**Application Number** 21-129

# CHEMISTRY REVIEW(S)

Ware

AUG 10 1999

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**
**Review of Chemistry, Manufacturing, and Controls**

**NDA #: 21-129** **CHEM.REVIEW # 1** **REVIEW DATE: 10-AUG-99**

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| ORIGINAL | 30-APR-99 | 03-MAY-99 | 08-MAY-99 |
| Amendment | 29-JUN-99 | 12-JUL-99 | 13-JUL-99 |

**NAME & ADDRESS OF APPLICANT:** Parke-Davis Pharmaceutical
2800 Plymouth Road
Ann Arbor, MI 481059

**DRUG PRODUCT NAME**

**Proprietary:** NEURONTIN (gabapentin oral solution)
**Nonproprietary/USAN:** Gabapentin
**Code Name/#:** CI-945; PD 87842; GOE 3450
**Chem.Type/Ther.Class:** Antiepileptic

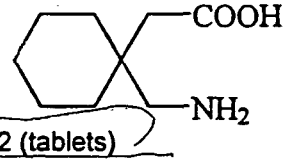
**PHARMACOL.CATEGORY/INDICATION:** ———

**DOSAGE FORM:** Oral solution
**STRENGTHS:** 250 mg/5 mL (480 mL bottles)
**ROUTE OF ADMINISTRATION:** Oral
**DISPENSED:** XXXXX Rx_____OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

***1-aminomethylcyclohexaneacetic acid***

$C_9H_{17}NO_2$; Molecular Weight: 171.24;
CAS #: 60142-96-3




**SUPPORTING DOCUMENTS:** IND 28,454; NDA 20-235 (capsules); 20-882 (tablets)
**RELATED DOCUMENTS:**
**REMARKS/COMMENTS: Unusual formulation that contains** ——— This dosage form was developed as an extension to the approved solid oral dosage forms for gabapentin of 100-, 300-, and 400-mg capsules (NDA 20-235) and 600- and 800-mg tablets (NDA 20-882). The liquid dosage form of the drug is intended for use by patients who have difficulty in swallowing the solid oral dosage forms on a TID basis. A bioequivalence study has been conducted which compared the proposed commercial gabapentin 250 mg/mL ——— formulation with commercial Neurontin (gabapentin) capsules. The ——— was found to be bioequivalent to the capsules. Neurontin@ (gabapentin) ——— 250 mg/5 mL is a clear colorless or slightly yellow liquid with a fruity flavor. It is packaged in 16 oz round amber glass bottles with child-resistant closures (CRCs). The product will be labeled to require refrigerated storage conditions. The product will be manufactured and released for commercial distribution at ——— as a contract manufacturer. Stability testing will be performed by Warner-Lambert Company at Morris Plains, New Jersey. Twelve months of stability data from ongoing stability studies are provided on commercial size batches ——— manufactured at the Warner- Lambert manufacturing facility in Lititz, Pennsylvania. Release data is provided on 3 commercial size batches ——— manufactured at the ——— The stability studies are performed in accordance with the guidelines recommended by the International Conference on Harmonization (ICH). The formulation, quality of excipients, and container/closure are the same for the batches manufactured at Warner-Lambert (Lititz) ——— The manufacturing process and equipment at the 2 facilities are considered equivalent and are described further in this Section. The amount of stability data provided at the time of submission for an original application conforms with the requirements proposed by the FDA in the March 31, 1999 amendment to the June 1998 Draft Guidance for Industry, Stability Testing of Drug Substances and Drug Products. This is a non-sterile oral solution and the change in manufacturing site is considered to have no impact

on the product. It is recommended that the final packaged product be stored under refrigerated conditions (2°C-8°C). [redacted] Based on the statistical analysis of the 12-month stability data on 3 lots of gabapentin [redacted] manufactured at the Lititz facility (a development place not the site of actual manufacturing) and presented in Appendix 12, the sponsor requests "a minimum expiration date of [redacted] ' The data presented so far supports only [redacted] of expiration dating.

**CONCLUSIONS & RECOMMENDATIONS**: Recommend NDA 21-129 approvable subject to an acceptable EER and an acceptable response to all questions contained in the RFI letter of 06-JUL-99.

cc:
Orig. NDA 21-129
HFD-120
HFD-120/WJRzeszotarski
HFD-120/JWare
HFD-120/MEGuzewska
R/D Init by:MEG 8.10.99

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: E:\msword\n21129r.001

APPEARS THIS WAY
ON ORIGINAL

**DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS**
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-129 **CHEM.REVIEW #** 4 **REVIEW DATE:** 23-FEB-00

| SUBMISSION TYPE | DOCUMENT DATE | CDER DATE | ASSIGNED DATE |
|---|---|---|---|
| Amendment (response to IR) | 21-FEB-00 | 23-JAN-00 | 23-FEB-00 |

**NAME & ADDRESS OF APPLICANT:** Parke-Davis Pharmaceutical
2800 Plymouth Road
Ann Arbor, MI 481059

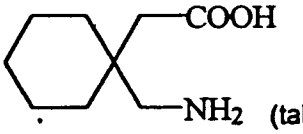
**DRUG PRODUCT NAME**
**Proprietary:** NEURONTIN (gabapentin) oral solution
**Nonproprietary/USAN:** Gabapentin
**Code Name/#:** CI-945; PD 87842; GOE 3450
**Chem.Type/Ther.Class:** Antiepileptic

**PHARMACOL.CATEGORY/INDICATION:** [redacted]

**DOSAGE FORM:** Oral solution
**STRENGTHS:** 250 mg/5 mL (480 mL bottles)
**ROUTE OF ADMINISTRATION:** Oral
**DISPENSED:** XXXXX Rx_____OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

***1-aminomethylcyclohexaneacetic acid***
$C_9H_{17}NO_2$; Molecular Weight: 171.24;
CAS #: 60142-96-3




**SUPPORTING DOCUMENTS:** IND 28,454; NDA 20-235 (capsules); 20-882 (tablets)
**RELATED DOCUMENTS:**
**REMARKS/COMMENTS:** Submitted in response to the FDA/Parke-Davis teleconference of February 9, 2000. The impurity designated as [redacted] in the NDA amendment of January 21, 2000 (Ref. No. 004) has been identified and designated as [redacted] The structural assignment and the determination of relative response factor for [redacted] are described in Attachment 2. The relative response factor for this impurity was determined to be [redacted] than gabapentin using the degradation product HPLC method. A specification of [redacted] has been established for this specified impurity. The level of [redacted] will be calculated based on a comparison of the peak response with the response of the [redacted] standard solution. Given the changes in specifications and analytical methodology it is imperative that the sponsor provides new MV packages. It is further to be clarified what should be done with the lots of capsules and tablets packaged in the old presentations where the label reads: Neurontin ( [redacted] ) or Neurontin [redacted] instead the proposed Neurontin (gabapentin) capsules) or Neurontin (gabapentin) tablets. See a copy of the E-mail attached. EER acceptable as of August 30, 1999 (see attached). Microbiology consult recommends approval as of August 16, 1999 (see Divisional File).

**CONCLUSIONS & RECOMMENDATIONS:** Recommend approval of NDA 21-129 with the expiration date of 18 months at 5°C.

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

cc:
Orig. NDA 21-129
HFD-120
HFD-120/WJRzeszotarski
HFD-120/JWare
HFD-120/MEGuzewska
R/D Init by:MEG 2/25/00

filename: E:\msword\n21129r.004

(A)

# Number of Pages Redacted 4

❖❖❖

Confidential,
Commercial Information