 6 years and older is 25 to 35 mg/kg/day. Dosages up to 50 mg/kg/day have been well tolerated in a long-term clinical study. The total daily dose should be divided in three single doses, the maximum time interval between doses should not exceed 12 hours.

It is not necessary to monitor gabapentin plasma concentrations to optimize gabapentin therapy. Further, gabapentin may be used in combination with other antiepileptic medicinal products without concern for alteration of the plasma concentrations of gabapentin or serum concentrations of other antiepileptic medicinal products.

Peripheral neuropathic pain

Adults

The therapy may be initiated by titrating the dose as described in Table 1. Alternatively, the starting dose is 900 mg/day given as three equally divided doses. Thereafter, based on individual patient response and tolerability, the dose can be further increased in 300 mg/day increments every 2-3 days up to a maximum dose of 3600 mg/day. Slower titration of gabapentin dosage may be appropriate for individual patients. The minimum time to reach a dose of 1800 mg/day is one week, to reach 2400 mg/day is a total of 2 weeks, and to reach 3600 mg/day is a total of 3 weeks.

In the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia, efficacy and safety have not been examined in clinical studies for treatment periods longer than 5 months. If a patient requires dosing longer than 5 months for the treatment of peripheral neuropathic pain, the treating physician should assess the patient's clinical status and determine the need for additional therapy.

Instruction for all areas of indication

In patients with poor general health, i.e., low body weight, after organ transplantation etc., the dose should be titrated more slowly, either by using smaller dosage strengths or longer intervals between dosage increases.

Use in elderly patients (over 65 years of age)

Elderly patients may require dosage adjustment because of declining renal function with age (see Table 2). Somnolence, peripheral oedema and asthenia may be more frequent in elderly patients.

Use in patients with renal impairment

Dosage adjustment is recommended in patients with compromised renal function as described in Table 2 and/or those undergoing haemodialysis. Gabapentin 100 mg capsules can be used to follow dosing recommendations for patients with renal insufficiency.

Table 2	
DOSAGE OF GABAPENTIN IN ADULTS BASED ON RENAL FUNCTION	
Creatinine Clearance (ml/min)	Total Daily Dose[a] (mg/day)
≥80	900-3600
50-79	600-1800
30-49	300-900
15-29	150[b]-600
<15[c]	150[b]-300

[a] Total daily dose should be administered as three divided doses. Reduced dosages are for patients with renal impairment (creatinine clearance < 79 ml/min).
[b] To be administered as 300 mg every other day.
[c] For patients with creatinine clearance <15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g., patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

Use in patients undergoing haemodialysis

For anuric patients undergoing haemodialysis who have never received gabapentin, a loading dose of 300 to 400 mg, then 200 to 300 mg of gabapentin following each 4 hours of haemodialysis, is recommended. On dialysis-free days, there should be no treatment with gabapentin.

For renally impaired patients undergoing haemodialysis, the maintenance dose of gabapentin should be based on the dosing recommendations found in Table 2. In addition to the maintenance dose, an additional 200 to 300 mg dose following each 4-hour haemodialysis treatment is recommended.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

If a patient develops acute pancreatitis under treatment with gabapentin, discontinuation of gabapentin should be considered (see section 4.8).

Although there is no evidence of rebound seizures with gabapentin, abrupt withdrawal of anticonvulsants in epileptic patients may precipitate status epilepticus (see section 4.2).

As with other antiepileptic medicinal products, some patients may experience an increase in seizure frequency or the onset of new types of seizures with gabapentin.

As with other anti-epileptics, attempts to withdraw concomitant anti-epileptics in treatment refractory patients on more than one anti-epileptic, in order to reach gabapentin monotherapy have a low success rate.

Gabapentin is not considered effective against primary generalized seizures such as absences and may aggravate these seizures in some patients. Therefore, gabapentin should be used with caution in patients with mixed seizures including absences.

No systematic studies in patients 65 years or older have been conducted with gabapentin. In one double blind study in patients with neuropathic pain, somnolence, peripheral oedema and asthenia occurred in a somewhat higher percentage in patients aged 65 years or above, than in younger patients. Apart from these findings, clinical investigations in this age group do not indicate an adverse event profile different from that observed in younger patients.

The effects of long-term (greater than 36 weeks) gabapentin therapy on learning, intelligence, and development in children and adolescents have not been adequately studied. The benefits of prolonged therapy must therefore be weighed against the potential risks of such therapy.

Laboratory tests
False positive readings may be obtained in the semi-quantitative determination of total urine protein by dipstick tests. It is therefore recommended to verify such a positive dipstick test result by methods based on a different analytical principle such as the Biuret method, turbidimetric or dye-binding methods, or to use these alternative methods from the beginning.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine *[this text will only be included in the capsules SPC]*.

4.5 Interaction with other medicinal products and other forms of interaction

In a study involving healthy volunteers (N=12), when a 60 mg controlled-release morphine capsule was administered 2 hours prior to a 600 mg gabapentin capsule, mean gabapentin AUC increased by 44% compared to gabapentin administered without morphine. Therefore, patients should be carefully observed for signs of CNS depression, such as somnolence, and the dose of gabapentin or morphine should be reduced appropriately.

No interaction between gabapentin and phenobarbital, phenytoin, valproic acid, or carbamazepine has been observed.

Gabapentin steady-state pharmacokinetics are similar for healthy subjects and patients with epilepsy receiving these antiepileptic agents.

Coadministration of gabapentin with oral contraceptives containing norethindrone and/or ethinyl estradiol, does not influence the steady-state pharmacokinetics of either component.

Coadministration of gabapentin with antacids containing aluminium and magnesium, reduces gabapentin bioavailability up to 24%. It is recommended that gabapentin be taken at the earliest two hours following antacid administration.

Renal excretion of gabapentin is unaltered by probenecid.

A slight decrease in renal excretion of gabapentin that is observed when it is coadministered with cimetidine is not expected to be of clinical importance.

4.6 Pregnancy and lactation

Risk related to epilepsy and antiepileptic medicinal products in general

The risk of birth defects is increased by a factor of 2 – 3 in the offspring of mothers treated with an antiepileptic medicinal product. Most frequently reported are cleft lip, cardiovascular malformations and neural tube defects. Multiple antiepileptic drug therapy may be associated with a higher risk of congenital malformations than monotherapy, therefore it is important that monotherapy is practised whenever possible. Specialist advice should be given to women who are likely to become pregnant or who are of childbearing potential and the need for antiepileptic treatment should be reviewed when a woman is planning to become pregnant. No sudden discontinuation of antiepileptic therapy should be undertaken as this may lead to breakthrough seizures, which could have serious consequences for both mother and child. Developmental delay in children of mothers with epilepsy has been observed rarely. It is not possible to differentiate if the developmental delay is caused by genetic, social factors, maternal epilepsy or the antiepileptic therapy.

Risk related to gabapentin

There are no adequate data from the use of gabapentin in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.

No definite conclusion can be made as to whether gabapentin is associated with an increased risk of congenital malformations when taken during pregnancy, because of epilepsy itself and the presence of concomitant antiepileptic medicinal products during each reported pregnancy.

Gabapentin is excreted in human milk. Because the effect on the breast-fed infant is unknown, caution should be exercised when gabapentin is administered to a breast-feeding mother. Gabapentin should be used in breast-feeding mothers only if the benefits clearly outweigh the risks.

4.7 Effects on ability to drive and use machines

Gabapentin may have minor or moderate influence on the ability to drive and use machines. Gabapentin acts on the central nervous system and may cause drowsiness, dizziness or other related symptoms. Even, if they were only of mild or moderate degree, these undesirable effects could be potentially dangerous in patients driving or operating machinery. This is especially true at the beginning of the treatment and after increase in dose.

4.8 Undesirable effects

The adverse reactions observed during clinical studies conducted in epilepsy (adjunctive and monotherapy) and neuropathic pain have been provided in a single list below by class and frequency (very common (≥ 1/10), common (≥1/100, <1/10), uncommon (≥1/1000, ≤1/100) and rare (≥1/10,000; ≤1/1,000). Where an adverse reaction was seen at different frequencies in clinical studies, it was assigned to the highest frequency reported.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations
Very Common: Viral infection
Common: Pneumonia, respiratory infection, urinary tract infection, infection, otitis media

Blood and the lymphatic system disorders
Common: leucopenia
Rare: thrombocytopenia

Immune system disorders
Rare: allergic reactions (e.g. urticaria)

Metabolism and Nutrition Disorders
Common: anorexia, increased appetite

Psychiatric disorders
Common: hostility, confusion and emotional lability, depression, anxiety, nervousness, thinking abnormal
Rare: hallucinations

Nervous system disorders
Very Common: somnolence, dizziness, ataxia,
Common: convulsions, hyperkinesias, dysarthria, amnesia, tremor, insomnia, headache, sensations such as paresthesia, hypaesthesia, coordination abnormal, nystagmus, increased, decreased, or absent reflexes
Rare: movement disorders (e.g. choreoathetosis, dyskinesia, dystonia)

Eye disorders
Common: visual disturbances such as amblyopia, diplopia

Ear and Labyrinth disorders
Common: vertigo
Rare: tinnitus

Cardiac disorders
Rare: palpitations

Vascular disorder
Common: hypertension, vasodilatation

Respiratory, thoracic and mediastinal disorders
Common: dyspnoea, bronchitis, pharyngitis, cough, rhinitis

Gastrointestinal disorders
Common: vomiting, nausea, dental abnormalities, gingivitis, diarrhea, abdominal pain, dyspepsia, constipation, dry mouth or throat, flatulence
Rare: pancreatitis

Hepatobiliary disorders
Rare: hepatitis, jaundice

Skin and subcutaneous tissue disorders
Common: facial oedema, purpura most often described as bruises resulting from physical trauma, rash, pruritus, acne
Rare: Stevens-Johnson syndrome, angioedema, erythema multiforme, alopecia

Musculoskeletal, connective tissue and bone disorders
Common: arthralgia, myalgia, back pain, twitching

Renal and urinary disorders
Common: incontinence
Rare: acute renal failure

Reproductive system and breast disorders
Common: impotence

General disorders and administration site conditions
Very Common: fatigue, fever
Common: peripheral or generalized oedema, abnormal gait, asthenia, pain, malaise, flu syndrome
Rare: withdrawal reactions (mostly anxiety, insomnia, nausea, pains, sweating), chest pain. Sudden unexplained deaths have been reported where a causal relationship to treatment with gabapentin has not been established.

Investigations
Common: WBC (white blood cell count) decreased, weight gain
Rare: Blood glucose fluctuations in patients with diabetes, elevated liver function tests

Injury and poisoning
Common: accidental injury, fracture, abrasion

Under treatment with gabapentin cases of acute pancreatitis were reported. Causality with gabapentin is unclear (see section 4.4).

Respiratory tract infections, otitis media, convulsions and bronchitis were reported only in clinical studies in children. Additionally, in clinical studies in children, aggressive behaviour and hyperkinesias were reported commonly.

4.9 Overdose

Acute, life-threatening toxicity has not been observed with gabapentin overdoses of up to 49 g. Symptoms of the overdoses included dizziness, double vision, slurred speech, drowsiness, lethargy and mild diarrhoea. All patients recovered fully with supportive care. Reduced absorption of gabapentin at higher doses may limit drug absorption at the time of overdosing and, hence, minimize toxicity from overdoses.

Although gabapentin can be removed by haemodialysis, based on prior experience it is usually not required. However, in patients with severe renal impairment, haemodialysis may be indicated.

An oral lethal dose of gabapentin was not identified in mice and rats given doses as high as 8000 mg/kg. Signs of acute toxicity in animals included ataxia, laboured breathing, ptosis, hypoactivity, or excitation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Other antiepileptics ATC code: N03AX12

The precise mechanism of action of gabapentin is not known.
Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but 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. *In vitro* studies with radiolabeled gabapentin have characterized a novel peptide binding site in rat brain tissues including neocortex and hippocampus that may relate to anticonvulsant and analgesic activity of gabapentin and its structural derivatives. The binding site for gabapentin has been identified as the alpha$_2$-delta subunit of voltage-gated calcium channels.

Gabapentin at relevant clinical concentrations does not bind to other common drug or neurotransmitter receptors of the brain including $GABA_A$, $GABA_B$, benzodiazepine, glutamate, glycine or N-methyl-d-aspartate receptors.

Gabapentin does not interact with sodium channels *in vitro* and so differs from phenytoin and carbamazepine. Gabapentin partially reduces responses to the glutamate agonist N-methyl-D-aspartate (NMDA) in some test systems *in vitro*, but only at concentrations greater than 100 µM, which are not achieved *in vivo*. Gabapentin slightly reduces the release of monoamine neurotransmitters *in vitro*. Gabapentin administration to rats increases GABA turnover in several brain regions in a manner similar to valproate sodium, although in different regions of brain. The relevance of these various actions of gabapentin to the anticonvulsant effects remains to be established. In animals, gabapentin readily enters the brain and prevents seizures from maximal electroshock, from chemical convulsants including inhibitors of GABA synthesis, and in genetic models of seizures.

A clinical trial of adjunctive treatment of partial seizures in paediatric subjects, ranging in age from 3 to 12 years, showed a numerical but not statistically significant difference in the 50% responder rate in favour of the gabapentin group compared to placebo. Additional post-hoc analyses of the responder rates by age did not reveal a statistically significant effect of age, either as a continuous or dichotomous variable (age groups 3-5 and 6-12 years). The data from this additional post-hoc analysis are summarised in the table below:

Response (≥ 50% Improved) by Treatment and Age MITT* Population			
Age Category	Placebo	Gabapentin	P-Value
< 6 Years Old	4/21 (19.0%)	4/17 (23.5%)	0.7362
6 to 12 Years Old	17/99 (17.2%)	20/96 (20.8%)	0.5144

*The modified intent to treat population was defined as all patients randomised to study medication who also had evaluable seizure diaries available for 28 days during both the baseline and double-blind phases.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, peak plasma gabapentin concentrations are observed within 2 to 3 hours. Gabapentin bioavailability (fraction of dose absorbed) tends to decrease with increasing dose. Absolute bioavailability of a 300 mg capsule is approximately 60%. Food, including a high-fat diet, has no clinically significant effect on gabapentin pharmacokinetics.

Gabapentin pharmacokinetics are not affected by repeated administration. Although plasma gabapentin concentrations were generally between 2 μg/ml and 20 μg/ml in clinical studies, such concentrations were not predictive of safety or efficacy. Pharmacokinetic parameters are given in Table 3.

Table 3
Summary of gabapentin mean (%CV) steady-state pharmacokinetic parameters following every eight hours administration

Pharmacokinetic parameter	300 mg (N = 7)		400 mg (N = 14)		800 mg (N=14)	
	Mean	%CV	Mean	%CV	Mean	%CV
C_{max} (μg/ml)	4.02	(24)	5.74	(38)	8.71	(29)
t_{max} (hr)	2.7	(18)	2.1	(54)	1.6	(76)
T1/2 (hr)	5.2	(12)	10.8	(89)	10.6	(41)
AUC (0-8) μg•hr/ml)	24.8	(24)	34.5	(34)	51.4	(27)
Ae% (%)	NA	NA	47.2	(25)	34.4	(37)

C_{max} = Maximum steady state plasma concentration
t_{max} = Time for C_{max}
T1/2 = Elimination half-life
AUC(0-8) = Steady state area under plasma concentration-time curve from time 0 to 8 hours postdose
Ae% = Percent of dose excreted unchanged into the urine from time 0 to 8 hours postdose
NA = Not available

Distribution

Gabapentin is not bound to plasma proteins and has a volume of distribution equal to 57.7 litres. In patients with epilepsy, gabapentin concentrations in cerebrospinal fluid (CSF) are approximately 20% of

corresponding steady-state trough plasma concentrations. Gabapentin is present in the breast milk of breast-feeding women.

Metabolism

There is no evidence of gabapentin metabolism in humans. Gabapentin does not induce hepatic mixed function oxidase enzymes responsible for drug metabolism.

Elimination

Gabapentin is eliminated unchanged solely by renal excretion. The elimination half-life of gabapentin is independent of dose and averages 5 to 7 hours.

In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin elimination-rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance.

Gabapentin is removed from plasma by haemodialysis. Dosage adjustment in patients with compromised renal function or undergoing haemodialysis is recommended (see section 4.2).

Gabapentin pharmacokinetics in children were determined in 50 healthy subjects between the ages of 1 month and 12 years. In general, plasma gabapentin concentrations in children > 5 years of age are similar to those in adults when dosed on a mg/kg basis.

Linearity/Non-linearity

Gabapentin bioavailability (fraction of dose absorbed) decreases with increasing dose which imparts non-linearity to pharmacokinetic parameters which include the bioavailability parameter (F) e.g. Ae%, CL/F, Vd/F. Elimination pharmacokinetics (pharmacokinetic parameters which do not include F such as CLr and T1/2), are best described by linear pharmacokinetics. Steady state plasma gabapentin concentrations are predictable from single-dose data.

5.3 Preclinical safety data

Carcinogenesis

Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for two years. A statistically significant increase in the incidence of pancreatic acinar cell tumors was found only in male rats at the highest dose. Peak plasma drug concentrations in rats at 2000 mg/kg/day are 10 times higher than plasma concentrations in humans given 3600 mg/day. The pancreatic acinar cell tumors in male rats are low-grade malignancies, did not affect survival, did not metastasize or invade surrounding tissue, and were similar to those seen in concurrent controls. The relevance of these pancreatic acinar cell tumors in male rats to carcinogenic risk in humans is unclear.

Mutagenesis

Gabapentin demonstrated no genotoxic potential. It was not mutagenic *in vitro* in standard assays using bacterial or mammalian cells. Gabapentin did not induce structural chromosome aberrations in mammalian cells *in vitro* or *in vivo*, and did not induce micronucleus formation in the bone marrow of hamsters.

Impairment of Fertility

No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (approximately five times the maximum daily human dose on a mg/m^2 of body surface area basis).

Teratogenesis

Gabapentin did not increase the incidence of malformations, compared to controls, in the offspring of mice, rats, or rabbits at doses up to 50, 30 and 25 times respectively, the daily human dose of 3600 mg, (four, five or eight times, respectively, the human daily dose on a mg/m^2 basis).

Gabapentin induced delayed ossification in the skull, vertebrae, forelimbs, and hindlimbs in rodents, indicative of fetal growth retardation. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during organogenesis and in rats given 500, 1000, or 2000 mg/kg prior to and during mating and throughout gestation. These doses are approximately 1 to 5 times the human dose of 3600 mg on a mg/m^2 basis.

No effects were observed in pregnant mice given 500 mg/kg/day (approximately 1/2 of the daily human dose on a mg/m^2 basis).

An increased incidence of hydroureter and/or hydronephrosis was observed in rats given 2000 mg/kg/day in a fertility and general reproduction study, 1500 mg/kg/day in a teratology study, and 500, 1000, and 2000 mg/kg/day in a perinatal and postnatal study. The significance of these findings is unknown, but they have been associated with delayed development. These doses are also approximately 1 to 5 times the human dose of 3600 mg on a mg/m^2 basis.

In a teratology study in rabbits, an increased incidence of post-implantation fetal loss, occurred in doses given 60, 300, and 1500 mg/kg/day during organogenesis. These doses are approximately 1/4 to 8 times the daily human dose of 3600 mg on a mg/m^2 basis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

Capsules: 20, 30, 50, 84, 90, 98, 100, 200, 500, 1000

Tablets: 20, 30, 45, 50, 84, 90, 100, 200, 500

Also supplied as a titration pack for treatment of neuropathic pain containing 40 x 300 mg capsules and 10 x 600 mg tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Neurontin and associated names 100 mg hard capsule
Neurontin and associated names 300 mg hard capsule
Neurontin and associated names 400 mg hard capsule
Neurontin and associated names 600 mg film-coated tablet
Neurontin and associated names 800 mg film-coated tablet

Gabapentin

[See Annex I - To be completed nationally]

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 100 mg hard capsule contains 100 mg of gabapentin.

Each 300 mg hard capsule contains 300 mg of gabapentin.

Each 400 mg hard capsule contains 400 mg of gabapentin.

Each 600 mg film-coated tablet contains 600 mg of gabapentin.

Each 800 mg film-coated tablet contains 800 mg of gabapentin.

[To be completed nationally]

3. LIST OF EXCIPIENTS

This product contains lactose monohydrate. See leaflet for further information
[This text will only be included on the labelling for the capsules]

4. PHARMACEUTICAL FORM AND CONTENTS

XX capsules or XX tablets

[To be completed nationally]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

For oral use. Take as directed by the doctor.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

[To be completed nationally]

9. SPECIAL STORAGE CONDITIONS

[To be completed nationally]

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

[To be completed nationally]

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

{Name and Address}
<{tel}>
<{fax}>
<{e-mail}>

[See Annex I - To be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

13. BATCH NUMBER

[To be completed nationally]

14. GENERAL CLASSIFICATION FOR SUPPLY

[To be completed nationally]

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

[To be completed nationally]

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Neurontin and associated names 100 mg hard capsule
Neurontin and associated names 300 mg hard capsule
Neurontin and associated names 400 mg hard capsule
Neurontin and associated names 600 mg film-coated tablet
Neurontin and associated names 800 mg film-coated tablet

Gabapentin

[See Annex I - To be completed nationally]

2. NAME OF THE MARKETING AUTHORISATION HOLDER

{Name}

[See Annex I - To be completed nationally]

3. EXPIRY DATE

[To be completed nationally]

4. BATCH NUMBER

[To be completed nationally]

5. OTHER

PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Neurontin and associated names 100 mg hard capsules
Neurontin and associated names 300 mg hard capsules
Neurontin and associated names 400 mg hard capsules
Neurontin and associated names 600 mg film-coated tablets
Neurontin and associated names 800 mg film-coated tablets
[See Annex I - To be completed nationally]
Gabapentin

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT [NEURONTIN AND ASSOCIATED NAMES] IS AND WHAT IT IS USED FOR

[Neurontin and associated names] belongs to a group of medicines used to treat epilepsy and peripheral neuropathic pain.

Epilepsy: [Neurontin and associated names] is 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). Your doctor will prescribe [Neurontin and associated names] for you to help treat your epilepsy when your current treatment is not fully controlling your condition. You should take [Neurontin and associated names] in addition to your current treatment unless told otherwise. [Neurontin and associated names] can also be used on its own to treat adults and children over 12 years of age.

Peripheral neuropathic pain: [Neurontin and associated names] is used to treat long lasting pain caused by damage to the nerves. A variety of different diseases can cause peripheral (primarily occurring in the legs and/or arms) neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles etc.

2. BEFORE YOU TAKE [NEURONTIN AND ASSOCIATED NAMES]

Do not take [Neurontin and associated names]
- if you are allergic (hypersensitive) to gabapentin or any of the other ingredients of [Neurontin and associated names].

Take special care with [Neurontin and associated names]
- if you suffer from kidney problems
- if you develop signs such as persistent stomach pain, feeling sick and being sick contact your doctor immediately.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you are taking any medicines containing morphine, please tell your doctor or pharmacist as morphine may increase the effect of [Neurontin and associated names].

[Neurontin and associated names] is not expected to interact with other antiepileptic drugs or the oral contraceptive pill.

[Neurontin and associated names] may interfere with some laboratory tests, if you require a urine test tell your doctor or hospital that you are taking [Neurontin and associated names].

If [Neurontin and associated names] and antacids containing aluminium and magnesium are taken at the same time, absorption of [Neurontin and associated names] from the stomach may be reduced. It is therefore recommended that [Neurontin and associated names] is taken at the earliest two hours after taking an antacid.

Taking [Neurontin and associated names] with food and drink
[Neurontin and associated names] can be taken with or without food.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine.

[Neurontin and associated names] should not be taken during pregnancy, unless you are told otherwise by your doctor. Effective contraception must be used by women of child-bearing potential.

There have been no studies specifically looking at the use of gabapentin in pregnant women, but other medications used to treat seizures have reported an increased risk of harm to the foetus, particularly when more than one seizure medication is taken at the same time. Therefore, whenever possible and only under the advice of your doctor, you should try to take only one seizure medication during pregnancy.

Do not suddenly discontinue taking this medicine as this may lead to breakthrough seizure, which could have serious consequences for you and your baby.

Contact your doctor immediately if you become pregnant, think you might be pregnant or are planning to become pregnant while taking [Neurontin and associated names].

Gabapentin, the active substance of [Neurontin and associated names], is excreted in human milk. Because the effect on the nursing infant is unknown, it is not recommended to breast-feed your baby while using [Neurontin and associated names].

Driving and using machines
[Neurontin and associated names] may produce dizziness, drowsiness and tiredness. You should not drive, operate complex machinery or engage in other potentially hazardous activities until you know whether this medication affects your ability to perform these activities.

Important information about some of the ingredients of [Neurontin and associated names]
The capsules contain lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. HOW TO TAKE [NEURONTIN AND ASSOCIATED NAMES]

Always take [Neurontin and associated names] exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Your doctor will determine what dose is appropriate for you.

If you have the impression that the effect of [Neurontin and associated names] is too strong or too weak, talk to your doctor or pharmacist.

If you are an elderly patient (over 65 years of age), you should take [Neurontin and associated names] normally except if you have problems with your kidneys.

Your doctor may prescribe a different dosing schedule and/or dose if you have problems with your kidneys.

Always swallow the capsules or tablets whole with plenty of water.

Continue taking [Neurontin and associated names] until your doctor tells you to stop.

Peripheral Neuropathic Pain:

Take the number of capsules or tablets as instructed by your doctor. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased stepwise up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 divided doses, i.e. once in the morning, once in the afternoon and once in the evening.

Epilepsy:

Adults and adolescents:

Take the number of capsules or tablets as instructed. Your doctor will usually build up your dose gradually. The starting dose will generally be between 300 mg and 900 mg each day. Thereafter, the dose may be increased stepwise up to a maximum of 3600 mg each day and your doctor will tell you to take this in 3 divided doses, i.e. once in the morning, once in the afternoon and once in the evening.

Children aged 6 years and above:

The dose to be given to your child will be decided by your doctor as it is calculated against your child's weight. The treatment is started with a low initial dose which is gradually increased over a period of approximately 3 days. The usual dose to control epilepsy is 25-35 mg/kg/day. It is usually given in 3 divided doses, by taking the capsule(s) or tablet(s) each day, usually once in the morning, once in the afternoon and once in the evening.

[Neurontin and associated names] is not recommended for use in children below 6 years of age.

If you take more [Neurontin and associated names] than you should
Call your doctor or go to the nearest hospital emergency unit immediately. Take along any capsules or tablets that are left, the container and the label so that the hospital can easily tell what medicine you have taken.

If you forget to take [Neurontin and associated names]
If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. Do not take a double dose to make up for a forgotten dose.

If you stop taking [Neurontin and associated names]

Do not stop taking [Neurontin and associated names] unless your doctor tells you to. If your treatment is stopped it should be done gradually over a minimum of 1 week. If you stop taking [Neurontin and associated names] suddenly or before your doctor tells you, there is an increased risk of seizures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, [Neurontin and associated names] can cause side effects, although not everybody gets them.

Very common side-effects which may affect more than 1 person in 10 are listed below:

- Viral infection
- Feeling drowsy, dizziness, lack of coordination
- Feeling tired, fever

Common side-effects which may affect more than 1 person in 100 are listed below:

- Pneumonia, respiratory infection, urinary tract infection, infection, inflammation of the ear
- Low white blood cell counts
- Anorexia, increased appetite
- Anger towards others, confusion, fluctuation in mood, depression, anxiety, nervousness, difficulty with thinking
- Convulsions, jerky movements, difficulty with speaking, loss of memory, tremor, difficulty sleeping, headache, sensitive skin, decreased sensation, difficulty with coordination, unusual eye movement, increased, decreased or absent reflexes
- Blurred vision, double vision
- Vertigo
- High blood pressure, flushing or dilation of blood vessels
- Difficulty breathing, bronchitis, sore throat, cough, dry nose
- Vomiting (being sick), nausea (feeling sick), problems with teeth, inflamed gums, diarrhoea, stomach pain, indigestion, constipation, dry mouth or throat, flatulence
- Facial swelling, bruises, rash, itch, acne
- Joint pain, muscle pain, back pain, twitching
- Incontinence
- Difficulties with erection
- Swelling in the legs and arms or swelling that may involve the face, trunk and limbs, difficulty with walking, weakness, pain, feeling unwell, flu-like symptoms
- Decrease in white blood cells, increase in weight
- Accidental injury, fracture, abrasion

Rare side-effects which may affect less than 1 person in 1000 are listed below:

- Decreased platelets (blood clotting cells)
- Allergic reaction such as hives
- Hallucinations
- Problems with abnormal movements such as writhing, jerking movements and stiffness
- Ringing in the ears
- Racing heartbeat
- Inflammation of the pancreas
- Inflammation of the liver, yellowing of the skin and eyes
- Severe skin reactions that require immediate medical attention, swelling of the lips and face, skin rash and redness, hair loss
- Acute kidney failure

- Adverse events following the abrupt discontinuation of gabapentin (anxiety, difficulty sleeping, feeling sick, pain, sweating), chest pain
- Blood glucose fluctuations in patients with diabetes, abnormal blood test results suggesting problems with the liver.

Additionally in clinical studies in children, aggressive behaviour and jerky movements were reported commonly.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE [NEURONTIN AND ASSOCIATED NAMES]

Keep out of the reach and sight of children.

Do not use [Neurontin and associated names] after the expiry date which is stated on the carton after [to be completed nationally]. The expiry date refers to the last day of that month.

[To be completed nationally]

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What [Neurontin and associated names] contains

– The active substance is gabapentin. Each capsule, hard contains either 100 mg, 300 mg or 400 mg gabapentin. Each film-coated tablet contains either 600 mg or 800 mg gabapentin.

– The other ingredients in [Neurontin and associated names] capsules are:

– The other ingredients in [Neurontin and associated names] tablets are:

[To be completed nationally]

What [Neurontin and associated names] looks like and contents of the pack

Capsule, hard

Film-coated tablet

[Description to be completed nationally]

Marketing Authorisation Holder and Manufacturer

[To be completed nationally]

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This medicinal product is authorised in the Member States of the EEA under the following names:
Austria Neurontin

Belgium	Neurontin
Cyprus	Neurontin
Czech Republic	Neurontin
Denmark	Gabapentin “Pfizer”
Estonia	Neurontin
Finland	Neurontin
France	Neurontin
Germany	Neurontin
Greece	Neurontin
Hungary	Neurontin
Iceland	Neurontin
Ireland	Neurontin
Italy	Neurontin
Latvia	Neurontin
Lithuania	Neurontin
Luxembourg	Neurontin
Malta	Neurontin
Netherlands	Neurontin
Norway	Neurontin
Poland	Neurontin
Portugal	Neurontin
Slovakia	Neurontin
Slovenia	Neurontin
Spain	Neurontin
Sweden	Neurontin
United Kingdom	Neurontin

This leaflet was last approved in {MM/YYYY}.

[To be completed nationally]