CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-216

PHARMACOLOGY REVIEW(S)

September 28, 2000

Review and Evaluation of Pharmacology and Toxicology
Pediatric efficacy claim

NDA: 21-216

Sponsor: Parke-Davis
Ann Arbor, MI

Rec'd: 12/22/99

Drug: Neurontin (gabapentin) [redacted]

Indication: [redacted]

Pharm/Tox submission contents:

Five preclinical toxicology study reports first submitted with the capsule NDA (20-235, submitted 1/15/92) and previously reviewed (original NDA review):

	Title	Location Within Original NDA		Location Within This NDA	
		Volume	Page	Volume	Page
1.	Acute toxicity of Gö 3450 in intragastric and intravenous administration to 3-week old mice and rats. RR 4188-0400, July 08, 1983.	1.18	145	2	4
2.	Acute oral toxicity study in 7-day old rats with CI-945. RR 745-01147, Jan 14, 1988.	1.18	241	2	12
3.	Acute oral toxicity study in 21-day old rats with CI-945. RR 745-01100, Apr 21, 1987.	1.18	293	2	64
4.	Seven-week oral toxicity study in rats with CI-945. RR 745-01199, Jan 11, 1988.	1.21	1	2	107
5.	CI-945 plasma concentrations in male and female rats in a 7-week oral toxicity study (Protocol 1114). RR-MEMO 4192-00333, Nov 23, 1988.	1.50	152	2	466

Evaluation and Recommendations:

The juvenile animal studies submitted with the original capsule NDA (listed above) are not adequate to support pediatric labeling for this chronic-use drug. Although the treatment period used in the 7-week study (pups dosed from PND 7-8) is appropriate, the endpoints evaluated (typical general toxicity parameters) are not. Since one of the primary safety concerns in pediatric age groups is for possible effects on the developing CNS, the potential for developmental neurotoxicity should be thoroughly evaluated in a repeated-dose juvenile rat study. This evaluation should include detailed neurohistopathology examinations and extensive longitudinal neurobehavioral assessments (measures of physical development, sensory function, locomotor activity, learning and memory). In addition, male and female sexual maturation and reproductive function should be evaluated. The protocol for such a study should be submitted for review prior to initiation. It was previously agreed that the new juvenile animal study could be conducted Phase 4.

/S/

J. E. Fisher, Ph.D.

NDA (21-216)
Div File
HFD-120/GFitzgerald/EFisher/JWare
/97 9/29/99

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2.	Acute oral toxicity study in seven-day old rats with CI-945. RR-745-01147, Jan 14, 1988.	2	12
3.	Acute oral toxicity study in 21-day old rats with CI-945. RR-745-01100, Apr 21, 1987.	2	64

[a] Item 4 included by cross-reference from pending syrup NDA 21-129. Numbers in ( ) indicate volume and page location within NDA 21-129, submitted April 30, 1999.
[b] Item 5 included by cross-reference from capsule NDA 20-235 submitted on January 15, 1992, copies included here as requested by FDA.

[c] Item 6.1 included by cross-reference from pending NDA 21-129. Numbers in ( ) indicate volume and page location within NDA 21-129, submitted April 30, 1999.

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2.	A single-dose study of gabapentin syrup (CI-945) pharmacokinetics in healthy neonates, infants, and children. RR 744-00458, Sep 20, 1999.		
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	An analysis of secondarily generalized tonic-clonic seizures in a 12-week, double-blind, placebo-controlled, parallel-group, multicenter study of gabapentin as add-on therapy in children with refractory partial seizures. RR 720-04417, Oct 14, 1999.		
	Protocols 945-305/405	21-23	1
2.	Gabapentin pediatric add-on trial: a randomized, double-blind, placebo-controlled, parallel-group, multicenter study in pediatric patients aged 1 month to 36 months with refractory partial seizures. RR 720-04333, Nov 17, 1999.		

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8.9.6.	Data Submitted in Safety Updates to NDA 20-235		
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	1. Double-blind, placebo-controlled, multicenter studies and their associated extended-treatment studies of the safety and efficacy of gabapentin monotherapy in patients with childhood absence epilepsy naive to antiepileptic drug therapy. RR 720-03365, Nov 26, 1997.		

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	Protocols 945-11 and 945-11X	(1.154)[e]	(1)[e]
2.	Double-blind and long-term safety and efficacy in juveniles with partial seizures. A report of a single-center pilot study comprising a 12-week, placebo-controlled, parallel-group, double-blind phase, followed by a long-term, open-label phase, to determine the efficacy and safety of gabapentin taken as oral daily doses as add-on therapy in juvenile patients with medically refractory partial seizures. RR 4301-00126, Sep 13, 1991.		

[e] Item 8.9.7 included by cross-reference from approved capsule NDA 20-235. Numbers in ( ) indicate volume and page location within NDA 20-235, submitted January 15, 1992.

[f] Item 10.3.1 included by cross-reference from pending [redacted] NDA 21-129. Numbers in ( ) indicate volume and page location within NDA 21-129, submitted April 30, 1999.

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	An analysis of secondarily generalized tonic-clonic seizures in a 12-week, double-blind, placebo-controlled, parallel-group, multicenter study of Gabapentin as add-on therapy in children with refractory partial seizures (Protocols 945-86/186). RR-MEMO 720-04417, Oct 14, 1999.	36	416
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2.	Gabapentin pediatric add-on trial: A randomized, double-blind, placebo-controlled, parallel-group, multicenter study in pediatric patients aged 1 month to 36 months with refractory partial seizures (Protocol 945-305/405). RR 720-04333, Nov 17, 1999.		
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ITEM 3.
SUMMARY

ITEM 3.1.
NDA Overview
[redacted] NDA 21-216
Capsule NDA 20-235/S14
Tablet NDA 20-882/S2

ITEM 3.1.
NDA Overview

The Neurontin capsule NDA 20-235 was approved December 30, 1993 for adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy. The approved dosage forms under this NDA are 100-, 300-, and 400-mg hard gelatin capsules. The Neurontin tablet NDA 20-882 was approved on October 9, 1998 for 600- and 800-mg film-coated tablets as an alternate dosage form. Both the capsule and the tablet NDAs use the same package insert.

A third gabapentin NDA 21-129 was submitted on April 30, 1999 to add a 250 mg/5 mL [redacted] as an alternate dosage form. The submission proposes use of the same package insert as the approved capsule and tablet NDAs noted above. NDA 21-129 is still pending at the time of this submission.

The Pediatric Use subsection of the approved Neurontin package insert states that "Safety and effectiveness in children below the age of 12 years have not been established." This submission provides data to support use in pediatric patients below 12 years of age.

Written Request for Neurontin Pediatric Studies

On October 9, 1998 FDA issued a formal Written Request under the approved capsule NDA 20-235, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic (FD&C) Act, for the conduct of pediatric studies. This Written Request was amended on February 4, 1999, August 10, 1999, and October 18, 1999. A copy of the October 18, 1999 Written Request, which incorporates the February 4 and August 10, 1999 amendments, is attached to the annotated Written Request (NDA Item 3.2.1). The pediatric data obtained in response to this Written Request and proposed labeling changes based on this data is being submitted as an NDA (NDA 21-216, [redacted] and as supplements to our approved NDAs (NDA 20-235, capsule and NDA 20-882, tablet). As instructed in the Written Request, the cover letter to each submission has been clearly marked as **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"**. A copy of the cover letters has also been sent to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

FDA's September 1999 revision to the Guidance for Industry on Qualifying for Pediatric Exclusivity under Section 505A of the FD&C Act encourages sponsors to submit an annotated Written Request indicating where in the reports of studies the sponsor has responded to each part of the Written Request. This is provided in NDA Item 3.2.

Pre-NDA Meetings

A pre-NDA meeting was held on July 22, 1999. A copy of our pre-meeting background material and minutes of this meeting are attached to this NDA Overview.

Regulatory Submission of Pediatric Data

A Neurontin adult [redacted] NDA 21-129 was submitted on April 30, 1999. Because this NDA is still pending, a new [redacted] NDA 21-216 is submitted to support use of the [redacted] in both adults and pediatric patients. To avoid duplication, the [redacted] NDA 21-129 Item 4 chemistry, manufacturing, and controls data and the Item 6 adult [redacted] pharmacokinetic and bioavailability data is included in the new [redacted] NDA 21-216 by cross reference from the pending adult [redacted] NDA 21-129. A full user-fee has been paid for NDA 21-216. As with the pending adult [redacted] NDA 21-129, it is proposed that the [redacted] formulation use the same package insert as the approved capsule and tablet NDAs.

This pediatric submission contains pharmacokinetic, safety, and efficacy data for gabapentin capsules and [redacted] in pediatric subjects 1-month to 12-years of age. Because the purpose of this submission is to support the pharmacokinetics, safety and efficacy of gabapentin in pediatric patients as requested in FDA's Written Request, the pediatric data for both the capsule and the [redacted] dosage forms is summarized together. However, to avoid incorrect "bundling", the Agency has specified that 2 separate applications should be submitted, one as a supplement under the NDA for the capsule dosage form (NDA 20-235), and one for the [redacted] dosage form ([redacted]. For the convenience of the reviewer, the data for both the [redacted] and the capsule is provided together in the [redacted] NDA 21-216 and submitted by cross reference as a supplement to the capsule NDA 20-235.

Neurontin 600- and 800-mg tablets are the subject of approved NDA 20-882. The approved capsule NDA 20-235 and tablet NDA 20-882 use the same package insert. No pediatric data was developed using the tablet because the higher mg dosage and the

physically larger size of the tablets make this alternate dosage form not appropriate for pediatric patients below 12 years of age. Because we are seeking to use the same package insert for the [redacted] capsule, and tablet dosage forms, this pediatric submission is also included by cross-reference to the approved tablet NDA 20-882.No user-fee has been paid for the pediatric supplements to NDA 20-235 and NDA 20-882.

Contents of the Submissions

The method of pagination for this supplement uses a number, located in a box in the upper right-hand corner of each page, that identifies the page number within the respective volume. Each volume begins with the Page 1 and a table of contents that identifies the documents contained within the volume. All documents within a volume retain their own internal table of contents and internal page number. The internal page number for the document appears in the top center of each page. The internal table of contents and internal page number should be used to locate information within a document, even if the document comprises more than one volume. Thus, the page number in the upper right-hand corner should be used to locate a document within a volume, while the page number in the upper center should be used to locate information within a particular document.

The same pediatric data is included in 3 pediatric regulatory submissions (the [redacted] NDA 21-216 and the supplement to the capsule NDA 20-235 and the tablet NDA 20-882). The following describes the data physically provided in each submission, and the data provided by cross-reference.

Index

The index for the new [redacted] NDA 21-216 lists all data both physically included in the NDA and included by cross-reference from other NDAs. For those sections included by cross reference, the appropriate NDA and volume and page numbers within that NDA are also identified. For the pediatric supplements to the approved capsule NDA 20-235 and tablet NDA 20-882, the actual physical contents of each supplement are identified in a "Contents of this Submission". The index to the [redacted] NDA 21-216 is included in each supplement to identify those sections included by cross-reference.

ITEM 2: LABELING

We are proposing one package insert for the Neurontin tablet, capsule, and [redacted] dosage forms. Thus, the same proposed revisions to the package insert are physically included in all 3 regulatory submissions.

ITEM 3: SUMMARY

The summary information is physically located in the [redacted] NDA 21-216 and is included by cross-reference to the pediatric supplement to the approved capsule NDA 20-235 and tablet NDA 20-882. However, to aid the FDA reviewer, a copy of this NDA overview is also physically included with the actual supplement to the approved capsule NDA 20-235 and tablet NDA 20-882.

ITEM 4: CHEMISTRY, MANUFACTURING, AND CONTROLS

The CMC information is physically located in the pending adult [redacted] NDA 21-129 and is included by cross-reference to the new [redacted] NDA 21-216. A separate environmental assessment is included with the [redacted] capsule, and tablet regulatory submissions.

ITEM 5: PRECLINICAL PHARMACOLOGY AND TOXICOLOGY

Five juvenile toxicology studies were submitted in support of the original capsule NDA 20-235 (submitted 1/15/92). At the request of the FDA reviewer, duplicate copies of the reports of these studies are provided again in this pediatric submission. The duplicate copies of the study reports are physically included in the [redacted] NDA 21-216.

ITEM 6: HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

Item 6 of this submission is divided into 2 sections:

The first section is the adult [redacted] pharmacokinetic and bioavailability information. This data is physically located in the pending [redacted] NDA 21-129 and is included by cross-reference to the new [redacted] NDA 21-216.

The second section is the pediatric [redacted] and capsule pharmacokinetic information. This section includes the single-dose pediatric pharmacokinetic data and the pediatric

population pharmacokinetics for both the capsule and the [redacted] The single-dose data for the capsules in pediatric subjects age 4 to 12 years is contained in the report for Protocol 945-202. The single dose data for the [redacted] in pediatric subjects age 1 month to 4 years of age is contained in the report for Protocol 945-296. The population pharmacokinetic data for the capsule and the [redacted] in pediatric patients 1-month to 12-years of age is contained in one report, RR 764-03220. The capsule population pharmacokinetic data was obtained from patients age 3 to 12 years participating in the pediatric safety and efficacy study 945-86/186 and from patients age 4 to 13 years participating in the study of benign childhood epilepsy with centrotemporal spikes (BECTS), Protocols 945-94 and 945-95. The [redacted] population pharmacokinetic data was obtained from patients age 1 month to 4 years participating in the pediatric safety and efficacy studies 945-301/401 and 945-305/405. All pediatric pharmacokinetic data is physically contained in the new [redacted] NDA 21-216 and is included by cross-reference to the pediatric supplements to the capsule NDA 20-235 and the tablet NDA 20-882.

ITEM 8: CLINICAL DATA

The safety and efficacy of gabapentin at the recommended doses in adults >12 years of age has been established in NDA 20-235. Since bioequivalence in adults has been established between the capsule and the proposed [redacted] dosage form (included by cross-reference from NDA 21-129), no additional safety and efficacy data for the [redacted] in adults has been included in this submission.

Item 8 of this submission contains safety data in pediatric patients 1-month to 13-years of age and efficacy data in pediatric patients 1-month to 12-years of age for both the [redacted] and capsule dosage forms.

Data is provided to support use in pediatric patients for the same indication as that in adults: adjunctive therapy in the treatment of partial seizures. The [redacted] safety and efficacy data for this indication in pediatric patients 1-month to 3-years of age is contained in the reports for Protocol 945-305/405 (double-blind, efficacy and short-term safety in 76 patients) and 945-301/401 (open-label, long-term safety in 145 patients). The capsule safety and efficacy data for this indication in pediatric patients 3 to 12 years of age is contained in the reports for Protocol 945-86/186 (double-blind, efficacy and short-term safety in 247 patients) and Protocol 945-87/187 (open label, long-term safety in 237 patients).

Data is also provided from studies of Neurontin in pediatric patients for indications other than the approved adult indication, to further support the safety of Neurontin in pediatric patients. The indications studied, all with the capsule formulation, include:

- Benign childhood epilepsy with centrotemporal spikes [BECTS] (Protocol 945-94, double-blind efficacy and short-term safety, and Protocol 945-95, open label, long-term safety in 205 patients)
- Lennox Gastault (Protocol 945-008, double-blind efficacy and safety in 6 patients).

As noted in our pre-NDA meeting submission, this pediatric supplement also contains safety data from 42 children under the age of 12 who were studied during the development of the adult NDA 20-235. Of these, 14 children participated in studies 877-34 and –34X, 945-11 and –11X, and 945-16. Complete research reports for these studies were submitted in NDA 20-235. Because these studies include many adults and only a few children, it was agreed at our pre-NDA meeting that we would include the research reports for these studies by cross-reference from the original NDA 20-235. The location of these reports in the original NDA is identified in the NDA Index. The remaining 28 of the 42 children participated in the absence study 945-19/20 and the open-label extension, 945-49/50. The data from these 28 children were included in safety updates to NDA 20-235. Since a complete research report for this study has not yet been submitted to FDA, a research report is provided in Item 8.9.5.

Item 8 also includes the literature review for pediatric use of gabapentin (Item 8.4.).

The data in NDA Item 8 is physically located in the new [redacted] NDA 21-216 and is included by cross reference in the supplements to the capsule NDA 20-235 and the tablet NDA 20-882.

ITEM 10: Statistical Section

The following information from Item 8 is included again in this section: description and location of each clinical study, investigator alphabetical listing, summary of pediatric pharmacokinetic data, integrated summary of efficacy, integrated summary of safety, benefit/risk, and the reports of the 2 adequate and well-controlled studies 945-86/186 and 945-305/405 submitted to support efficacy for adjunctive treatment of partial seizures in pediatric patients. The report of the controlled efficacy study 945-94 is not included here

as this submission does not seek approval of the BECTS indication. This data is physically located in the new [redacted] NDA 21-216 and is included by cross-reference in the supplement to the capsule NDA 20-235 and the tablet NDA 20-882.

ITEM 11: Case Report Forms Tabulations

As agreed at our pre-NDA meeting, these tabulations are submitted only in electronic .PDF format. No paper copy is submitted. Tabulations are provided for the 3 recently completed double-blind, placebo-controlled studies and their long term extensions 945-86/186 and 945-87/187 (capsules, partial seizures), 945-305-405 and 945-301/401 (syrup, partial seizures), and 945-94 and 945-95 (capsules, BECTS). This data is physically located in the new [redacted] NDA 21-216 and is included by cross-reference in the supplement to the capsule NDA 20-235 and the tablet NDA 20-882. As agreed at our pre-NDA meeting, CRF tabulations are not provided for the remaining studies that also included pediatric patients.

ITEM 12: Case Report Forms

CRFs for all patients who died or withdrew due to an adverse event from all pediatric patients participating in all studies referenced in this pediatric submission are submitted in electronic .PDF format. No paper copy is provided. This data is physically located in the new [redacted] NDA 21-216 and is included by cross reference in the supplement to the capsule NDA 20-235 and the tablet NDA 20-882.

ITEM 13: Patent Information

This is physically located behind the appropriate tab in Volume 1 for all 3 regulatory submissions (the new [redacted] NDA 21-216, the supplement to the capsule NDA 20-235 and the supplement to the tablet NDA 20-882).

ITEM 16: Debarment Certification

This is physically located behind the appropriate tab in Volume 1 in the new [redacted] NDA 21-216 and is included by cross reference in the supplement to the capsule NDA 20-235 and the tablet NDA 20-882.

Neurontin
Pediatric

ITEM 18: User Fee Cover Sheet

A full user fee has been paid for the new — NDA 21-216. Because the supplement to the capsule NDA 20-235 is a pediatric supplement, no user fee has been paid. Because the supplement to the tablet NDA 20-882 is a pediatric supplement and because it contains no clinical safety or efficacy data for the tablet, no user fee has been paid. A user fee cover sheet is physically located behind the appropriate tab in Volume 1 for all 3 regulatory submissions (the new — NDA 21-216, the supplement to the capsule NDA 20-235 and the supplement to the tablet NDA 20-882).

ITEM 19: Other

Financial Disclosure: This is physically located behind the appropriate tab in Volume 1 for the — NDA 21-216. It is included by cross reference to the supplement to the capsule NDA 20-235 and — NDA 20-882.

Attachments:

Pediatric Pre-NDA Meeting Request and Meeting Minutes

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