CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-129

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Time Sensitive Patent Information
Pursuant to 21 C.F.R. 314.53
for
NDA #21-129

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: 250 mg/5 mL
- Dosage Form: [redacted]
- 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 the composition, formulation and/or method of use of Neurontin®. Neurontin® is approved under section 505 of the Federal Food, Drug, and Cosmetic Act.

Date: April 16, 1999

Elizabeth M. Anderson

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

EA1P4892.doc

Exclusivity Summary for NDA 21-129

Exclusivity Summary Form

Trade Name: **Neurontin** Generic Name: **gabapentin oral solution**

Applicant Name: **Parke-Davis Pharmaceutical Research**
for Parke-Davis Pharmaceuticals Limited

HFD#: **HFD-120** Approval Date If Known: March 2, 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 question about the submission.*

a) Is it an original NDA? YES /_X_/ NO /__/

b) Is it an effectiveness supplement? YES /__/ NO /_X_/
If yes, what type? (SE1, SE2, etc.)

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 /__/ NO /_X_/

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.

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:

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d) Did the applicant request exclusivity? YES /__/ NO /_X_/

If the answer to (d) is "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 ON PAGE 5.

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) YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 5.

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

3. Is this drug product or indication a DESI upgrade? YES /__/ NO/_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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. YES /_X_/
NO /__/

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

NDA# 20-235 Neurontin (gabapentin) capsules
NDA# 20-882 Neurontin (gabapentin) tablets

2. Combination product – **not applicable**

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.) YES/__/
NO /__/

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

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 5. IF "YES" GO TO PART III.

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Summary for NDA 21-129

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 /__/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 5.

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 /__/ NO /__/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 5:**

_____

(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? YES /__/ 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. YES /__/ 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? YES /__/ 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:

Exclusivity Summary for NDA 21-129

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 YES /___/ NO /__/ Investigation #2 YES /___/ NO /___/

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

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 YES /___/ NO /__/ Investigation #2 YES /___/ NO /___/

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

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"):

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 # YES /__/ NO /___/

If no, explain: _____

investigation #2 IND #_____ YES /___/ NO /___/

If no, explain: _____

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cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

Exclusivity Summary for NDA 21-129

(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?

Investigation #1 IND # YES /___/ NO /___/

If no, explain: _____

Investigation #2 IND # _____ YES /___/ NO /___/

If no, explain: _____

(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.) YES /___/ NO /__/

If yes, explain: _____

Signature: /S/ ***Date:*** 3/1/00

Title: Regulatory Project Manager

Signature of Office/Division Director

Signature: /S/ ***Date:*** 3/2/00

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

APPEARS THIS WAY
ON ORIGINAL

Form OGD-011347 Revised 10/13/98
cc: Original NDA, Division File, HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21129	**Trade Name:**	NEURONTIN(GABAPENTIN)250MG/5ML [redacted]
Supplement Number:		**Generic Name:**	GABAPENTIN
Supplement Type:		**Dosage Form:**	Solution; Oral
Regulatory Action:	PN	**Proposed Indication:**	As adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No data was submitted for this indication, however, plans or ongoing studies exist for pediatric patients

What are the INTENDED Pediatric Age Groups for this submission?

___NeoNates (0-30 Days) _X_ Children (25 months-12 Years)

_X_ Infants (1-24 Months) _X_ Adolescents (13-16 Years)

Label Adequacy	Inadequate for ALL pediatric age groups
Formulation Status	NEW FORMULATION developed with this submission
Studies Needed	STUDIES needed. Applicant has COMMITTED to doing them
Study Status	Required studies are ongoing

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

Pediatric study requirements are waived for the 0-1 month age group and deferred for all other age groups. 3/1/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JACKIE WARE

/S/ _____ 3/1/00

Signature Date

Gabapentin [redacted]
250 mg/5 mL

ITEM 16.
DEBARMENT CERTIFICATION

4

Gabapentin [redacted]
250 mg/5 mL

ITEM 16.
DEBARMENT CERTIFICATION

Warner-Lambert Company hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

APPEARS THIS WAY
ON ORIGINAL

PROJECT MANAGER LABELING REVIEW

Applications Reviewed/Date Submitted:
NDA 21-129 April 30, 1999 (Initial submission)
February 24, 2000 (Revised labeling)

Products:
NDA 21-129 Neurontin (gabapentin) oral solution

Sponsor/Agent:
Parke-Davis Pharmaceutical Research for Parke-Davis Pharmaceuticals Limited

Description of Application:

Application	Description
NDA 21-129	Provides for a new oral dosage form of gabapentin (same indications as approved gabapentin capsule and tablet)

Description of Materials Reviewed:

The base document for this labeling comparison was the approved labeling for NDA 20-882/Neurontin tablet (approved 10/9/98 and was a combined package insert for Neurontin capsule and tablet; ID#0416G030). Label #0416G030 was electronically compared to the sponsor's draft labeling submitted as a minor labeling amendment on February 21, 2000 to NDA 21-129 using Microsoft Word 97 and its "Compare Documents" tool. Deletions to Label #0416G030 were indicated by "strikeout" text and additions by "underline" text.

Conclusions:
Revisions are located on pages 1, and 16-18 of the attached labeling comparison. The majority of revisions in the proposed package insert for Neurontin oral solution are related to nomenclature and the addition of the new dosage form (oral solution) to the package insert. Other revisions are editorial.

Recommendation:

With concurrence from the Division Director and the Division's chemists, an approval letter should issue for the above application.

/S/ 2/24/00

Jacqueline H. Ware, Pharm.D. Date
Project Manager

/S/ 2/24/00

John S. Purvis Date
Chief, Project Management Staff

APPEARS THIS WAY
ON ORIGINAL

cc: NDA 21-129
HFD-120 Division File

APPEARS THIS WAY
ON ORIGINAL

(C)

Number of Pages Redacted 18

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Draft Labeling
(not releasable,

MEMORANDUM

DATE: February 24, 2000

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

TO: File, NDA 21-129

SUBJECT: Approval Action for NDA 21-129, for the use of Neurontin oral solution

On 4/30/99, Parke-Davis Pharmaceuticals submitted NDA 21-129, for the use of Neurontin (gabapentin) [redacted] Neurontin is currently approved as capsules and tablets for adjunctive treatment of partial seizures with and without generalization in adults. In support of this application, the sponsor submitted relevant CMC information, as well as a bioequivalence study comparing a single 300 mg dose of gabapentin given as oral solution and capsule in 20 healthy subjects. The application has been reviewed by Dr. Zakaria Wahba of the Office of Clinical Pharmacology and Biopharmaceutics (review dated 9/20/99), Dr. Rzeszotarski, chemist (reviews dated 8/10/99, 11/1/99, 2/10/00, and 2/24/00), Dr. Brian Riley, Microbiology staff of the Office of New Drug Chemistry (review dated 8/30/99), and Dr. Lauren Lee of the Office of Post Marketing Drug Risk Assessment (nomenclature review dated 12/6/99).

Dr. Wahba has found the oral solution and capsules to be bioequivalent. No formal statistical tests were performed on the comparisons of the Tmax of the 2 products; the estimate of the mean Tmax for the solution was 2.7 hours, and 3.3 hours for the capsule, with a ratio of 81. While it is likely that the 90% CI for this ratio would fall outside of the required 80-125%, the fact that the solution has an earlier Tmax makes this difference of no consequence clinically.

Dr. Rzeszotarski recommends approval, as does Dr. Riley.

Dr. Lee recommends that the sponsor not use "syrup" as a dosage form descriptor because it does not meet the USP definition of a syrup (indeed, according to Dr. Lee's review, USP no longer uses the term syrup to describe solutions). Dr. Lee does suggest, however, that if the sponsor wishes, [redacted]

COMMENTS

The sponsor has documented the bioequivalence of the oral solution and the capsule. I have only a few comments.

Dr. Wahba recommends that the labeling [redacted] Since the 2 are bioequivalent, I believe there is no reason to add this statement.

The critical bioequivalence study has not been inspected. However, both the clinical and analytic sites were inspected in late 1997, because they were the same sites utilized by the sponsor for their studies of the gabapentin tablets, the NDA for which was approved in 10/98. The bioequivalence study for the solution was performed between 1/98-2/98. For these reasons, an inspection of the clinical and analytic sites was not necessary.

The package insert will be labeled as Neurontin (gabapentin) capsules, Neurontin (gabapentin) tablets, Neurontin (gabapentin) oral solution. At the moment, there are capsule and tablet product on the market with the current labeling (package insert and box label) of Neurontin (gabapentin capsules) or Neurontin (gabapentin tablets). Once the solution NDA is approved, there will be capsules and tablets on the market with labels that are different from this new label. This is acceptable, but the old labeling should be replaced at the next printing.

The proposed labeling differs from the currently approved labeling only in the name at the top of the label (as described above), Description, Dosage and Administration, and How Supplied sections, in which relevant language describing the oral solution has been added. It is acceptable.

Finally, the sponsor is required, under the Pediatric Rule, to submit studies in pediatric patients for this new dosage form. They have submitted a plan for such development (see their submission of 8/4/99) with which we agree. In particular, we have agreed that they need not study patients below the age of 1 month, and that the submission of the required studies be deferred until a later date.

For the reasons stated above, I will issue the attached Approval letter.

/S/

Russell Katz, M.D.

APPEARS THIS WAY
ON ORIGINAL

Cc:
NDA 21-129
HFD-120
HFD-120/Katz/Rzesotarski/Guzewska/Ware
HFD-860/Wahba/Baweja

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: February 24, 2000
APPLICATION NUMBER: NDA 21-219; Neurontin (gabapentin) oral solution
BETWEEN:

Name: Alexander Brankiewicz, CMC Manager, Worldwide Regulatory Affairs
Phone: 734-622-1399
Representing: Parke-Davis

AND

Name: Jackie Ware, Pharm.D.
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Implementation of Revised Labeling for Neurontin capsule and tablet

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On February 23, 2000, I phoned Mr. Brankiewicz and asked when Parke-Davis planned to put into use revised labeling for Neurontin capsules and tablet NDAs (20-235/20-882) given the nomenclature proposed in their February 21, 2000 submission to NDA 21-129/Neurontin oral solution. At this time, I also requested that he submit 3 copies of the new methods validation package for Neurontin oral solution.

On February 24, 2000, Mr. Brankiewicz phoned and advised me of the following. Parke-Davis will begin phasing in new carton and container labels as well as a revised package insert for Neurontin capsule and tablet beginning in March, 2000 and anticipate completion in early July, 2000. The carton and container labels will be printed with Neurontin (gabapentin) capsule and Neurontin (gabapentin) tablet, respectively. The package insert for these 2 applications will be as illustrated in the February 21, 2000 submission to NDA 21-129 MINUS all references to Neurontin oral solution. Once NDA 21-129/Neurontin oral solution is approved, the combined package insert, which includes all 3 dosage forms (capsule, tablet, and oral solution), will be implemented in October, 2000. Additionally, he informed me that he would be sending the new methods validation packages as requested.

/S/ 2/24/00

Jackie Ware, Pharm.D.
Project Manager

cc: NDA 20-235, NDA 20-882, NDA 21-129
HFD-120/Div. File
HFD-120/JWare
HFD-120/Katz/Guzewska/Rzeszotarski

TELECON

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-129

NOV 10 1999

INFORMATION REQUEST LETTER

Parke-Davis Pharmaceuticals Ltd
Attention: Mr Alexander J. Brankiewicz
Manager
Worldwide Regulatory Affairs
2800 Plymouth Road
Ann Arbor, MI 48106-1047

Dear Mr Brankiewicz:

Please refer to your April 30, 1999 new drug application for Neurontin (gabapentin) [redacted]
We also refer to your submission dated September 15, 1999.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

We do not agree with your response of September 15, 1999 addressing the specification for unknown, unidentified impurities. Although you are correct stating that:..." the maximum daily effective dose specified in the approved package insert for gabapentin capsules, tablets and [redacted] is 1800 mg," the maximum approved dose is twice that (3600 mg). Therefore, any unknown impurity present at the level greater than [redacted] must be identified. We suggest that either you identify all impurities present in the gabapentin [redacted] at the level greater than [redacted] or edit your specifications to read: unknown, unidentified impurities [redacted]

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/ 11.10.99

Maryla Guzewska, Ph.D.
Chemistry Team Leader, Neurology Drugs for the
Division of Neuropharmacological Drug Products,
(HFD-120)
DNDC I, Office of New Drug Chemistry
Center for Drug Evaluation and Research

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

PARKE-DAVIS

August 4, 1999

NDA 21-129
Ref. No. 002
Neurontin® (gabapentin) [redacted]

Re: Pediatric drug development plan for infants and children
Request for waiver for the study of neonates

NEW CORRESP
NC
DUPLICATE

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 05 1999
RECEIVED HFD-120

Russell G. Katz, M.D.
Acting Division Director
Division of Neuropharmacological Drug Products (HFD-120)
Document Control Room 4008
Center for Drug Evaluation and Research
Food and Drug Administration
Woodmont II
1451 Rockville Pike
Rockville, Maryland 20850

Dear Dr. Katz:

On behalf of and as agent for Parke-Davis Pharmaceuticals Limited, reference is made to Mr. John Purvis' letter of May 27, 1999 requesting that we submit pediatric drug development plans for the Neurontin [redacted] formulation within 120 days. Reference is additionally made to our approved NDA 20-235 for Neurontin capsules, and to the Agency's October 9, 1998 Written Request and revision to this Request dated February 4, 1999 for the conduct of pediatric studies with Neurontin capsules and other formulations as appropriate for younger patients. Finally, reference is made to a draft Written Agreement for pediatric studies to meet the Agency's Written Request submitted to NDA 20-235 on July 30, 1999. A copy of this draft Written Agreement, dated July 29, 1999 is attached (Attachment 1). This Agreement outlines our plans to evaluate both gabapentin capsules (NDA 20-235) and gabapentin [redacted] (NDA 21-129) in pediatric patients 1 month to 12 years of age as adjunctive therapy in the treatment of partial seizures. Please accept the attached draft Written Agreement as our pediatric drug development plan for gabapentin [redacted] in pediatric patients age 1 month to 12 years. Since Neurontin capsules are already approved for use in patients above 12 years of age, they are not included in our pediatric drug development plan.

In accordance with 21 CFR 314.55, we request a waiver from the study of gabapentin [redacted] as adjunctive therapy in the treatment of partial seizures in neonates (0 to 1 month of age). We do not feel it is appropriate to label Neurontin for use in neonates. The clinical seizure types seen in neonates, due to brain maturation differences, do not

conform to those seen in older individuals. Because classification of seizures in neonates in accordance with the International League Against Epilepsy (ILAE) is not applicable, the approved indication for partial seizures in adults is not translatable to neonates. Additionally, it is unlikely that unsatisfactory treatment with current anticonvulsant therapy can be identified within the first month of life. Thus the adult indication for treatment of refractory seizures is also not translatable to neonates. Based on the above, we do not feel it is appropriate to label Neurontin for use in neonates, as this information will not produce health benefits in the pediatric population. Thus we feel that it is not appropriate to study gabapentin's efficacy, safety, or pharmacokinetics in neonates. Supporting documentation for this request is provided in Attachment 2. Please note that this information was also submitted as Attachment A to NDA 20-235 on November 13, 1998 (Ref. No. 228) as support for excluding neonates from the Agency's Neurontin Written Request for pediatric studies. A copy of publications referenced in this supporting documentation were provided in the November 13, 1998 submission and will be provided again upon request.

If there are any questions or comments regarding this submission, please contact me at 734/622-7426 or via FAX at 734/622-3283.

Sincerely,

Janeth L. Turner, R.N., B.S.N.
Director
Worldwide Regulatory Affairs

JT:kb
08-04-1999\RN-002\21-129\CI-0945\Letter

Attachments

**APPEARS THIS WAY
ON ORIGINAL**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-129

MAY 27 1999

Ware

Parke-Davis Pharmaceutical Research
Attention: Sean Brennan, Ph.D.
Vice President, Worldwide Regulatory Affairs
28000 Plymouth Road, P.O. Box 1047
Ann Arbor, MI 48106-1047

Dear Dr. Brennan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Neurontin (gabapentin) [redacted]

Therapeutic Classification: Standard (S)

Date of Application: April 30, 1999

Date of Receipt: May 3, 1999

Our Reference Number: 21-129

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on July 1, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be March 3, 2000, and the secondary user fee goal date will be May 3, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in

accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, contact Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/ for 5/26/99

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7596
Facsimile: (734) 622-7890

PARKE-DAVIS

April 30, 1999

Sean Brennan, Ph.D.
Vice President
Worldwide Regulatory Affairs

NDA 21-129
Ref. No. 000
Neurontin® (gabapentin) [redacted]
250 mg/5 mL

Re: New Drug Application

Food and Drug Administration
Center for Drug Evaluation and Research
Park Building, Room 214
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Sir or Madam:

On behalf of and as agent for Parke-Davis Pharmaceuticals Limited, pursuant to 21 CFR 314.50, enclosed is a New Drug Application for Neurontin® (gabapentin) [redacted] 250 mg/5 mL. This NDA seeks approval of an oral liquid dosage form for gabapentin in a strength of 250 mg/5 mL (50mg/mL) for the indications identified in approved NDA 20-235 for Neurontin® (gabapentin) Capsules. The NDA number 21-129 was pre-assigned by the Central Document Room on April 14, 1999.

As required under the Prescription Drug and User Fee Act, 50% of the 1999 application fee for a new dosage form without clinical data ($136,141.00) has been sent to the Food and Drug Administration in care of the Mellon Bank, Pittsburgh, Pennsylvania on April 23, 1999. The User Fee Identification Number for this submission is 3708.

Please note that Patent Information (Item 13), Debarment Certification (Item 16), Field Copy Certification (Item 17), and User Fee cover sheet (Form 3397) (Item 18) are provided in Volume 1 of this NDA, immediately preceding Item 1. DMF Authorization Letters are provided following this cover letter. Please refer to the attached Form FDA 356h and the NDA Index which detail the complete contents of this NDA. This NDA consists of 7 Volumes.

Pursuant to 21 CFR 314.440, a copy of the Chemistry, Manufacturing and Controls section (Item 4) of this NDA has been sent to the FDA District Office in North Brunswick, New Jersey.

If you need additional information or have any questions regarding this submission, please contact me at 734/622-7596, FAX 734/622-7890, or Mr. Alexander Brankiewicz at 734/622-1399.

Sincerely,

APPEARS THIS WAY
ON ORIGINAL

Sean Brennan

Sean Brennan

SB/dp
04-30-1999\RN-000\21-129\CI-0945\Letter

Attachments

cc: Pre-Approval Coordinator
North Brunswick, New Jersey District Office
Vol 1 (Items 1, 3, 13, 16, 17, and 18)
Vol 2-6 (Item 4)

APPEARS THIS WAY
ON ORIGINAL