CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-216

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

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NDA 21-216 Neurontin (gabapentin) oral solution
NDA 20-235/S-015 Neurontin (gabapentin) capsule
NDA 20-882/S-002 Neurontin (gabapentin) tablet
For adjunctive therapy of partial onset seizures
in pediatric patients 1 month to 12 years of age

Approval Package

ITEM 13.
PATENT INFORMATION

ITEM 13.
PATENT AND MARKET EXCLUSIVITY INFORMATION

13.1. Patent Information

Time Sensitive Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA #21-216

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

- Trade Name: Neurontin®
- Active Ingredient: 1-(aminomethyl)-1-cyclohexaneacetic acid
- Strengths: 50 mg/mL
- Dosage Form: [redacted] for oral administration
- Approval Date:

U.S. Patent Number:	4,087,544
Expiration Date:	January 16, 2000
Type of Patent:	Method of Use (to treat epilepsy)
Assignee:	Warner-Lambert Company
U.S. Patent Number:	4,894,476
Expiration Date:	May 2, 2008
Type of Patent:	Drug Substance (Active Ingredient)
Assignee:	Warner-Lambert Company
U.S. Patent Number:	5,084,479
Expiration Date:	January 2, 2010
Type of Patent:	Method of Use (to treat neurodegenerative diseases)
Assignee:	Warner-Lambert Company

The undersigned declares that Patent Numbers 4,087,544, 4,894,476, and 5,084,479 cover a crystal form and the use of Neurontin® (gabapentin) (1-(aminomethyl)-1-cyclohexaneacetic acid). Neurontin® is approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: November 9, 1999

Elizabeth M. Anderson
Senior Patent Agent
Warner-Lambert Company
Registration No. 31,585

EA1P41135.doc

Exclusivity Summary for NDA 20-882/S-002

NDA:	**20-882/S-002**
Trade Name:	**Neurontin tablet**
Generic Name:	**gabapentin**
Applicant Name:	**Parke Davis**
Division:	**HFD-120**
Project Manager:	**Jacqueline H. Ware, Pharm.D.**
Approval Date:	**October 12, 2000**

PART I
IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a.	Is it an original NDA?	**No**
b.	Is it an effectiveness supplement? If yes, what type? (SE1, SE2, etc.)	**Yes** **SE1**
c.	Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	**Yes**
	If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.	**N/A**
	If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:	**N/A**
d.	Did the applicant request exclusivity? If the answer "yes," how many years of exclusivity did the applicant request?	**No**
e.	Has pediatric exclusivity been granted for this Active Moiety?	**Yes**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such) **No**

   If yes, what is NDA number

   If yes, what is Drug Name

   IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? **No**

   IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

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PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. **Yes**

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **20-235**
   21-129

2. Combination product. **N/A**

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

Yes- by right of reference to NDA 20-235/S-015

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

      If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

If yes, explain:

c. If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 **No**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA: Study: **N/A**

b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 - **No**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study: - **N/A**

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 Study #: 945-86/186

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 IND#: 28,454 **Yes**

If no, explain:

b. For each investigation not carried out under an IND or for which the applicant **N/A**

was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) **No**

If yes, explain:

Jacqueline H. Ware, Pharm.D.
Project Manager
DNDP, HFD-120

Russell Katz, M.D.
Director
DNDP, HFD-120

Form OGD-011347, Revised 10/13/98
c:\wpfiles\jwndas\N20882\S002\excl_sum.doc
Final: October 12, 2000

cc:
Original NDA
Division File
HFD-120/Ware
HFD-93/Holovac

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/s/

Russell Katz
11/7/00 03:02:18 PM

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ON ORIGINAL

Exclusivity Summary for NDA 21-216

NDA:	**21-216**
Trade Name:	**Neurontin oral solution**
Generic Name:	**gabapentin**
Applicant Name:	**Parke Davis**
Division:	**HFD-120**
Project Manager:	**Jackie Ware, Pharm.D.**
Approval Date:	**October 12, 2000**

PART I
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a.	Is it an original NDA?	**Yes**
b.	Is it an effectiveness supplement? If yes, what type? (SE1, SE2, etc.)	**No**
c.	Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	**Yes**
	If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.	**N/A**
	If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:	**N/A**
d.	Did the applicant request exclusivity? If the answer "yes," how many years of exclusivity did the applicant request?	**No**
e.	Has pediatric exclusivity been granted for this Active Moiety?	**Yes**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such) **No**

   If yes, what is NDA number

   If yes, what is Drug Name

   IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? **No**

   IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II

FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. **Yes**

   Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **20-235, 20-882, 21-129**

2. Combination product. **N/A**

   If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

   If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

Yes-by right of reference to NDA 20-235/S-015

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

      If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

   b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data

would not independently support approval of the application?

1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

   If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

   If yes, explain:

c. If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

   Investigation #1, Study #:

   Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

   Investigation #1 **No**

   If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA: Study: **N/A**

b. For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 **No**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study: **N/A**

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 Study #: 945-86/186

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 IND#: 28,454 **Yes**

If no, explain:

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A**

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) **No**

If yes, explain:

Jacqueline H. Ware, Pharm.D.
Project Manager
DNDP, HFD-120

Russell Katz, M.D.
Director
DNDP, HFD-120

Form OGD-011347, Revised 10/13/98
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Final: October 12, 2000

cc:
Original NDA
Division File
HFD-120/Ware
HFD-93/Holovac

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ON ORIGINAL

/s/

Russell Katz
11/7/00 02:57:06 PM

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Summary for NDA 20-235/S-015

NDA:	**20-235/S-015**
Trade Name:	**Neurontin capsule**
Generic Name:	**gabapentin**
Applicant Name:	**Parke Davis**
Division:	**HFD-120**
Project Manager:	**Jacqueline H. Ware, Pharm.D.**
Approval Date:	**October 12, 2000**

PART I
IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a.	Is it an original NDA?	**No**
b.	Is it an effectiveness supplement?	**Yes**
	If yes, what type? (SE1, SE2, etc.)	**SE1**
c.	Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	**Yes**
	If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.	**N/A**
	If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:	**N/A**
d.	Did the applicant request exclusivity?	**No**
	If the answer "yes," how many years of exclusivity did the applicant request?	
e.	Has pediatric exclusivity been granted for this Active Moiety?	**Yes**

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such) **No**

   If yes, what is NDA number

   If yes, what is Drug Name

   IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.

3. Is this drug product or indication a DESI upgrade? **No**

   IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).

PART II
FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product. **Yes**

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s). **20-882 21-129**

2. Combination product. **N/A**

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III

THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. **Yes**

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   a. In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement? **Yes**

      If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

b. Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application? **No**

1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO. **No**

If yes, explain:

2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product? **No**

If yes, explain:

c. If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study #: **945-86/186**

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a. For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 **No**

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA: Study: **N/A**

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Investigation #1 **No**

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA: Study: **N/A**

c. If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 Study #: 945-86/186

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 IND#: 28,454 **Yes**

If no, explain:

b. For each investigation not carried out under an IND or for which the applicant **N/A**

was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.) **No**

If yes, explain:

Jacqueline H. Ware, Pharm.D.
Project Manager
DNDP, HFD-120

Russell Katz, M.D.
Director
DNDP, HFD-120

Form OGD-011347, Revised 10/13/98
c:\wpfiles\jwndas\N20235\S015\excl_sum.doc
Final: October 12, 2000

cc:
Original NDA
Division File
HFD-120/Ware
HFD-93/Holovac

APPEARS THIS WAY
ON ORIGINAL

/s/

Russell Katz
11/7/00 02:59:49 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020882	**Trade Name:**	NEURONTIN (GABAPENTIN) 600/800MG TABS
Supplement Number:	002	**Generic Name:**	GABAPENTIN TABS
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	[redacted]
Action Date:	12/15/99		

Indication # 1 Use of Neurontin as adjunctive therapy in the treatment of partial seizures in pediatric patients. [redacted]

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): See information entered for NDA 21-216 (original application) and NDA 20-235/S-015 for complete pediatric information. This supplement was a complete cross-reference to those applications.

Lower Range	Upper Range	Status	Date
1 months	12 years	Completed	

This page was last edited on 10/11/00

Signature - /S/ 10/11/00

Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	020235	**Trade Name:**	NEURONTIN (GABAPENTIN) CAPSULES
Supplement Number:	015	**Generic Name:**	GABAPENTIN
Supplement Type:	SE1	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	[redacted]
Action Date:	12/15/99		

Indication # 1 Use of Neurontin as adjunctive therapy in the treatment of partial seizrues in pediatric patients. [redacted]

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): 10/11/00: Upon submission, this application provided effectiveness data in patients 1 month - 12 years of age. Upon review, a claim for use in pediatric patients age 3 - 12 years will be granted. A waiver for patients 0 - 1 month of age was granted with the issuance of the 1st revision to the pediatric WR letter for gabapentin (dated 2/4/99). The original WR letter issued 10/8/98 and was followed by 3 revisions dated 2/4/99, 8/10/99, and 10/18/99.

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	

Comments: Studies in this pediatric population were waived based on the clinical decision that partial seizures did not exist or were not easily detectable in this age group.

1 months	3 years	Completed	10/12/00
3 years	12 years	Completed	10/12/00

This page was last edited on 10/11/00

Signature - /S/ — 10/11/00 Date

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number:	021216	**Trade Name:**	NEURONTIN (GABAPENTIN) 250MG/5ML
Supplement Number:	000	**Generic Name:**	GABAPENTIN
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	[redacted]
Action Date:	12/15/99		

Indication # 1 Use of Neurontin as adjunctive therapy in the treatment of partial seizures in pediatric patients [redacted]

Label Adequacy: Adequate for SOME pediatric age groups

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any): 10/11/00: Upon submission, the application provided effectiveness data in patients 1 month - 12 years of age. Upon review, a claim for pediatric patients age 3 - 12 years will be granted. A waiver to study this indication in pediatric patients age 0 - 1 month was granted with the issuance of the 1st revision to the pediatric written request letter for gabapentin (dated 2/4/99). The original WR letter issued 10/9/98 and 3 revisions issued 2/4/99, 8/10/99, and 10/18/99.

Lower Range	Upper Range	Status	Date
0 months	1 months	Waived	
Comments: Studies in this pediatric population were waived based on the clinical decision that partial seizures did not exist or were not easily detectable in this age group.			
1 months	3 years	Completed	10/12/00
3 years	12 years	Completed	10/12/00

This page was last edited on 10/11/00

Signature /S/ — 10/11/00 Date

APPEARS THIS WAY
ON ORIGINAL

ITEM 16.
DEBARMENT CERTIFICATION

ITEM 16.
Debarment Certification

Warner-Lambert Company certifies that it is not debarred, and to the best of its knowledge Warner-Lambert Company did not and will not use in any capacity the services of any person debarred under Section 306(a) or 306(b) of the Federal Food, Drug, and Cosmetic Act in connection with the application.

ITEM 1.
sNDA INDEX

ITEM	DESCRIPTION	sNDA LOCATION
Application Form (FDA 356h)		
1.	sNDA INDEX	
2.	LABELING	
2.1.	Age Categories and Type of Pediatric Data Submitted	
2.2.	CFR Paragraph Supporting Labeling Revision	
2.3.	Draft Labeling	
3.	SUMMARY	
3.1.	sNDA Overview	
3.2.	Foreign Marketing History	
3.3.	Description and Location of Each Clinical Study	
3.4.	Clinical Comprehensive Summary	
3.5.	Benefit/Risk	
5.	PRECLINICAL PHARMACOLOGY AND TOXICOLOGY	
5.1.	Notes to Reviewer	
5.2.	Pharmacology and Toxicology References	

sNDA

LOCATION

ITEM DESCRIPTION

1. Acute toxicity of Gö 3450 in intragastric and intravenous administration to 3-week old mice and rats.
RR 4188-0400, Jul 8, 1983.

2. Acute oral toxicity study in seven-day old rats with CI-945.
RR 745-01147, Jan 14, 1988.

3. Acute oral toxicity study in 21-day old rats with CI-945.
RR 745-01100, Apr 21, 1987.

4. Seven-week oral toxicity study in rats with CI-945.
RR 745-01199, Jan 11, 1988.

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.

6. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

Item 6 Index

6.1. Summary of Gabapentin Pharmacokinetics in Pediatric Subjects

6.2. Study Reports

1. A single-dose study of Neurontin® (gabapentin; CI-945) pharmacokinetics in healthy pediatric subjects (Protocol 945-202).
RR 744-00377, Dec 9, 1997.

2. Protocol 945-296

ITEM	DESCRIPTION	sNDA LOCATION
3.	Pop PK RR-MEMO	

8. CLINICAL DATA

Item 8 Index

8.1. Description and Location of Each Clinical Study

8.2. Investigators Alphabetical Listing

8.3. Investigators' Curriculum Vitae

8.4. Literature Review

8.5. Summary of Gabapentin Pharmacokinetics in Pediatric Subjects

8.6. Integrated Summary of Efficacy

8.7. Integrated Summary of Safety

8.8. Benefit/Risk

8.9. Study Reports

8.9.1. Pediatric Pharmacokinetics

1. A single-dose study of Neurontin® (gabapentin; CI-945) pharmacokinetics in healthy pediatric subjects. RR 744-00377, Dec 9, 1997.
2. Protocol 945-296
3. RR-MEMO Pop PK

8.9.2. Controlled Efficacy Studies Supporting Pediatric Indication

1. A 12-week, double-blind, placebo-controlled, parallel-group, multicenter study of gabapentin as add-on therapy in children with refractory partial seizures

ITEM	DESCRIPTION	sNDA LOCATION
	(Protocols 945-86 and 945-186). RR 720-03891, Nov 20, 1997.	
	2. Protocol 945-305	
8.9.3.	Other Controlled Efficacy Study	
	1. Protocol 945-94	
8.9.4.	Open Label Study	
	1. Report of an open-label extension of a double-blind, placebo-controlled, multicenter study of gabapentin (CI-945, Neurontin®) as add-on therapy in children with partial seizures (Protocol 945-87/187). RR 720-03893, Dec 2, 1997.	
	2. Protocol 945-95	
	3. Protocol 945-301	
8.9.5.	Other Studies	
	1. A double-blind, placebo-controlled, multicenter study, with an open-label extension, of the safety and efficacy of gabapentin as add-on therapy in the treatment of pharmacotherapy-resistant childhood symptomatic epilepsies (Protocol 945-008). RR 720-03483, Jul 11, 1997.	

APPEARS THIS WAY
ON ORIGINAL

ITEM	DESCRIPTION	sNDA LOCATION
8.9.6	Data Submitted in Safety Updates to NDA 20-235	
	1. A 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 (double-blind Protocols 945-19 [US] and 945-20 [Non-US] and extended-treatment Protocols 945-49 [US] and 945-50 [Non-US]). RR 720-03365, Nov 26, 1997.	
10.	STATISTICAL SECTION	
Item 10 Index		
10.1.	Description and Location of Each Clinical Study	
10.2.	Investigators Alphabetical Listing	
10.3.	Summary of Gabapentin Pharmacokinetics in Pediatric Subjects	
10.4.	Integrated Summary of Efficacy	
10.5.	Integrated Summary of Safety	
10.6.	Benefit/Risk	
10.7.	Study Reports	
10.7.1.	Controlled Efficacy	
	1. A 12-week, double-blind, placebo-controlled, parallel-group, multicenter study of gabapentin as add-on therapy in children with refractory partial seizures	

sNDA

LOCATION

ITEM DESCRIPTION

(Protocols 945-86 and 945-186).
RR 720-03891, Nov 20, 1997.

2. Protocol 945-305

11. CASE REPORT FORMS TABULATIONS (PROVIDED ELECTRONICALLY)

12. CASE REPORT FORMS (PROVIDED ELECTRONICALLY)

13. PATENT INFORMATION

16. DEBARMENT CERTIFICATION

18. USER FEE COVER SHEET

19. OTHER—ENVIRONMENTAL ASSESSMENT

APPEARS THIS WAY
ON ORIGINAL

Gabapentin Pediatric Integrated Summary of Efficacy

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This Page is Missing from the Original Approval Package

pages 100 - 376
(ISS from sponsor)

ITEM 19.1. Financial Disclosure Notes to Reviewer

The following narrative describes our approach to compliance with the Financial Disclosure by Clinical Investigators Rule, 21 CFR 54, as revised on December 31, 1998 (63 FR 72171-72181).

The following "covered clinical studies" were ongoing as of February 2, 1999:

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 (Protocols 945-305/405). RR 720-04333, Nov 17, 1999. (study period ended 8/19/99)

A single-dose study of gabapentin syrup (CI-945) pharmacokinetics in healthy neonates, infants, and children (Protocol 945-296). RR 744-00458, Sep 20, 1999. (study period ended 2/26/99)

Note: Protocol 945-296 is a descriptive pharmacokinetic study that would normally not be considered to be a "covered clinical study" under 21 CFR 54.2(e). However, since it was conducted in response to the Written Request for Pediatric Studies dated October 19, 1999, we have chosen to treat it as a "covered clinical study"

. Protocol 945-296 is a descriptive study characterizing the pharmacokinetics of gabapentin in children of different age groups. Since there is no comparison of treatment groups or hypothesis testing related to safety or efficacy conducted in this study, we believe that there is extremely limited potential for investigator bias to have influenced the outcome of this study.

The following "covered clinical studies" were completed prior to February 2, 1998, and therefore only require certification relative to 21 CFR 54.4(a)(3)(i) and (iii):

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 720-03891, Nov 20, 1997. (study period ended 11/20/96)

Gabapentin Pediatric Monotherapy Trial: A Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group Study in Pediatric Patients with Benign Childhood Epilepsy With Centrotemporal Spikes (BECTS) (Protocol 945-094). RR 720-04231, Jul 13, 1999. (study period ended 1/13/98)

A single-dose study of Neurontin® (gabapentin; CI-945) pharmacokinetics in healthy pediatric subjects (Protocol 945-202).RR 744-00377, Dec 9, 1997. (study period ended 2/10/95).

The following studies are referenced in the sNDA, however, they are not "covered clinical studies". These studies are not submitted to establish that the product is effective; nor are they studies where any single investigator has made a significant contribution to the demonstration of safety. None of these studies was included in the Written Request for Pediatric Studies dated October 19, 1999.

A double-blind, placebo-controlled, multicenter study, with an open-label extension, of the safety and efficacy of gabapentin as add-on therapy in the treatment of pharmacotherapy-resistant childhood symptomatic epilepsies (Protocol 945-008). RR 720-03483, Jul 11, 1997.

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 (double-blind Protocols 945-19 [US] and 945-20 [Non-US] and extended-treatment Protocols 945-49 [US] and 945-50 [Non-US]). RR 720-03365, Nov 26, 1997.

Report of an open-label extension of a double-blind, placebo-controlled, multicenter study of gabapentin (CI-945, Neurontin®) as add-on therapy in children with partial seizures (Protocols 945-87/187). RR 720-03893, Dec 2, 1997.

An extended open-label gabapentin (CI-945) pediatric monotherapy trial following a double-blind study (Protocol 945-094) in pediatric patients with benign childhood epilepsy with centrotemporal spikes (BECTS) (Protocol 945-095). RR 720-04362, Aug 27, 1999.

A single-dose bioequivalence study comparing CI-945 syrup to 300-mg gabapentin [redacted] capsules (Protocol 945-201). RR 744-00409, Apr 20, 1999.

An interim safety report of an open-label, safety study of Gabapentin (CI-945) as adjunct therapy in children aged 1 month through 4 years with seizures uncontrolled by current anticonvulsant drugs (Protocol 945-301/401). RR 720-04335, Nov 17, 1999.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See attached list.	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Janeth L. Turner	Director, FDA Liaison
FIRM/ORGANIZATION: Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company	
SIGNATURE: Janeth L Turner	DATE: 11/19/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

6 pages

(E)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

The following information concerning [redacted]; who participated as a clinical investigator in the submitted study Protocol 945-296, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Name of clinical investigator

Name of clinical study

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Janeth L. Turner	Director, FDA Liaison
FIRM/ORGANIZATION: Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company	
SIGNATURE: Janeth L Turner	DATE: 11/19/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
2800 Plymouth Road
Ann Arbor, MI 48106

2. TELEPHONE NUMBER *(Include Area Code)*

734/622-5168

3. PRODUCT NAME

Neurontin [redacted]

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

3838

6. LICENSE NUMBER / NDA NUMBER

21-216

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THIS APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Please DO NOT RETURN this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
William Rosen	Director Worldwide Regulatory Affairs	December 3, 1999

MEMORANDUM

DATE: October 9, 2000

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 21-216

SUBJECT: Action Memo for NDA 21-216, for the use of Neurontin (gabapentin) as adjunctive treatment for pediatric patients with partial seizures

[redacted] for the use of gabapentin oral solution as adjunctive treatment for partial seizures in pediatric patients, was submitted by Parke-Davis Pharmaceutical Research on 12/14/99. In addition, on the same date, the sponsor also submitted NDA 20-235/S-015 (gabapentin capsules) and NDA 20-882/S-002 (gabapentin tablets). These applications each contained the same data, namely the results of pharmacokinetic studies in pediatric subjects and 2 randomized controlled trials: Study 86/186, a parallel group, placebo controlled trial in patients between the ages of 3-12 years, and Study 305/405, a randomized, placebo controlled trial in patients between the ages of 1 and 36 months. These studies were submitted by the sponsor in response to a Written Request issued by the Agency in a letter dated 10/18/99; therefore, the submission of this application resulted in the granting of an additional 6 months of marketing exclusivity for gabapentin.

The applications have been reviewed by Drs. Maria Sunzel and Elena Mishina, Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/6/00), Dr. Ed Fisher, pharmacologist (review dated 9/28/00), Dr. Ranjit Mani, medical officer (review dated 9/28/00), Dr. Sharon Yan, statistician (review dated 10/4/00), and Dr. John Feeney, Neurology Team Leader (memo dated 10/6/00). The review team (Drs. Mani and Feeney) recommends that the application be approved with labeling to which they have agreed with the sponsor. In this memo, I will briefly note some issues that I believe require further clarification, and offer support for the Division's action.

EFFICACY

As described in detail by Drs. Mani and Yan, the sponsor has submitted the results of 2 randomized controlled trials.

Study 305/405 was a study in which patients aged 1-36 months were randomized (at 73 centers in the US and Canada) to gabapentin or placebo and treated for 72 hours. The protocol was the subject of considerable discussion between the division and the sponsor, and was agreed to by both. The primary outcome was the Response Ratio (RR). Although the gabapentin group was favored

numerically (on the primary as well as several secondary measures), the p-value for the primary contrast was 0.37.

Study 86/186 was a multi-national trial done under 2 separate protocols (86 and 186), which the sponsor explicitly declared would be considered as a single study for analytic purposes. In this trial, patients received gabapentin as adjunctive treatment for partial seizures, and were entered into a 6 week baseline phase, followed by a 12 week treatment period. As the reviewers note, the protocol describes 2 outcomes as primary: the Response Ratio (RR) and the Responder Rate. Further, as Dr. Mani explains, while the protocol was never amended to clarify which one of these, if either, was to be considered the sole primary outcome, an internal company analysis plan, signed off as final several months prior to the documented breaking of the blind, made clear that the Response Ratio was to be the primary measure on which interpretation of the trial was to depend. I find acceptable both the use of the Response Ratio as the primary measure (we have used it in the analyses of the original approval of gabapentin) as well as the documentation that this determination was made by the sponsor prior to the breaking of the blind, the absence of a protocol amendment describing this plan notwithstanding. In addition, also as noted by Drs. Mani and Yan, the raw data were not normally distributed (an observation with which Dr. Yan and the sponsor agree), so, as specified in the protocol, a transformation was performed. The results of this analysis of the Response Ratio yielded a p-value of 0.03 (for the intent-to-treat population). Were there no other problems in the interpretation of this trial, I would easily agree that it would support amending gabapentin labeling to include language describing the effectiveness of the drug in (some) pediatric patients. However, several points need to be made.

The protocol stated that the following seizure types were to be considered in the primary analysis: simple partial seizures, complex partial seizures, and secondarily generalized seizures. The latter seizure type was presumably considered to be a "surrogate" for partial seizures; that is, these secondary seizures were considered to have been preceded, by definition, by a partial seizure, even though this presumed partial seizure was not witnessed. The validity of this assumption is important in this case, because inspection of Dr. Mani's figure and table 5.14.5 and (pages 19 and 20, respectively, of his review), suggests that the largest between treatment difference seen was in this seizure type. For example, the difference in mean RR for the 3 seizure types was –.035, -0.062, and –0.154, respectively (the 95% confidence intervals for each seizure type individually included zero-the individual cells were small-but the interval is much less symmetric around zero for the secondarily generalized seizures). In the absence of evidence that these seizures were, in fact, preceded by a partial seizure, it is difficult to assess the effects of the treatment on partial seizures.

However, I have discussed this issue in detail with the review team. The figure and table referred to above represent results of analyses of the Modified intent-

to-treat population (defined as those patients who had at least 28 days of treatment, and considered by the sponsor as the primary population for analysis). Examination by Dr. Yan of the intent-to-treat population as ordinarily defined (including all patients who had at least one dose of drug and any on-treatment seizure data) yielded the following results for the various seizure types:

Sz Type	Difference in Mean RR	95% CI
Simple partial	-0.005	(-.132, .142)
Complex partial	-.079	(-.210, .052)
Secondary Generalized	-.102	(-.228, .084)
Simple + Complex partial	-.061	(-.168, .046)

These analyses suggest that, although the largest treatment effect is still seen in the secondarily generalized seizure group, the effect in Complex partial seizures (and to a lesser extent in the Complex + Simple partial groups combined) is of a similar magnitude. Further, there appears to be general acceptance in the community that generalized tonic-clonic seizures that occur in patients with a known seizure focus associated with partial seizures are invariably secondarily generalized, unless the patient has a specific syndrome associated with primary generalized seizures, which is presumably not the case here. While the sponsor has submitted no data to support this widely held view, I believe that given 1) that the re-analysis of the intent-to-treat population suggests that the overall effect is not coming primarily from an effect on the generalized seizures, 2) gabapentin's known effect on partial seizures in adults, 3) that it appears that in previous applications, we have included generalized tonic-clonic seizures as being secondary to partial seizures, even in the absence of these partial seizures having been witnessed, and 3) the almost universally held view that generalized seizures in patients with partial seizures are almost always secondary events, it is reasonable to conclude that this study supports the effectiveness of gabapentin as adjunctive treatment for partial seizures in pediatric patients.

However, the lowest age to which this conclusion should apply is not clear.

In this trial, patients as young as 3 years old were enrolled. However, only a total of 8 patients below the age of 5 were treated with gabapentin (14 on placebo), far too few to be able to reach any independent conclusion about the drug's utility in this age group. In fact, Dr. Yan has performed additional analyses (not in her review) which demonstrate essentially no difference between drug and placebo treated patients in these patients. We also know, from the pharmacokinetic analysis of the pediatric database, that patients below the age of 5 years have about a 30% increased clearance compared to older pediatric patients. In this trial, patients received a dose of between 24-35 mg/kg/day. It is quite possible that patients below the age of 5 years were systematically underdosed (for example, patients in Study 305/405 received a dose of 40 mg/kg/day). It is clear that neither the lower age limit nor the dosing regimen in this trial appear to have

been chosen on the basis of PK considerations. Nonetheless, had effectiveness been demonstrated in patients below the age of 3 years, these considerations would not be particularly problematic (it would be eminently reasonable to conclude that gabapentin is effective in 3 and 4 year olds if it had been shown to be effective in patients below 3 and in patients 5 and above). However, since effectiveness has not be demonstrated in patients below the age of 3 years and we have no empirical evidence of gabapentin's effectiveness in patients aged 3 and 4 years, it would seem problematic to conclude that it is effective below the age of 5 years. We could, of course, simply consider adjusting the dose (or range) found to be effective in patients over the age of 5 years (based on the relative PK in the younger ages) and include these in dosing recommendations for 3 and 4 year olds. However, this would presuppose that the exposure achieved at these doses in 3 and 4 year olds is **effective**, a conclusion for which there is no support in evidence (again, especially given the "negative" result in Study 305/405).

The generic problem of how to conclude whether or not effectiveness has been established at the younger ages enrolled in a clinical trial is difficult and has not been settled. In general, we are loath to create post-hoc subgroups of any sort (including ones defined by specific ages) and attempt to identify an independent effect in that group (as I have described above). Ordinarily, we permit a sponsor to claim effectiveness in the entire group studied in a trial (e.g., both sexes, various disease severities, different ages, etc.), assuming there is more than a handful of patients in these subgroups. In particular, in this case, there is no reason to assume that 3 and 4 year olds with partial seizures (or for that matter 5 year olds) will respond differently than older pediatric patients with partial seizures. In this regard, it is worth noting that at a meeting of the Peripheral and Central Nervous Systems Advisory Committee on 9/27/94, at which this generic issue was discussed in the context of considering the approval of carbamazepine in patients below the age of 6 years, the committee concluded that partial seizures are "the same" in children above the age of 2 years old as partial seizures in adults. While it is true, as I have noted above, that examination of these patients revealed essentially no treatment effect, these analyses are post hoc, the groups in which they were performed were quite small, and it is entirely unclear how best to assess effectiveness in specific age cohorts when not prospectively described in the protocol. Further, we have permitted several other sponsors to indicate their anti-seizure drugs down to the age of the youngest patients included in the trial, without performing specific analyses of each specific year of age. For these reasons, I believe that it is reasonable to conclude that

language stating the effectiveness in patients 3 years old and older can be permitted in labeling.

Regarding the dose that should be recommended in these younger patients, I would agree with the biopharmaceutics recommendation that the higher doses be recommended, on the basis of the increased clearance in these patients. While I note my comments earlier about this approach being predicated on the **assumption** that the exposures to be achieved at these higher doses are effective (in the absence of empirical evidence that they are), I further note that I have already concluded that it is reasonable to accept that the drug **is** effective in these patients, for the reasons just given. Given this, it seems reasonable to recommend a dose in these younger patients that would be expected to yield exposures that have been **shown** to be associated with effectiveness in the older pediatric patients.

SAFETY

As Dr. Mani notes, the sponsor has presented safety data gained in a total of approximately 450 patient-years of experience in patients with epilepsy below the age of 12 years. This represents 227 patients between the ages of 3-12 years who received gabapentin as adjunctive therapy (127 for at least 6 months, 1 for at least 1 year) and 205 patients between the ages of 4-13 years who received gabapentin as monotherapy (174 for at least 6 months, and 146 for at least 1 year). In general, the experience did not differ substantively from that gained in adults. However, as Drs. Mani and Feeney note, behavioral disturbances, including hostility, emotional lability, and agitation, were seen at a perhaps surprisingly higher rate in gabapentin treated patients compared to placebo treated patients in the controlled trials (this was not seen in the trials in adults). While these events were usually not considered serious, and rarely led to treatment discontinuation, I agree with the review team that these events should be fairly prominently placed in labeling.

CONCLUSIONS

For the reasons stated above, I have concluded that the sponsor has submitted substantial evidence of effectiveness and safety for gabapentin as adjunctive treatment of partial seizures in pediatric patients 3-12 years old. Accordingly, I will issue the attached Approval letter with included draft labeling.

/S/

Russell Katz, M.D.

Cc:
NDA 21-216
NDA 20-235/S-015
NDA20-882/S-008
HFD-120
HFD-120/Katz/Mani/Feeney/Ware/Fisher/Fitzgerald
HFD-710/Yan/Jin
HFD-860/Sunzel/Mishina/Fadiran

COMPLETED JUL 21 2000

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: July 13, 2000

TO: Jacqueline Ware, Pharm. D., Project Manager
Ranjit B. Mani, M.D., Clinical Reviewer
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-216; 20-235/SE-015; and 20-882/SE-002

APPLICANT: Parke-Davis

DRUG: Neurontin (gabapentin)

CHEMICAL CLASSIFICATION: 3S

THERAPEUTIC CLASSIFICATION: Standard

INDICATION: Adjunctive therapy in the treatment of partial onset seizures in pediatrics [redacted]

CONSULTATION REQUEST DATE: January 4, 2000

ACTION GOAL DATE: October 15, 2000

I. BACKGROUND:

As requested by HFD-120, one routine clinical inspection was conducted in support of the above-noted applications. Wendy G. Mitchell, M.D., was selected for inspection based on the fact that Dr. Mitchell's was the largest domestic site involved, and individual foreign sites had not enrolled large numbers. The inspection focused on Dr. Mitchell's conduct of protocol #945-186.

II. RESULTS:

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Mitchell	Los Angeles	California	March 6, 2000	April 7, 2000	VAI

Protocol #945-186

Site: Wendy G. Mitchell, M.D. – Los Angeles, California

Seven subjects were enrolled at this site, two of whom completed the study. The remaining five subjects discontinued the double-blind phase due to lack of efficacy but entered the open-label phase of the study.

Records for all enrolled subjects were reviewed. No serious adverse events were noted. No significant deviations from federal regulations or GCPs were uncovered during inspection. However, review of the establishment inspection report found that the informed consent document used at this site was inadequate in that it failed to include a statement that the study involved research. This one finding was the sole basis for the VAI classification.

Data acceptable

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The data generated at Dr. Mitchell's site appear valid, as no significant deficiencies were noted during inspection. It is therefore recommended that data from this site may be used in support of NDA 20-216, NDA 20-882/SE-002, and NDA 20-235/SE-015.

Key to Classification:

NAI = No deviation from regulations. Data acceptable
VAI = Minor deviation(s) from regulations. Data acceptable
VAI-r = Deviation(s) from regulations, response requested. Data acceptable
OAI = Significant deviations from regulations. Data unreliable

/S/ 7/13/00

Constance Lewin, M.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

/S/ 7/13/00

Antoine El-Hage, Ph.D., Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
NDA 20-216
NDA 20-882
NDA 20-235
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Hajarian/Lewin
HFD-47/GCP II Branch Chief
HFD-47/Kline for GCPB File 10,039
HFD-47/Reading File

DEPARTMENT OF HEALTH & HUMAN SERVICES

iware

Food and Drug Administration
Rockville MD 20857

Wendy G. Mitchell, M.D.
Children's Hospital of Los Angeles
Neurology Division: Box 82
4650 Sunset Boulevard
Los Angeles, California 90027

MAY 12 2000

Dear Dr. Mitchell:

Between March 28 and 31, 2000, Mr. Ronald L. Koller, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol #945-186) of the investigational drug gabapentin, performed for Parke-Davis Pharmaceutical Research. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note, however, that the informed consent document used in this study was inadequate in that it failed to include a statement that the study involved research. This statement is required by Part 50.25 of our regulations (copy enclosed). Please note item (a) 1.

We appreciate the cooperation shown Investigator Koller during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me at (301)594-1032.

Sincerely yours,

/S/

for

Antoine El-Hage, Ph.D.
Branch Chief
Good Clinical Practice II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place
Rockville, MD 20855

Enclosure:
21 CFR 50.25

FEI: 3000207263
Field Classification: NAI
Headquarters Classification: VAI
_____1)NAI
__X__2)VAI-no response required
_____3)VAI-response requested

If Headquarters classification is a different classification, explain why:
Inadequate informed consent was not noted during inspection.

Deficiencies noted:
__X__inadequate informed consent
_____inadequate drug accountability
_____failure to adhere to protocol
_____inadequate records
_____failure to report ADRS _____
_____other

cc:
HFA-224
HFC-230
HFD-120 Review Div. Dir./Katz
HFD-120 MO/Mani
HFD-120 PM/Ware
HFD-120 Doc. Rm. NDA #21-216/#20882/#20-235
HFD- 45 r/f
HFD- 47 c/r/s GCP file #10,039
HFD- 47 Lewin/Hajarian
HFR-PA250 DIB/Kozick
HFR-PA2565 BIMO Monitor/Koller

r/d: CL:05-05-00
reviewed:JAC:**(5/9/00)**
f/t:mb:**(5/10/00)**

o:\cl\Mitchell May00 VAI.doc

Note to Rev. Div. M.O.

This routine data audit was conducted in support of pending NDA #21-216, NDA #20-882/SE-002, and NDA #20-235/SE-015.

Seven (7) subjects enrolled in protocol #945-186 at this site, two (2) of whom completed the study. The remaining five (5) subjects discontinued the double-blind phase due to lack of efficacy but entered the open-label phase of this study. No serious adverse events were noted.

Records for all enrolled subjects were reviewed. No significant deviations from federal regulations or GCPs were uncovered during the inspection, although the informed consent deficiencies outlined in the foregoing letter were noted at headquarters.

Data appear acceptable.

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

December 3, 1999

NDA 21-216
Neurontin® [redacted]

Re: FDA User Fee -
User Fee I.D. No. 3838

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, Pennsylvania 15259-0001

To Whom It May Concern:

As required by the Prescription Drug User Act II, please find enclosed a check (No. 528047) for $272,282.00 as our payment for a new drug application for Neurontin® (gabapentin) [redacted] NDA 21-216.

If you have any questions regarding this payment, please call me at 734/622-5168 or send a facsimile to 734/622-1702.

Sincerely,

William Rosen

William Rosen
Director
Worldwide Regulatory Affairs

WR\kb
i2-03-1999\21-216\CI-0945\Userfee

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Item 3.2.1.
Final Written Request

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages
+ 6 pages
18 pages

28 pages

(F)