CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 20882

Trade Name: NEURONTIN TABLETS

Generic Name: GABAPENTIN

Sponsor: PARKE-DAVIS PHARMACEUTICAL RESEARCH, DIVISION OF WARNER-LAMBERT COMPANY

Approval Date: 10/9/98

Indication(s): SEIZURE DISORDERS AND EPILEPSY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20882

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI				X
Pharmacology Review(s)	X			
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20882

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-882

Parke-Davis Pharmaceutical Research
Division of Warner-Lambert Company
Attention: Sean Brennan, Ph.D.
2800 Plymouth Road
Ann Arbor, MI 48105

OCT 9 1998

Dear Dr. Brennan:

Please refer to your new drug application (NDA) dated July 1, 1997, received July 2, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Neurontin (gabapentin) Tablets.

We acknowledge receipt of your submissions dated August 12, 1998, and August 18, 1998. Your submission of August 12, 1998 constituted a full response to our July 1, 1998 action letter. The user fee goal date for this application is October 13, 1998.

This new drug application provides for the use of Neurontin (gabapentin) Tablets for use as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted labeling (package insert submitted August 12, 1998, immediate container and carton labels submitted August 12, 1998) with the revisions listed below. Accordingly, the application is approved effective on the date of this letter.

The biowaiver request for 800 mg tablets may be granted based on established bioequivalence of 600 and 800 mg tablets manufactured on a commercial and pilot scale, respectively, and results of dissolution profiles, compositional proportionality, and solubility of the drug. Please adopt the following dissolution method and specifications:

Apparatus:	II (Paddle)
Speed:	50 rpm
Medium:	900 mL 0.06 N HCL at 37°C
Specification	Not less than (b)(4)(G dissolved at 45 minutes

The approved expiration date is 24 months for 600 mg tablets, and 12 months for 800 mg tablets.

(b)(4)(TS)

(b)(4)(TS)

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the

product misbranded and an unapproved new drug.

1. In the **DESCRIPTION** section, "**NF**" should be deleted from the first line of the 3rd paragraph.

2. In the **HOW SUPPLIED** section, the following sentence shall replace the current one under **Storage (Tablets)**:

   Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F)
   [see USP Controlled Room Temperature]

3. Please note the changes following the approval letter of September 29, 1998 for NDA 20-235/S-011 Neurontin Capsules. In the **DOSAGE AND ADMINISTRATION** section, the sentences below have been deleted:

   Titration to an effective dose can take place rapidly, over a few days, giving 300 mg on Day 1, 300 mg twice a day on Day 2, and 300 mg three times a day on Day 3. To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime.

   To replace the above sentences, the following sentence has been added:
   The starting dose is 300 mg three times a day.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-882." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Lana Chen, R.Ph., Regulatory Management Officer, at (301) 594-2850.

Sincerely,

/S/

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20882

MEDICAL REVIEW(S)

MEMORANDUM

DATE: October 1, 1998

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

TO: File, NDA 20-882

SUBJECT: Supervisory Review of Sponsor's Response to Not Approvable Letter for NDA 20-882 for Neurontin 600 and 800 mg Tablets.

Parke-Davis Pharmaceutical Research submitted NDA 20-882 for the introduction of 2 new dosage strengths of Neurontin (600 and 800 mg tablets) on 7/1/97. In that application, they proposed

On 7/1/98, the Division issued a Not Approvable letter for this application, primarily based on the absence of sufficient information to support the safety of the levels of this lactam to which patients would be exposed at the proposed specification. In that letter, we informed the sponsor that the current data would support 18 month expiration for the 600 mg tablet, and 6 month expiration of the 800 mg tablet

In addition, we had several other comments, including a nomenclature issue, a provisional judgment that their request for a waiver of the need for a bioequivalence study of the 800 mg tablet manufactured would be granted, a request for a specific dissolution specification, and several minor chemistry comments.

The sponsor responded to the Not Approvable letter in a submission dated 8/12/98. This submission has been reviewed by Dr. Tammara of OCPB (review dated 9/15/98), Dr. Rzeszotarski, chemist (reviews dated 8/31/98 and 9/15/98), and Dr. Yan of Biometrics (review dated 9/14/98). In addition, Ms. Lana Chen, Project Manager, has reviewed the draft labeling submitted by the sponsor (review dated 9/28/98). In brief, the sponsor has agreed to not change the specification and has submitted additional stability data. They have also proposed an alternate dissolution specification, and agreed to our labeling comments.

Drs. Tammara and Rzeszotarski agree that the application can now be approved. Specifically, the request for a bioequivalence study has been granted (see Dr. Tammara's original NDA review), a dissolution specification has been agreed to (the sponsor's proposal; it is slightly different from the one we proposed in our NA letter), and stability data support a 24 month expiration for the 600 mg tablet and 12 month expiration for the 800 mg tablet.

RECOMMENDATION

I agree that the application can be approved with the labeling accompanying this package.

/S/

Russell Katz, M.D.

cc:
NDA 20-882
HFD-120
HFD-120/Katz/Leber/Chen

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20882

CHEMISTRY REVIEW(S)

SEP 16 1998

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

NDA #: 20-882 **CHEM.REVIEW # 4** **REVIEW DATE:** 15-SEP-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Consult Review	18-AUG-98	18-AUG-98	18-AUG-98

NAME & ADDRESS OF APPLICANT: WARNER-LAMBERT
2800 Plymouth Road
Ann Arbor, MI 48105

DRUG PRODUCT NAME
Proprietary: NEURONTIN®
Nonproprietary/USAN: Gabapentin
Code Name/#: CI-945
Chem.Type/Ther.Class: Antiepileptic

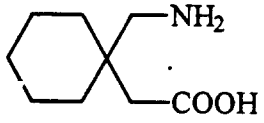
PHARMACOL.CATEGORY/INDICATION: Treatment of Epilepsy

DOSAGE FORM: Tablets
STRENGTHS: 600 mg and 800 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

1-(aminomethyl)cyclohexaneacetic acid

$C_9H_{17}NO_2$ Mol. Wt. 171.24 CAS # 60142-96-3
SUPPORTING DOCUMENTS: IND , NDA 20-235
REMARKS/COMMENTS: Consult review of



CONCLUSIONS & RECOMMENDATIONS:

revised as requested to "Neurontin® (Gabapentin Capsules and Gabapentin Tablets) and is acceptable. From the CMC point of view: the agreed specifications are in place and adequate. The stability data, provided from stability batches manufactured at Morris Plains, NJ using the same formulation although different batch sizes supports the requested expiration dating of 24 months for 600 mg tablets in 100 count, 500 count bottles and in The expiration time for the 800 mg tablets can be only increased to 12 months (with six months real-time data on hand). **Recommend approval of NDA 20-882 with 24 months expiration dating for 600 mg tablets, and 12 months expiration dating for 800 mg tablets.**

cc:Orig. NDA 20-882
HFD-120
HFD-120/WJRzeszotarski
HFD-[redacted]
HFD-120/MGuzewska
HFD-810/JSimmons
R/D Init by:MEG 9.16.98

/S/
W. Janusz Rzeszotarski, Ph.D., Chemist

filename:E:\MSWord\N20882r.004

SEP 15 1998

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

NDA #: 20-882 **CHEM.REVIEW #** 3 **REVIEW DATE:** 31-AUG-98

SUBMISSION TYP	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	12-AUG-98	13-AUG-98	13-AUG-98

NAME & ADDRESS OF APPLICANT: WARNER-LAMBERT
2800 Plymouth Road
Ann Arbor, MI 48105

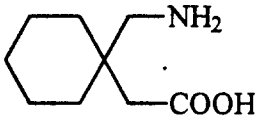
DRUG PRODUCT NAME
Proprietary: NEURONTIN®
Nonproprietary/USAN: Gabapentin
Code Name/#: CI-945
Chem.Type/Ther.Class: Antiepileptic

PHARMACOL.CATEGORY/INDICATION: Treatment of Epilepsy

DOSAGE FORM: Tablets
STRENGTHS: 600 mg and 800 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

1-(aminomethyl)cyclohexaneacetic acid



$C_9H_{17}NO_2$ Mol. Wt. 171.24 CAS # 60142-96-3
SUPPORTING DOCUMENTS: IND NDA 20-235
REMARKS/COMMENTS: Response to non-approval letter of 01-JUL-98. The sponsor

in 100 count and 500 count
CONCLUSIONS & RECOMMENDATIONS: The statistical analysis demonstrating that gabapentin tablets

The dissolution specification has to be reviewed and approved by the Biopharmaceutics Division . The nomenclature has been revised as requested to "Neurontin® (Gabapentin Capsules and Gabapentin Tablets) and is acceptable. From the CMC point of view: once the agreed on specifications are in place and given the adequate, supporting stability data provided from stability batches manufactured at Morris Plains, NJ using the same formulation although different batch sizes the requested expiration dating of 24 months for 600 mg tablets in 100 count, 500 count bottles and in is acceptable. The expiration time for the 800 mg tablets can be only increased to 12 months (with six months real-time data on hand). **Recommend approval of NDA 20-882 subject to favorable reviews by the statistics and biopharm divisions.**

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

cc:Orig. NDA 20-882
HFD-120
HFD-120/WJRzeszotarski
HFD-1[redacted]
HFD-120/MGuzewska
HFD-810/JSimmons /S/ 10/5/98
R/D Init by:MEG

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

NDA #: 20-882 **CHEM.REVIEW # 2** **REVIEW DATE:** 28-MAY-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	02-APR-98	03-APR-98	03-APR-98
Amendment	12-APR-98	15-APR-98	15-APR-98

NAME & ADDRESS OF APPLICANT: WARNER-LAMBERT
2800 Plymouth Road
Ann Arbor, MI 48105

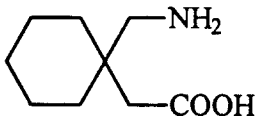
DRUG PRODUCT NAME

Proprietary:	**NEURONTIN®**
Nonproprietary/USAN:	Gabapentin
Code Name/#:	CI-945
Chem.Type/Ther.Class:	Antiepileptic
PHARMACOL.CATEGORY/INDICATION:	Treatment of Epilepsy
DOSAGE FORM:	Tablets
STRENGTHS:	600 mg and 800 mg
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

1-(aminomethyl)cyclohexaneacetic acid

$C_9H_{17}NO_2$ Mol. Wt. 171.24 CAS # 60142-96-3



SUPPORTING DOCUMENTS: IND ; NDA 20-235

REMARKS/COMMENTS: New formulation (tablets) and new strengths (600 & 800 mg tablets vs the approved 100 mg, 300 mg & 400 mg capsules). The April 2, 1998 amendment provides a revised methods validation package that indicates the origin of the and the name of the contact person. The April 14, 1998 major amendment provides a limited, 3 months of accelerated and real time stability data for 800 mg tablets manufactured at the indicated production site: and emends the previously provided stability data for 600 mg tablets of manufacture [to 12 months] and for the supporting 600 mg and 800 mg tablets of Morris Plains manufacture [to 18 months]. Based on the data provided the sponsor asks for 24 months expiration date combined
- gabapentin Also amended are the specifications for the noncompendial component copolyvidone [copolyvidonium] in accordance with the 3rd ed of EurPharm.

CONCLUSIONS & RECOMMENDATIONS: The stability data provided supports the expiration dates: 18 months for 600mg tablets and 6 months for 800 mg tablets.

Similarly unacceptable is the proposed labeling to call the drug product : Neurontin (Gabapentin Capsules and Tablets) Recommend NDA 20-882 NON-APPROVABLE

cc:
Orig. NDA 20-882
HFD-120
HFD-120/WJRzeszotarski
HFD-120/JWare
HFD-120/MGuzewska
HFD-810/JSimmons
R/D Init by:MEG

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

filename: D:\wpfiles\N20882r.002

APR 2 1998

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

NDA #: 20-882 **CHEM.REVIEW #** 1 **REVIEW DATE:** 18-MAR-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	01-JUL-97	02-JUL-97	11-JUL-97
Amendment	09-JAN-98	12-JAN-98	05-FEB-98
Amendment	12-MAR-98	16-MAR-98	16-MAR-98

NAME & ADDRESS OF APPLICANT: WARNER-LAMBERT
2800 Plymouth Road
Ann Arbor, MI 48105

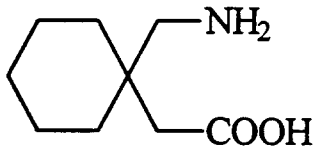
DRUG PRODUCT NAME
Proprietary: **NEURONTIN®**
Nonproprietary/USAN: Gabapentin
Code Name/#: CI-945
Chem.Type/Ther.Class: Antiepileptic

PHARMACOL.CATEGORY/INDICATION: Treatment of Epilepsy

DOSAGE FORM: Tablets
STRENGTHS: 600 mg and 800 mg
ROUTE OF ADMINISTRATION: Oral
DISPENSED: XXXXX Rx_____OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT

1-(aminomethyl)cyclohexaneacetic acid



$C_9H_{17}NO_2$ Mol. Wt. 171.24 CAS # 60142-96-3

SUPPORTING DOCUMENTS: IND NDA 20-235

REMARKS/COMMENTS: New formulation (tablets) and new strengths (600 & 800 mg tablets vs the approved 100 mg, 300 mg & 400 mg capsules). The issue of proposed specifications

the stability studies, the promised amendment never arrived. EER not completed at the time of this review. samples requested.

CONCLUSIONS & RECOMMENDATIONS: Recommend **NOT APPROVAL** of NDA 20-882 due to an unjustified for the 800 mg strength.

/S/

W. Janusz Rzeszotarski, Ph.D., Chemist

cc:
Orig. NDA 20-882
HFD-120
HFD-120/WJRzeszotarski
HFD-120/JWare
HFD-120/MGuzewska
HFD-810/JSimmons
R/D Init by:MEG 4.2.98

filename: D:\wpfiles\N20882o.000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20882

PHARMACOLOGY REVIEW(S)

Consult #868 (HFD-120)

NEURONTIN gabapentin capsules and tablets

The brand name NEURONTIN is already in use on a marketed product, therefore the Committee has no comment on this name.

Insofar as the established name, the convention of (gabapentin capsules and tablets) should not be used because the USP will not title the subsequent monograph this way. However, the firm could use (gabapentin tablets) and (gabapentin capsules) separately or the following presentation:

NEURONTIN
(gabapentin)
Capsules and tablets

/S/ 1/28/98, Chair
CDER Labeling and Nomenclature Committee

April 30, 1998

Review and Evaluation of Pharmacology and Toxicology
Original NDA Review

NDA: 20-882

Sponsor: Park-Davis
Ann Arbor, MI

Drug: Gabapentin (Neurontin) tablets (600 and 800 mg)

Category: Antiepileptic

Related NDA: NDA 20-235 for gabapentin capsules (100, 300, and 400 mg); approved 12/30/93

Summary and Evaluation:

This NDA is for a new formulation (tablets) and two new dosage strengths (600 and 800 mg) of gabapentin. The dose will be the same as that already approved for the capsules, and all excipients The only pharmacology/toxicology issue

No relevant new preclinical data have been submitted in support of this change, but summaries of the previous toxicology studies of the lactam (submitted to NDA 20-235) were included; these include acute toxicity studies in mice and rats, a 4-week toxicity study in rats, and a mutagenicity assay (Ames test).

The acute toxicity studies indicate that the than gabapentin itself: the oral LD50 of the lactam was 300 mg/kg in mice and between 200 and 500 mg/kg in rats, while no mortality occurred in mice or rats given oral gabapentin doses of up 8000 mg/kg. There was also an indication from the repeated-dose rat study that at least one of the toxic effects of gabapentin (albeit one which is not thought to be clinically relevant) is produced at lower doses (~1/10) and with a shorter latency by the lactam. Based on the toxicity observed following acute administration of an oral dose of 200 mg/kg to rats (abnormal gait and stance, straub tail, hypoactivity), 80 mg/kg was chosen as the high dose for the 1-month study of the lactam (10/sex/grp given 20, 40, or 80 mg/kg by gavage; SD rats). No deaths, clinical signs, body weight effects, or clinical chemistry changes were observed in the study. The only significant finding was microscopic evidence of hyaline droplet accumulation in the renal proximal tubular epithelium of males in all treatment groups. In a comparable 4-week toxicity study of gabapentin in SD rats, no treatment-related clinical or pathologic findings were reported at oral doses of up to 900 mg/kg. However, in a 6-month oral toxicity study of gabapentin in SD rats (100, 300, or 900 increased to 1500 mg/kg after 6 wks), hyaline droplet accumulation (thought to be a male rat-specific effect) was found at doses 300 mg/kg or greater. The other effects reported in the 6-month rat study of gabapentin were increased liver and kidney weights and minimal glomerulonephritis at the HD. The lactam was not mutagenic in the Ames test.

These lactam studies cannot be considered adequate for characterization of the toxic potential of the degradant, even by ICH standards, because of the short duration and low doses used in the repeated-dose study and the lack of reproductive and developmental toxicity assessments. The sponsor calculated a safety margin based on a maximum human daily lactam dose of 0.6 mg/kg (0.6% of 4800 mg/day) and the highest no adverse effect dose in the 1-month rat study, which the sponsor considered to be 80 mg/kg. This provides However, there is too little data to conclude that 80 mg/kg is without significant toxic effects in animals. There is no information on the levels of lactam that were present in the drug

lots used in the gabapentin toxicology studies or in clinical trials. The preclinical lots probably contained very little, however, since stability data for the tablet (see Chemistry review) indicate that levels of the degradation product are low initially and increase fairly gradually. At the initial levels found in tablets, the dose of lactam at the highest gabapentin dose used in the chronic animal studies (2000 mg/kg) would have been similar to the human maximum daily dose of at the proposed specification on a mg/kg basis (0.4 - 0.8 mg/kg).

Recommendations:

The application is not approvable from a pharmacology/toxicology standpoint because the major degradation product, gabapentin lactam, has not been adequately qualified. Additional studies necessary for preclinical qualification would include a 3-month toxicity study using appropriate doses, a second *in vitro* genetic toxicology study (chromosomal aberration assay), and an embryofetal development study.

NDA (20-648)
Div File
HFD-120/GFitzgerald/EFisher/JWare

Rcd 7/21/98
/S/

/S/
E. Fisher, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20882

STATISTICAL REVIEW(S)

Chen
DRAFT RECEIVED SEP 16 1998

Statistical Review and Evaluation
Stability Review

SEP 14 1998

NDA#: 20-882

APPLICANT: Parke-Davis Pharmaceutical Research

NAME OF DRUG: Neurontin (Gabapentin)

DOCUMENTS REVIEWED: Sponsor's Submission Dated August 18, 1998

CHEMISTRY REVIEWER: Janusz Rzeszotarski, Ph.D. (HFD-120)

Background

This submission is a revision of the previously submitted Stability Analysis of Neurontin (Gabapentin) 600- and 800-mg Tablets Report (RR-943-0008) in response to the FDA Action Letter of July 1, 1998. The previous version contains several incorrectly specified estimate statements in the SAS code.

Sponsor's Findings

This submission does not include the results of statistical analysis for potency assay. The sponsor calculated expiration dating and the supportive data. The shelf life was estimated for each of the strengths stored at 25°C/60%RH. The sponsor found that there was no discernable difference in the shelf life between 100-count bottle and 500-count bottle. The blister configuration provided a significant improvement in stability relative to blisters. The primary stability lots for the 600-mg strength had a higher degradation slope and a higher initial level of lactam compared to the other batches. The estimates of shelf life are presented below:

Strength	Package	Estimated Shelf Life
600-mg	100 Count and 500 Count Bottle	26 months
800-mg	100 Count and 500 Count Bottle	36 months
600- and 800-mg	Blister	32 months

Reviewer's Findings

The sponsor's statistical analyses are technically correct. However, combining the data from the primary study and the supportive study may not be appropriate. The stability profiles of the drug may be different for different study types because of the changes of manufacturing sites and other conditions. Larger variation may arise, and that could lead to less accurate estimates from the combined data. This reviewer re-analyzed data stored

. The statistical analysis was done for each package type and study type separately. The detailed estimation of shelf life for the lactam level is presented below:

Estimated Shelf Life for Lactam Analysis

Strength	Package	Primary Data	Supportive Data
600-mg	100 Count Bottle	25 months	26 months
	500 Count Bottle	25 months	33 months
	Blister	32 months	31 months
	Blisters		24 months
800-mg	100 Count Bottle	24 months	35 months
	500 Count Bottle	24 months	36 months
	Blister	24 months	31 months

This reviewer found that the 600-mg strength has a higher initial level of lactam and a higher degradation slope than the 800-mg strength, which agree with the findings from the sponsor. The 800-mg strength appears to be more stable than the 600-mg strength. However, as there are only three observations available for the 800-mg strength in the primary study, the when more data become available. The estimated shelf life of 24 months in the primary study was extrapolated far beyond the available data of 6 months, which raises the question of the reliability of the predicted shelf life of the 800-mg strength. The blister package showed more consistent stability (flatter slopes and lower intercepts) across study types and strengths, compared to other package types. The sponsor claimed that blister provided a significant improvement in stability relative to Blisters. This claim is questionable for two reasons. First, the stability data for blister package is not available in the primary study; and second, the stability analysis for potency assay does not show such improvement.

This reviewer also re-analyzed the potency data in the same way that the lactam level was analyzed. The minimum shelf life for the primary study data was estimated as 46 months for the 600-mg strength, and 24 months for the 800-mg strength. The data from the supportive study predicted longer shelf life with minimum estimated shelf life of 40 months.

APPEARS THIS WAY
ON ORIGINAL

Summary

The estimated expiration dating periods from the primary study and the supportive study are substantially different. It is not appropriate to combine the data from the primary study and the supportive study, as was done by the sponsor, because of the changes in manufacturing sites and other conditions. By analyzing the primary study and the supportive study separately, this reviewer obtained the expiration dating period of 25 months for the 600-mg strength and 24 months for the 800-mg strength. The 600-mg

strength has a higher initial level of lactam and a higher degradation rate compared to the 800-mg strength. The three available observations up to 6 months for the 800-mg strength are not sufficiently enough to provide reliable estimates of the expiration dating period, and the resulting predicted shelf life of 24 months is extrapolated far beyond the available data. Therefore, the requested 24 months of expiration dating period is not well supported by the data.

/S/

Sharon Yan, Ph.D.
Mathematical Statistician

/S/

Kun Jin, Ph.D.
Team Leader

/S/

George Chi, Ph.D.
Director, Division of Biometrics I

Cc: Archival NDA 20-882 Neurontin (Gabapentin) Tablets, Parke-Davis
HFD-120/Dr. Ware, CSO
HFD-120/Dr. Guzewska
HFD-120/Dr. Rzeszotarski
HFD-710/Dr.Chi
HFD-710/Dr. Jin
HFD-710/Dr. Yan
This review consists of 3 pages. 09/09/98. MS Word: gabapent_stab

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20882

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

RECEIVED MAR 16 1998 MAR 12 1998

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20, 882
Gabapentin (Neurontin®)
600 and 800 mg Tablets

Parke-Davis Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI 48105

Reviewer: Vijay K. Tammara, Ph. D.

Submission Dates:
July 01, 1997
February 10, 1998

Type of Submission: New NDA (New Dosage Form)

The Gabapentin original NDA 20-235 was approved on December 30, 1993 for adjunctive therapy in the treatment of partial seizures with and without secondary generalization. The effective dose range was 900-1800 mg/day, and the maximum recommended daily dose was 3600 mg. The approved dosage forms were 100, 200, 300, and 400 mg hard gelatin capsules. The purpose of this NDA is to include alternative 600 and 800 mg film coated tablets of gabapentin.

In this submission, the sponsor has provided study reports on bioavailability and bioequivalence of the 600 mg gabapentin tablets (both pilot batch (Study # 945-189-0) and commercial batch (Study # 945-205-0) manufactured at Morris Plains, NJ
respectively) to two 300 mg marketed gabapentin capsules. The sponsor also provided a study report on bioavailability and bioequivalence of the 800 mg gabapentin tablets (pilot batch only (study # 945-208-0) manufactured at Morris Plains, NJ) to two 400 mg marketed gabapentin capsules. Further, the sponsor is seeking a biowaiver for 800 mg gabapentin tablets manufactured at to two 400 mg marketed gabapentin tablets based on established bioequivalence of 800 mg tablets manufactured on a of 800 mg tablets to 600 mg tablets.

Bioequivalence:

Study 945-189-0: In this study, the sponsor tested whether 600 mg gabapentin tablets (pilot batch manufactured at Morris Plains, NJ) were bioequivalent to two 300 mg marketed gabapentin capsules. This study was conducted as a single-dose, randomized, open-label, 2-way cross over study in 20 healthy subjects (14M, 6F). Using capsules as the reference treatment for statistical comparisons, tablets were found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I.=103-116%) and C_{max} (90% C.I.=104-120%) for gabapentin. No statistically significant difference in Tmax was observed (Attachment 1).

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20, 882
Gabapentin (Neurontin®)
600 and 800 mg Tablets

Parke-Davis Pharmaceutical Research
2800 Plymouth Road
Ann Arbor, MI 48105

Reviewer: Vijay K. Tammara, Ph. D.

Submission Date:
August 12, 1998

Type of Submission: Response to Not Approvable Letter

In this submission, the sponsor provided responses to Agency's NA letter dated July 1, 1998.

The sponsor proposes the dissolution specification be changed to) in 45 minutes instead of the 30 minutes as recommended in the NA letter. To support the proposed change, the sponsor provided the dissolution profiles for the 600 and 800 mg tablets for all lots initially and over the course of stability studies. The Agency's recommendation was based on the data provided in the original submission. However, up on review of the data presented in this submission (Attachment 1), the reviewer concurs with the sponsors request for a change in specification.

The dissolution methodology and specification proposed by the sponsor is as follows:

Apparatus	:	II (Paddle)
Speed	:	50 rpm
Medium	:	900 mL of 0.06 N HCl at 37°C
Specification	:	Not less than at 45 minutes

Recommendation: The dissolution methodology and specification as proposed by the sponsor are acceptable. Please, forward this **Recommendation** to the sponsor.

/S/ 9/15/98

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

FT Initialed by C. Sahajwalla, Ph. D. /S/ 9/15/98

CC: N 20, 882 (Suppl.), HFD-120, HFD-860 (Tammara, Sahajwalla, Malinowski), CDR (for Drug Files).

ATTACHMENT 1

8 PAGES REDACTED

CONTAINED TRADE SECRETS and/or CONFIDENTIAL/ COMMERCIAL INFORMATION

Study 945-205-0: In this study, the final production 600 mg tablets
were compared with two 300 mg marketed gabapentin capsules. This study was conducted as a randomized, single-dose, open-label, two-period cross over study in 20 healthy subjects (7M, 13F). Using Capsules as the reference treatment for statistical comparisons, tablets were found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I.=99-121%) and C_{max} (90% C.I.=97-121%) for gabapentin. No statistically significant difference in Tmax was observed (Attachment 2).

Study 945-208-0: In this study, the sponsor tested whether 800 mg gabapentin tablets (pilot batch manufactured at Morris Plains, NJ) were bioequivalent to two 400 mg marketed gabapentin capsules. This study was conducted as a single-dose, randomized, open-label, 2-way cross over study in 20 healthy subjects (8M, 12F), but only 19 subjects completed the study. One subject was dropped from the study due to compliance problems. Using capsules as the reference treatment for statistical comparisons, tablets were found to be bioequivalent in terms of log transformed extent of absorption, i.e., $AUC_{0-\infty}$ (90% C.I.=83-103%) and C_{max} (90% C.I.= 80-106%) for gabapentin. No statistically significant difference in Tmax was observed (Attachment 3).

C: Waiver Request: The sponsor is seeking waiver for 800 mg tablets to be manufactured on commercial scale at i.e., a site change. Based on the considerations given below, a biowaiver could be granted for 800 mg tablets to be manufactured on commercial scale at

- The 800 mg tablets are compositionally proportional to 600 mg tablets
- Gabapentin is highly soluble
- Established bioequivalence of 600 mg tablets manufactured on a commercial and pilot scale, respectively
- Established bioequivalence of 800 mg tablets manufactured on a pilot scale
- 600 and 800 mg tablets and 800 mg tablets manufactured on pilot and commercial scale, respectively, and
- Similar dissolution profiles of 800 mg tablets manufactured at Morris Plains, NJ

Dissolution Method: Dissolution testing of gabapentin tablets is performed using presently approved dissolution method and specification for capsules, which is as follows:

Apparatus	:	II (Paddle)
Speed	:	50 rpm
Medium	:	900 mL of 0.06 N HCl at 37°C
Specification	:	Not less than

Comments:

1) The sponsor is requested to adopt the dissolution methodology and specification for Neurontin tablets as follows:

Apparatus	:	II (Paddle)
Speed	:	50 rpm
Medium	:	900 mL of 0.06 N HCl at 37°C
Specification	:	Not less than

Recommendation: This submission (NDA 20-882) has been reviewed by the Office of Clinical Pharmacology and Biopharmaceutics and has been found to be acceptable to meet office's requirements. The biowaiver request for 800 mg tablets can be granted based on established bioequivalence of 600 and 800 mg tablets manufactured on a commercial and pilot scale, respectively, and results of dissolution profiles, compositional proportionality, and solubility of the drug. The sponsor is recommended to adopt the dissolution methodology and specification as outlined in **Comment** 1.

/S/

3/11/98

Vijay K. Tammara, Ph. D.
Division of Pharmaceutical Evaluation I

First Draft Prepared on February 24, 1998
First Draft Initialed by Dr. Chandra Sahajwalla on February 27, 1998
Intra-Division CP/B Briefing Date: March 9, 1998
Attendees: Drs. Henry Malinowski, Mehul Mehta, Chandra Sahajwalla, and Vijay Tammara.

FT Initialed by C. Sahajwalla, Ph. D. /S/ 3/11/98

CC: N 20, 882 (orig.), HFD-120, HFD-860 (Tammara, Sahajwalla, Malinowski), CDR (for Drug Files).

ATTACHMENT 1

Name of Company: Warner-Lambert	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Neurontin	Referring to Part of the Dossier	
Name of Active Ingredient: Gabapentin	Volume: Page:	

Title of Study: A Single-Dose Bioequivalence Study Comparing 600-mg CI-945 Tablets to 300-mg Gabapentin Capsules (Protocol 945-189-0)

Investigators:

Study Center:

Publication (reference): None

Studied Period (years): 04/17/95 to 04/28/95 **Clinical Phase:** Phase 1

Objective(s): To determine whether 600-mg gabapentin tablets are bioequivalent to two 300-mg gabapentin capsules

Methodology: The study was an open-label, single-dose, 2-way crossover design conducted in healthy subjects. On Days 1 and 8, each subject received a single AM dose following an overnight fast.

Number of Subjects (total and for each treatment): Twenty healthy subjects (14 males and 6 females) were enrolled and completed the study. All subjects received each treatment.

Diagnosis and Criteria for Inclusion: Healthy adult male and female volunteers

Reference Treatment, Dose and Mode of Administration, Batch Number: Two 300-mg gabapentin capsules Lot CF 039073) were administered with 8 ounces of water to fasting subjects.

Test Treatment, Dose and Mode of Administration, Batch Number: One 600-mg gabapentin tablet Lot CM 0190295) was administered with 8 ounces of water to fasting subjects.

Duration of Treatment: Single 600-mg gabapentin doses were administered on Study Days 1 and 8.

Pharmacokinetic Sampling and Analysis: Blood and urine samples were collected serially for 48 hours following dosing on Days 1 and 8. Plasma and urine samples were analyzed for gabapentin using specific procedures. Methods were validated over the concentration ranges of in plasma and in urine.

Criteria for Evaluation: Data from all 20 subjects were used in the safety and pharmacokinetic evaluations.

Name of Company: **Warner-Lambert**	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **Neurontin**	Referring to Part of the Dossier	
Name of Active Ingredient: **Gabapentin**	Volume: Page:	

Protocol 980-003-1 (Page 2)

Pharmacokinetic Statistical Methods: Pharmacokinetic parameters were calculated using standard noncompartmental methods. Ratios (test/reference) of formulation least-squares mean values and corresponding 90% confidence intervals were calculated. Bioequivalence would be established if the 90% confidence intervals for the ratio (test/reference) of formulation mean values, calculated using log-transformed Cmax and AUC(0-∞) data, are within the interval of 80% to 125%.

SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition All 20 subjects completed the study. Mean (range) age, weight, and height were 35.3 years , 76.9 kg , and 176.6 cm , respectively.

Clinical Eighteen of 20 subjects reported primarily CNS adverse events associated with each treatment. The adverse event profiles were similar in both treatment groups. There were no serious or severe adverse events reported in this study. There were no withdrawals related to adverse events.

Pharmacokinetics Parameter values are summarized in the following table:

Parameter	Mean[a] One 600-mg Tablet (Test)	Mean[a] Two 300-mg Capsules (Reference)	Ratio	90% Confidence Interval
Cmax (µg/mL)	4.53	4.07	112	104 - 120
AUC(0-∞) (µg•hr/mL)	49.5	45.1	109	103 - 116

Ratio of Test to Reference values expressed as a percentage of Reference value
90% Confidence Interval based on log-transformed parameter values
[a] Antilog of least-squares mean log-transformed value

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Bioequivalence criteria for Cmax and AUC(0-∞) values were met. Ratios of formulation least-squares mean values for secondary parameters [untransformed Cmax, untransformed and log-transformed AUC(0-tldc), and untransformed AUC(0-∞)] and corresponding 90% confidence intervals corroborated the bioequivalence of 600-mg gabapentin tablets to 300-mg gabapentin capsules.

Conclusions Six-hundred milligrams gabapentin tablets are bioequivalent to gabapentin capsules.

TABLE 6. Summary of Mean Gabapentin Pharmacokinetic Parameters Following Administration of One 600-mg Gabapentin Tablet and Two 300-mg Gabapentin Capsules

Parameter	One 600-mg Tablet (Test) N = 20			Two 300-mg Capsules (Reference) N = 20		
	Mean	SD	%RSD	Mean	SD	%RSD
Cmax	4.65	1.15	24.8	4.19	1.05	25.1
tmax	4.1	1.2	29.4	3.4	1.2	36.3
AUC(0-tldc)	50.1	13.0	25.9	45.6	12.6	27.7
AUC(0-∞)	51.0	13.3	26.0	46.6	12.7	27.3
t½	8.5	1.6	18.4	9.1	3.6	39.9
Ae%	47.7	12.2	25.5	43.6	12.1	27.8

N = Number of observations (subjects).
Mean = Arithmetic treatment mean.
SD = Standard deviation (N-1).
%RSD = Relative standard deviation (% of mean value).
Cmax = Maximum observed plasma gabapentin concentration (µg/mL).
tmax = Time of Cmax (hr).
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time (µg•hr/mL).
t½ = Terminal elimination half-life (hr).
Ae% = Percent of gabapentin dose excreted unchanged in urine (%).

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TABLE 7. Summary of Statistical Evaluation of Gabapentin Pharmacokinetic Parameters Following Administration of One 600-mg Gabapentin Tablet and Two 300-mg Gabapentin Capsules

Parameter	Least-Squares Mean Value		Ratio	90% CI
	One 600-mg Tablet (Test) N = 20	Two 300-mg SUPRO Capsules (Reference) N = 20		
ln(Cmax)	1.51 (4.53)	1.40 (4.07)	112	104 - 120
ln[AUC(0-∞)]	3.90 (49.5)	3.81 (45.1)	109	103 - 116
Cmax	4.65	4.19	111	104 - 118
tmax	4.1	3.4	121	106 - 136
AUC(0-tldc)	50.1	45.6	110	104 - 116
ln[AUC(0-tldc)]	3.88 (48.4)	3.79 (44.1)	109	103 - 117
AUC(0-∞)	51.0	46.6	109	103 - 116

ln = Natural log-transformed parameter value.
Cmax = Maximum observed plasma gabapentin concentration (µg/mL).
tmax = Time of Cmax (hr).
AUC(0-tldc) = Area under the plasma concentration-time curve from time zero to the time of last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time (µg•hr/mL).
Ratio = Ratio (test/reference) of antilogs of treatment least-squares mean values (for log-transformed data) or ratio of treatment least-squares mean values (for untransformed data), expressed as a percentage.
90% CI = 90% confidence interval estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage.

Note: Numbers in parentheses are antilogs of least-squares mean log-transformed values

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10. FIGURES

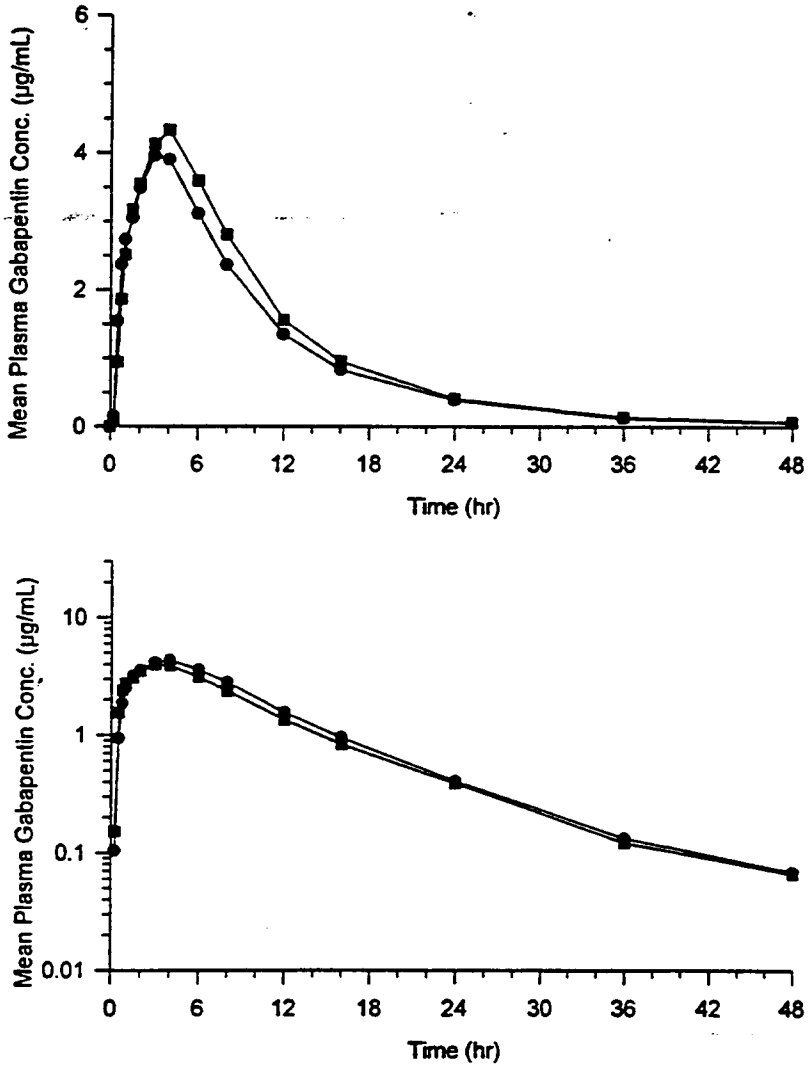

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FIGURE 1. Mean Plasma Gabapentin Concentration-Time Profiles Following Administration of One 600-mg Gabapentin Tablet (■) and Two 300-mg Gabapentin Capsules (●) to Healthy Subjects

Top panel, linear scale; bottom panel, semilogarithmic scale (Protocol 945-189-0)

ATTACHMENT 2

Name of Company: **Warner-Lambert**	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **Neurontin®**	Referring to Part of the Dossier	
Name of Active Ingredient: **Gabapentin**	Volume: Page:	

Title of Study: A Single-Dose Bioequivalence Study Comparing 600-mg Gabapentin Tablets Manufactured in to 300-mg Gabapentin Capsules

Investigators

Study Center(s):

Publication (reference): None

Studied Period (years): 12/10/96 to 02/10/97 **Clinical Phase:** 4

Objective(s): To determine whether 600-mg gabapentin tablets (VB) are bioequivalent to two 300-mg gabapentin capsules

Methodology: The study was an open-label, single-dose, 2-way crossover design conducted in healthy subjects. On Days 1 and 8, each subject received a single AM dose following an overnight fast.

Number of Subjects (total and for each treatment): Twenty healthy subjects (7 males and 13 females) completed the study. Twenty subjects received each treatment.

Diagnosis and Criteria for Inclusion: Healthy adult male and female volunteers

Test Product, Dose and Mode of Administration, Batch Number:
- Gabapentin [CI-945] 600-mg tablets , Lot CV 1771196

Administration: Oral, with 8 ounces of water to fasting subjects.

Duration of Treatment: Single 600-mg gabapentin doses were administered on Study Days 1 and 8.

Reference Therapy, Dose and Mode of Administration, Batch Number:
- Gabapentin [CI-945] 300-mg capsules Lot 02166V

Administration: Oral, with 8 ounces of water to fasting subjects.

Criteria for Evaluation: Data from all 20 subjects were used in the safety evaluation and in the pharmacokinetic evaluations.

Pharmacokinetic Sampling and Analysis: Blood samples were collected serially for 72 hours following dosing on Days 1 and 8. Plasma samples were analyzed for gabapentin using a specific procedure. Method was validated over the concentration range of in plasma.

Pharmacokinetic and Statistical Methods: Pharmacokinetic parameters were calculated using standard noncompartmental methods. Analysis of variance of parameter values and subsequent evaluation of 90% confidence intervals based on log-transformed Cmax and AUC values were performed. Bioequivalence would be established if these confidence intervals are within the 80% to 125% range.

Name of Company: **Warner-Lambert**	INDIVIDUAL STUDY — TABLE	(For National Authority Use Only)
Name of Finished Product: **Neurontin®**	Referring to Part of the Dossier	
Name of Active Ingredient: **Gabapentin**	Volume: Page:	

Protocol 945-205-0 (Page 2)

SUMMARY - CONCLUSIONS:

Patient Characteristics and Disposition Twenty subjects completed the study. Mean (range) age, weight, and height of the subjects who completed the study were 45.3 years, 75.5 kg, and 171.4 cm, respectively.

Clinical Gabapentin oral 600-mg tablet and capsules doses were generally well-tolerated, with expected CNS adverse events of mild to moderate intensity frequently reported.

Pharmacokinetics Data from all 20 subjects who completed the study were included in the pharmacokinetic and statistical analyses. Mean Cmax and AUC values presented in this synopsis were calculated as the antilogs of least-squares mean log-transformed values (analogous to geometric mean). Ratios and confidence intervals for Cmax and AUC values were also based on log transformed values. Least-squares means for the remaining pharmacokinetic parameters are reported in this synopsis. Ratios for these parameters are based on untransformed values.

Parameter values from this study are summarized in the following table:

Parameter	Mean[a]		Ratio	90% Confidence Interval
	Two 300-mg Capsules (Reference)	One 600-mg Tablet (Test)		
Cmax[a] (µg/mL)	4.35	4.71	108.	97.3% to 120.7%
tmax (hr)	3.5	3.2	91.4	Not Applicable
AUC(0-tldc)[a] (µg•hr/mL)	45.2	48.9	108.	97.7% to 120.1%
AUC(0-∞)[a] (µg•hr/mL)	46.1	50.4	109.	99.4% to 120.5%
t½ (hr)	15.2	15.4	101.	Not Applicable

Ratio (test/reference) of antilogs of treatment least-squares mean values expressed as a percent of reference mean (for log-transformed data) or ratio of treatment least-squares mean values expressed as a percent of reference mean (for untransformed data)
90% Confidence Interval is an estimate for the ratio (test/reference) of treatment mean values, expressed as a percent of the reference mean
[a] Means and confidence intervals based on log-transformed data

Bioequivalence criteria for Cmax and AUC(0-∞) values were met. Ratios of formulation least-squares mean values for secondary parameters based on untransformed Cmax, untransformed and log-transformed AUC(0-tldc), and untransformed AUC(0-∞) data and corresponding 90% confidence intervals further support the bioequivalence of 600-mg gabapentin tablets to 300-mg gabapentin capsules.

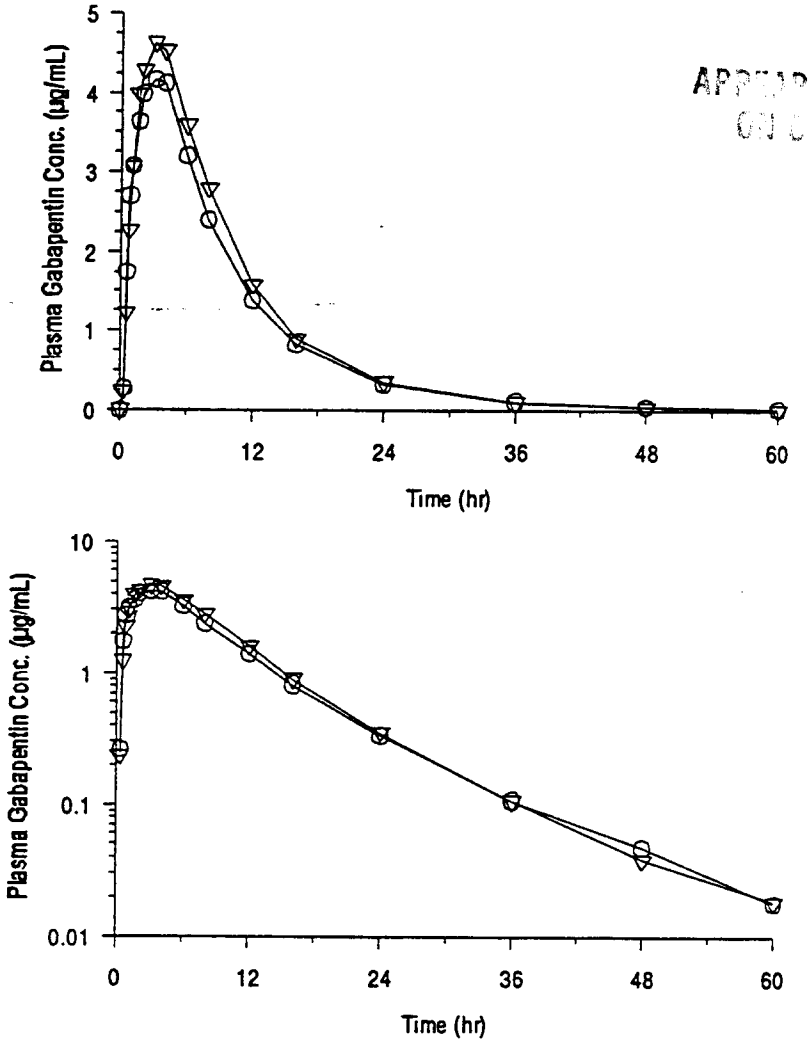

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FIGURE 1. Mean Plasma Gabapentin Concentration-Time Profiles Following Administration of One 600-mg Gabapentin Tablet (▽) and Two 300-mg Gabapentin Capsules (○) to Healthy Subjects (Protocol 945-205)

Top panel linear scale; bottom panel, semilogarithmic scale

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Gabapentin pharmacokinetic parameter values and confidence intervals are given in Table 6.

TABLE D.5. Summary of Mean Gabapentin Pharmacokinetic Parameters Following Administration of Two 300-mg Gabapentin Capsules and One 600-mg Gabapentin Tablet (Protocol 945-205)

Parameter	Two 300-mg Capsules (Reference) N = 20			One 600-mg Tablet (Test) N = 20		
	Mean	SD	%RSD	Mean	SD	%RSD
Cmax	4.48	1.16	25.9	4.94	1.52	30.9
tmax	3.5	1.2	34.1	3.2	0.9	27.3
AUC(0-tldc)	46.8	13.3	28.4	51.3	16.3	31.8
AUC(0-∞)	47.7	12.9	27.1	52.5	15.8	30.2
t½	15.4	13.9	90.5	15.6	13.7	88.2

N = Number of observations.
Mean = Arithmetic treatment mean.
SD = Standard deviation.
%RSD = Relative standard deviation (% of mean value).
Cmax = Maximum plasma concentration (µg/mL).
tmax = Time (hr) for Cmax.
AUC(0-tldc) = Area under plasma concentration-time curve from time 0 to time of the last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg•hr/mL).
t½ = Elimination half-life (hr).

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ON ORIGINAL

TABLE 6. Summary of Statistical Evaluation of Gabapentin Pharmacokinetic Parameters Following Administration of Two 300-mg Gabapentin Capsules and One 600-mg Gabapentin Tablet and(Protocol 945-205)

Parameter	Least-Squares Mean Value		Ratio	90% CI
	Two 300-mg Capsules (Reference) N = 20	One 600-mg Tablet (Test) N = 20		
Cmax[a]	4.35	4.71	108	97.4% to 120.7%
AUC(0-∞)[a]	46.1	50.4	109	99.4% to 120.5%
Cmax	4.48	4.94	110	98.1% to 122.4%
tmax	3.5	3.2	91.4	78.7% to 104.2%
AUC(0-tldc)	46.8	51.3	110	98.5% to 120.8%
AUC(0-tldc)[a]	45.2	48.9	108	97.7% to 120.1%
AUC(0-∞)	47.7	52.5	110	99.3% to 120.8%

Cmax = Maximum plasma concentration (µg/mL).
tmax = Time (hr) for Cmax.
AUC(0-tldc) = Area under plasma concentration-time curve from time 0 to time of the last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg•hr/mL).
Ratio = (test/reference) of antilogs of treatment least-squares mean values expressed as a percent of reference mean (for log-transformed data) or ratio of treatment least-squares mean values expressed as a percent of reference mean (for untransformed data).
90% CI = 90% confidence interval estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage.

[a] Parameter values are antilogs of least-squares mean log transformed values

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ATTACHMENT 3

Name of Company: Warner-Lambert	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Neurontin	Referring to Part of the Dossier	
Name of Active Ingredient: Gabapentin	Volume: Page:	

Title of Study: A Single-Dose Bioavailability Study Comparing 800-mg CI-945 Tablets to 400-mg Gabapentin ® Capsules (Protocol 945-208-0)

Investigators:

Study Center(s):

Publication (reference): None

Studied Period (years): 03/05/96 to 03/28/96 **Clinical Phase:** 4

Objective(s): To determine whether 800-mg CI-945 tablets are bioequivalent to two 400-mg gabapentin SUPRO capsules

Methodology: The study was an open-label, single-dose, 2-way crossover design conducted in healthy subjects. On Days 1 and 8, each subject received a single AM dose following an overnight fast.

Number of Subjects (total and for each treatment): Twenty healthy subjects enrolled and 19 subjects (8 males and 11 females) completed the study. Nineteen subjects received each treatment.

Diagnosis and Criteria for Inclusion: Healthy adult male and female volunteers

Test Product, Dose and Mode of Administration, Batch Number:
- Gabapentin [CI-945] 800-mg tablets , Lot CM 1731095

Administration: Oral, with 8 oz of water to fasting subjects

Duration of Treatment: Single 800-mg gabapentin doses were administered on Study Days 1 and 8.

Reference Therapy, Dose and Mode of Administration, Batch Number:
- Gabapentin [CI-945] 400-mg apsules Lot 01905V

Administration: Oral, with 8 oz of water to fasting subjects

Criteria for Evaluation: Data from all 20 subjects were used in the safety evaluation, and data from the 19 subjects who completed the study were used in the pharmacokinetic evaluations.

Pharmacokinetic Sampling and Analysis: Blood and urine samples were collected serially for 72 hours following dosing on Days 1 and 8. Plasma and urine samples were analyzed for gabapentin using specific procedures. Methods were validated over the concentration ranges of in plasma and in urine.

Pharmacokinetic Statistical Methods: Pharmacokinetic parameters were calculated using standard noncompartmental methods. Analysis of variance of parameter values and subsequent evaluation of 90%

Name of Company: **Warner-Lambert**	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **Neurontin**	Referring to Part of the Dossier	
Name of Active Ingredient: **Gabapentin**	Volume: Page:	

Protocol 945-208-0 (Page 2)

confidence intervals based on log-transformed Cmax and AUC values were performed. Bioequivalence would be established if these confidence intervals are within the 80% to 125% range.

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SUMMARY - CONCLUSIONS:

Subject Characteristics and Disposition Nineteen of the 20 subjects completed the study. Mean (range) age, weight, and height of the subjects who completed the study were 34.4) years, 78.7 kg, and 175.4 cm, respectively.

Clinical In general, gabapentin was well-tolerated by healthy volunteers. CNS adverse events, primarily mild in intensity, were frequently reported following gabapentin administration.

Pharmacokinetics Data from the 19 subjects who completed the study were included in the pharmacokinetic and statistical analyses. Mean Cmax and AUC values presented in this synopsis were calculated as the antilogs of least-squares mean log-transformed values (analogous to geometric mean). Ratios and confidence intervals for Cmax and AUC values are also based on log transformed values. Least-squares means for the remaining pharmacokinetic parameters are reported in this synopsis. Ratios for these parameters are based on untransformed values.

Parameter values from this study are summarized in the following table:

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Parameter	Mean[a]		Ratio	90% Confidence Interval
	Two 400-mg Capsules (Reference)	One 800-mg Tablet (Test)		
Cmax[a] (µg/mL)	4.66	4.31	92.5	80.1% to 106.4%
tmax (hr)	3.2	3.0	93.7	Not Applicable
AUC(0-tldc)[a] (µg•hr/mL)	47.5	43.8	92.2	82.2% to 103.7%
AUC(0-∞)[a] (µg•hr/mL)	48.4	44.7	92.4	82.5% to 103.3%
t½ (hr)	14.3	14.3	100	Not Applicable

Ratio (test/reference) of antilogs of treatment least-squares mean values expressed as a percent of reference mean (for log-transformed data) or ratio of treatment least-squares mean values expressed as a percent of reference mean (for untransformed data).
90% Confidence Interval is an estimate for the ratio (test/reference) of treatment mean values, expressed as percent of the reference mean.
[a] Means and confidence intervals based on log-transformed data

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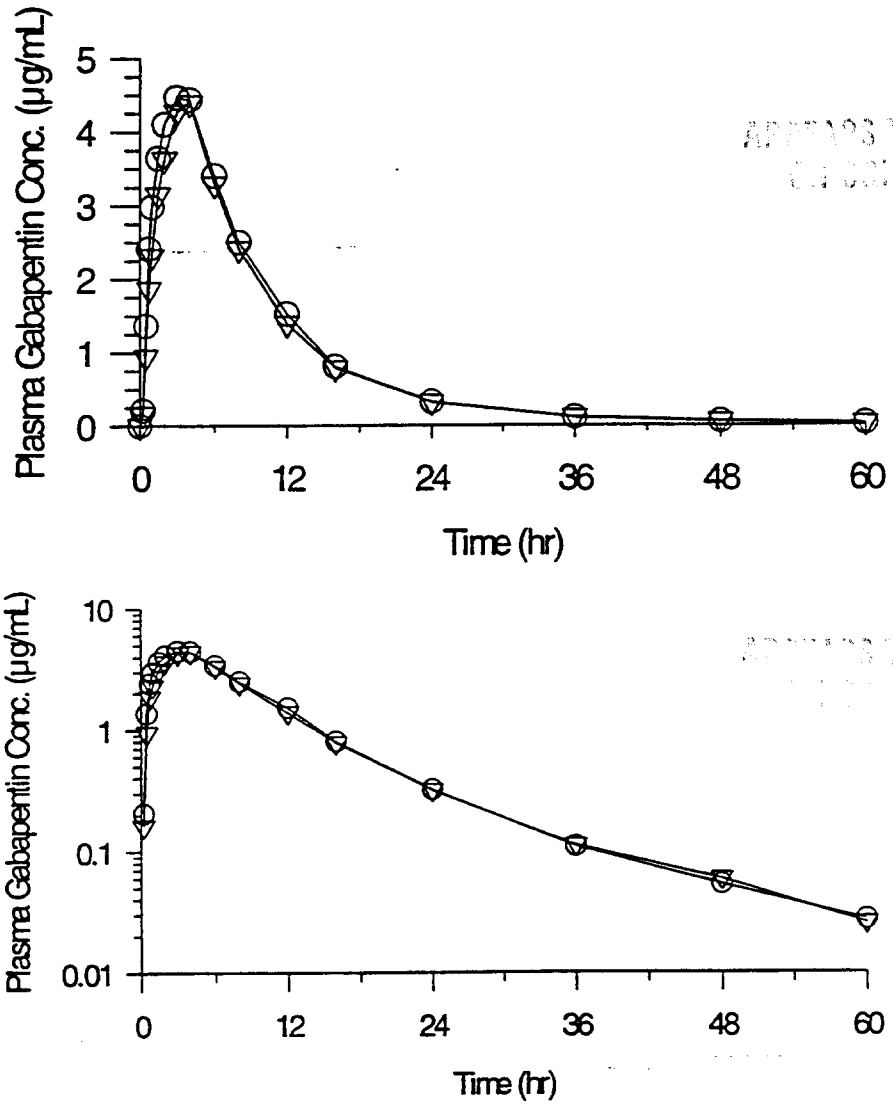

FIGURE 1. Mean Plasma Gabapentin Concentration-Time Profiles Following Administration of One 800-mg Gabapentin Tablet (▽) and Two 400-mg Gabapentin Capsules (○) to Healthy Subjects (Protocol 945-208-0)

Top panel linear scale; bottom panel, semilogarithmic scale

TABLE D.6. Summary of Statistical Evaluation of Gabapentin Pharmacokinetic Parameters Following Administration of One 800-mg Gabapentin Tablet and Two 400-mg Gabapentin Capsules (Protocol 945-208)

Parameter	Least-Squares Mean Value		Ratio	90% CI
	One 800-mg Tablet (Test) N = 19	Two 400-mg Capsules (Reference) N = 19		
Cmax[a]	4.30	4.68	92.5	80.1 to 106.4
AUC(0-∞)[a]	44.8	48.6	92.4	82.5 to 103.3
Cmax	4.64	4.78	97.1	84.7 to 109.5
tmax	3.0	3.2	93.7	78.6 to 108.9
AUC(0-tldc)	46.7	49.2	94.9	84.8 to 105.0
AUC(0-tldc)[a]	43.8	47.5	92.2	82.2 to 103.7
AUC(0-∞)	47.5	50.0	95.0	85.1 to 104.9

Cmax	=	Maximum plasma concentration (µg/mL).
tmax	=	Time (hr) for Cmax.
AUC(0-tldc)	=	Area under plasma concentration-time curve from time 0 to time of the last detectable concentration (µg·hr/mL).
AUC(0-∞)	=	Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg·hr/mL).
Ratio	=	Ratio (test/reference) of antilogs of treatment least-squares mean values expressed as a percent of reference mean (for log-transformed data) or ratio of treatment least-squares mean values expressed as a percent of reference mean (for untransformed data).
90% CI	=	90% confidence interval estimate for ratio (test/reference) of treatment least-squares mean values expressed as a percentage.

[a] Parameter values are antilogs of least-squares mean log transformed values.

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ATTACHMENT 4

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PARKE-DAVIS PHARMACEUTICAL RESEARCH
DIVISION OF WARNER-LAMBERT COMPANY
ANN ARBOR, MICHIGAN

RESEARCH REPORT NO.: RR 744-00249

DATE ISSUED: February 04, 1997

CLINICAL INVESTIGATOR(S):

PERIODS COVERED: 04/17/95 to 04/28/95

GABAPENTIN (CI-945) ANALYST(S)

DEPARTMENT: Pharmacokinetics/Drug Metabolism and Clinical Pharmacology

COMPOUND NUMBERS (PD,WL,GOE,CI):
CI-945, PD 087842-0000

LOT NUMBER(S):
CM 0190295, CF 0390793

PHASE:
1

PROTOCOL NUMBER:
945-189-0

NOTEBOOK (OR OTHER REFS):

SUGGESTED KEY WORDS:
Gabapentin, Neurontin, Single Dose, Bioequivalence, Anticonvulsant, Human

TITLE: A Single-Dose Bioequivalence Study Comparing 600-mg CI-945 Tablets to 300-mg Gabapentin Capsules (Protocol 945-189-0)

TABLE 4.1. Individual Gabapentin Pharmacokinetic Parameters Following Administration of One 600-mg Gabapentin Tablet (Test) (Protocol 945-189)

Subject	Sequence	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUC_{extrap} (%)	λz (1/hr)	t½ (hr)	Ae% (%)
1	B								
2	B								
3	A								
4	A								
5	B								
6	B								
7	A								
8	A								
9	B								
10	B								
11	A								
12	A								
13	A								
14	A								
15	B								
16	B								
17	A								
18	B								
19	A								
20	B								
Mean		4.65	4.1	50.1	51.0	1.7	0.0834	8.5	47.7
SD		1.15	1.2	13.0	13.3	0.7	0.0140	1.6	12.2
%RSD		24.8	29.4	25.9	26.0	43.9	16.7	18.4	25.5
N		20	20	20	20	20	20	20	20

AUC_{extrap} = Portion of AUC(0-∞) due to extrapolation, expressed as a percentage of AUC(0-∞).
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).
Sequence = Treatment sequence; A= one 600-mg gabapentin tablet/two 300-mg gabapentin capsules; B = two 300-mg gabapentin capsules/one gabapentin 600-mg tablet.
Other parameters are as defined in Section 5.6.

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TABLE 4.2. Individual Gabapentin Pharmacokinetic Parameters Following Administration of Two 300-mg Gabapentin SUPRO Capsules (Reference) (Protocol 945-189)

Subject	Sequence	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUC_{extrap} (%)	λz (1/hr)	t½ (hr)	Ae% (%)
1	B								
2	B								
3	/								
4	A								
5	B								
6	B								
7	A								
8	A								
9	B								
10	B								
11	A								
12	A								
13	A								
14	A								
15	B								
16	B								
17	A								
18	B								
19	A								
20	B								
Mean		4.19	3.4	45.6	46.6	2.2	0.0835	9.1	43.6
SD		1.05	1.2	12.6	12.7	2.7	0.0208	3.6	12.1
%RSD		25.1	36.3	27.7	27.3	123	24.9	39.9	27.8
N		20	20	20	20	20	20	20	20

AUC_{extrap} = Portion of AUC(0-∞) due to extrapolation, expressed as a percentage of AUC(0-∞).
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).
Sequence = Treatment sequence; A = one 600-mg gabapentin tablet/two 300-mg gabapentin capsules; B = two 300-mg gabapentin capsules/one gabapentin 600-mg tablet.
Other parameters are as defined in Section 5.6.

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TABLE 5.1. Comparison of Individual Gabapentin Cmax Values Following Administration of One 600-mg Gabapentin Tablet to Two 300-mg Gabapentin Capsules (Protocol 945-189)

Subject	Sequence	Cmax Values by Formulation		Difference	Ratio	ln(Ratio/100)
		One 600-mg Tablet	Two 300-mg Capsules			
1	B					
2	B					
3	A					
4	A					
5	B					
6	B					
7	A					
8	A					
9	B					
10	B					
11	A					
12	A					
13	A					
14	A					
15	B					
16	B					
17	A					
18	B					
19	A					
20	B					
Mean		4.65	4.19	0.46	113	0.108
SD		1.15	1.05	0.77	21.8	0.183
%RSD		24.8	25.1	165	19.2	170
N		20	20	20	20	20

Sequence = Treatment sequence; A = one 600-mg gabapentin tablet/two 300-mg gabapentin capsules; B = two 300-mg gabapentin capsules/one 600-mg gabapentin tablet.
Cmax = Maximum observed plasma gabapentin concentration (µg/mL).
Difference = Difference (tablet - capsules) in Cmax values (µg/mL).
Ratio = Ratio (tablet/capsules) of Cmax values expressed as a percentage.
ln(Ratio/100) = Natural logarithm of the ratio of Cmax values.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).

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TABLE 5.2. Comparison of Individual Gabapentin AUC(0-∞) Values Following Administration of One 600-mg Gabapentin Tablet to Two 300-mg Gabapentin Capsules (Protocol 945-189)

Subject	Sequence	AUC(0-∞) Values by Formulation		Difference	Ratio	ln(Ratio/100)
		One 600-mg Tablet	Two 300-mg Capsules			
1	B					
2	B					
3	A					
4	A					
5	B					
6	B					
7	A					
8	A					
9	B					
10	B					
11	A					
12	A					
13	A					
14	A					
15	B					
16	B					
17	A					
18	B					
19	A					
20	B					
Mean		51.0	46.6	4.41	111	0.0931
SD		13.3	12.7	7.40	17.2	0.16
%RSD		26.0	27.3	168	15.5	167
N		20	20	20	20	20

Sequence = Treatment sequence; A = one 600-mg gabapentin tablet/two 300-mg gabapentin capsules; B = two 300-mg gabapentin capsules/one 600-mg gabapentin tablet.
AUC(0-∞) = Area under the plasma concentration-time curve from time zero to infinite time (µg•hr/mL).
Difference = Difference (tablet capsules) in AUC(0-∞) values (µg•hr/mL).
Ratio = Ratio (tablet/ capsules) of AUC(0-∞) values expressed as a percentage.
ln(Ratio/100) = Natural logarithm of the ratio of AUC(0-∞) values.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations (subjects).

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PARKE-DAVIS PHARMACEUTICAL RESEARCH
DIVISION OF WARNER-LAMBERT COMPANY
ANN ARBOR, MICHIGAN

RESEARCH REPORT NO.: RR 744-00337

DATE ISSUED: June 9, 1997

INVESTIGATOR(S):

PERIODS COVERED: 12/10/96 to 02/10/97

CI-945 ANALYST(S):

DEPARTMENT: Pharmacokinetics/Drug Metabolism and Clinical Pharmacology

COMPOUND NUMBERS (PD,WL,GOE,CI):
CI-945, PD 087842-0000

LOT NUMBER(S):
CV1771196, 02166VA

PHASE:
4

PROTOCOL NUMBER:
945-205-0

NOTEBOOK (OR OTHER REFS):

SUGGESTED KEY WORDS:
Gabapentin, Neurontin®, Single Dose, Bioequivalence, Anticonvulsant, Human

TITLE: A Single-Dose Bioequivalence Study Comparing 600-mg Gabapentin Tablets Manufactured in to 300-mg Gabapentin Capsules

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TABLE D.3.1. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of Two 300-mg Gabapentin Capsule (Reference) (Protocol 945-205)

Subject	Day	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUCextrap (%)	λz (1/hr)	t½ (hr)
1	1							
2	8							
3	8							
4	1							
5	8							
6	8							
7	1							
8	1							
9	1							
10	8							
11	8							
12	1							
13	1							
14	1							
15	8							
16	8							
17	1							
18	1							
19	8							
20	8							
Mean		4.48	3.5	46.8	47.7	2.3	0.0718	15.4
SD		1.16	1.2	13.3	12.9	3.3	0.0387	13.9
%RSD		25.9	34.1	28.4	27.1	139.4	53.9	90.5
N		20	20	20	20	20	20	20
Median		4.63	3.5	43.6	44.1	1.2	0.0730	9.5
Minimum								
Maximum								

Cmax = Maximum plasma concentration (µg/mL).
tmax = Time (hr) for Cmax.
AUC(0-tldc) = Area under plasma concentration-time curve from time 0 to time of the last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg•hr/mL).
λz = Elimination rate constant (1/hr).
t½ = Elimination half-life (hr).

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TABLE D.3.2. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of One 600-mg Gabapentin Tablet (Test) (Protocol 945-205)

Subject	Day	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUCextrap (%)	λz (1/hr)	t½ (hr)
1	8							
2	1							
3	1							
4	8							
5	1							
6	1							
7	8							
8	8							
9	8							
10	1							
11	1							
12	8							
13	8							
14	8							
15	1							
16	1							
17	8							
18	8							
19	1							
20	1							
Mean		4.94	3.2	51.3	52.5	2.7	0.0736	15.6
SD		1.52	0.9	16.3	15.8	3.8	0.0437	13.7
%RSD		30.9	27.3	31.8	30.2	140.5	59.3	88.2
N		20	20	20	20	20	20	20
Median		4.61	3	48.2	49.8	1.5	0.0661	10.6
Minimum								
Maximum								

Cmax = Maximum plasma concentration (µg/mL).
tmax = Time (hr) for Cmax.
AUC(0-tldc) = Area under plasma concentration-time curve from time 0 to time of the last detectable concentration (µg•hr/mL).
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg•hr/mL).
λz = Elimination rate constant (1/hr).
t½ = Elimination half-life (hr).

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TABLE D.4.1. Comparison of Individual Gabapentin Cmax Values Following Administration of One 600-mg Gabapentin Tablet to Two 300-mg Gabapentin Capsules (Protocol 945-205)

Subject	Sequence	Cmax Values by Formulation		Difference	Ratio	ln(Ratio)
		One 600-mg Tablet	Two 300-mg SUPRO Capsules			
1	A					
2	B					
3	B					
4	A					
5	B					
6	B					
7	A					
8	A					
9	A					
10	B					
11	B					
12	A					
13	A					
14	A					
15	B					
16	B					
17	A					
18	A					
19	B					
20	B					
Mean		4.94	4.48	0.46	1.13	0.0885
SD		1.52	1.16	1.38	0.33	0.2786
%RSD		30.9	25.9	303.62	28.6	314.8
N		20	20	20	20	20

Sequence = Treatment sequence; A = two 300-mg gabapentin capsules/one 600-mg gabapentin tablet; B = one 600-mg gabapentin tablet/two 300-mg gabapentin capsules.
Cmax = Maximum observed plasma gabapentin concentration (µg/mL).
Difference = Difference (tablet - capsules) in Cmax values (µg/mL).
Ratio = Ratio (tablet capsules) of Cmax values.
ln(Ratio) = Natural logarithm of the ratio of Cmax values.
SD = Standard deviation.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations.

TABLE D.4.2. Comparison of Individual Gabapentin AUC(0-∞) Values Following Administration of One 600-mg Gabapentin Tablet to Two 300-mg Gabapentin Capsules (Protocol 945-205)

Subject	Sequence	AUC(0-∞) Values by Formulation		Difference	Ratio	ln(Ratio)
		One 600-mg Tablet	Two 300-mg Capsules			
1	A					
2	B					
3	B					
4	A					
5	B					
6	B					
7	A					
8	A					
9	A					
10	B					
11	B					
12	A					
13	A					
14	A					
15	B					
16	B					
17	A					
18	A					
19	B					
20	B					
Mean		52.5	47.7	4.8	1.13	0.0884
SD		15.8	12.9	12.9	0.286	0.2491
%RSD		30.2	27.1	271.2	25.4	281.8
N		20	20	20	20	20

Sequence = Treatment sequence; A = two 300-mg gabapentin capsules/one 600-mg gabapentin tablet; B = one 600-mg gabapentin tablet/two 300-mg gabapentir capsules.
AUC(0-∞) = Maximum observed plasma gabapentin concentration (µg/mL).
Difference = Difference (tablet - capsules) in AUC(0-∞) values (µg/mL).
Ratio = Ratio (table capsules) of AUC(0-∞) values.
ln(Ratio) = Natural logarithm of the ratio of AUC(0-∞) values.
SD = Standard deviation.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations.

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PARKE-DAVIS PHARMACEUTICAL RESEARCH
DIVISION OF WARNER-LAMBERT COMPANY
ANN ARBOR, MICHIGAN

RESEARCH REPORT NO.: RR 744-00328

DATE ISSUED: June 9, 1997

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PERIODS COVERED: 03/05/96 to 03/28/96

CI-945 ANALYST(S):

DEPARTMENT: Pharmacokinetics/Drug Metabolism and Clinical Pharmacology

COMPOUND NUMBERS (PD,WL,GOE,CI):
CI-945, PD 087842-0000

LOT NUMBER(S):
CM 1731095
01905V

PHASE:
4

PROTOCOL NUMBER:
945-208-0

NOTEBOOK (OR OTHER REFS):

SUGGESTED KEY WORDS:
Gabapentin, Neurontin, Single Dose, Bioequivalence, Anticonvulsant, Human

TITLE: A Single-Dose Bioavailability Study Comparing 800-mg CI-945 Tablets to 400-mg Gabapentin Capsules (Protocol 945-208-0)

Name of Company: **Warner-Lambert**	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: **Neurontin**	Referring to Part of the Dossier	
Name of Active Ingredient: **Gabapentin**	Volume: Page:	

Protocol 945-208-0 (Page 3)

Bioequivalence criteria for Cmax and AUC(0-∞) values were met. Ratios of formulation least-squares mean values for secondary parameters [untransformed Cmax, untransformed and log-transformed AUC(0-tldc), and untransformed AUC(0-∞)] and corresponding 90% confidence intervals further support the bioequivalence of 800-mg gabapentin tablets to 400-mg gabapentin capsules.

Conclusions Eight-hundred milligram gabapentin tablets are bioequivalent to 2 × 400-mg gabapentin capsules.

TABLE D.4.1. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of One 800-mg Gabapentin Tablet (Test) (Protocol 945-208)

Subject	Day	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUC_{extrap} (%)	λz (1/hr)	t½ (hr)	Ae% (%)
1	1								
2	8								
4	8								
5	8								
6	8								
7	1								
8	1								
9	1								
10	8								
11	8								
12	1								
13	8								
14	8								
15	1								
16	1								
17	1								
18	8								
19	1								
20	8								
Mean		4.60	3.0	46.4	47.2	2.1	0.0627	14.3	34.8
SD		1.78	1.0	16.4	16.3	2.0	0.031	8.0	10.8
%RSD		38.8	32.8	35.4	34.4	95.0	49.5	55.9	31.1
N		19	19	19.0	19.0	19	19	19	19
Median		4.36	3.0	43.1	43.8	1.5	0.0577	12.0	36.4
Minimum									
Maximum									

Cmax	=	Maximum plasma concentration.
tmax	=	Time for Cmax.
AUC(0-tldc)	=	Area under plasma concentration-time curve from time 0 to time of the last detectable concentration.
AUC(0-∞)	=	Area under plasma concentration-time curve from time 0 extrapolated to infinite time.
λz	=	Elimination rate constant.
t½	=	Elimination half-life.
Ae%	=	Percent of Dose excreted in Urine (%).

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TABLE D.4.2. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of Two 400-mg Gabapentin Capsule (Reference) (Protocol 945-208)

Subject	Day	Cmax (µg/mL)	tmax (hr)	AUC(0-tldc) (µg•hr/mL)	AUC(0-∞) (µg•hr/mL)	AUC_{extrap} (%)	λz (1/hr)	t½ (hr)	Ae% (%)
1	1								
2	8								
4	8								
5	8								
6	8								
7	1								
8	1								
9	1								
10	8								
11	8								
12	1								
13	8								
14	8								
15	1								
16	1								
17	1								
18	8								
19	1								
20	8								
Mean		4.77	3.2	49.0	49.9	2.0	0.0710	14.5	37.1
SD		0.91	0.9	12.3	11.9	2.6	0.0393	11.5	9.09
%RSD		19.1	26.4	25.0	23.8	124.9	55.4	79.3	24.5
N		19	19	19	19	19	19	19	19
Median		4.86	3	49.5	50.5	1	0.0646	10.7	40.5
Minimum									
Maximum									

Cmax = Maximum plasma concentration.
tmax = Time for Cmax.
AUC(0-tldc) = Area under plasma concentration-time curve from time 0 to time of the last detectable concentration.
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time.
λz = Elimination rate constant.
t½ = Elimination half-life.
Ae% = Percent of dose excreted in urine.

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TABLE D.5.1. Comparison of Individual Gabapentin Cmax Values Following Administration of One 800-mg Gabapentin Tablet to Two 400-mg Gabapentin Capsules (Protocol 945-208)

Subject	Sequence	Cmax Values by Formulation		Difference	Ratio	ln(Ratio)
		One 800-mg Tablet	Two 400-mg Capsules			
1	B					
2	A					
4	A					
5	A					
6	A					
7	B					
8	B					
9	B					
10	A					
11	A					
12	B					
13	A					
14	A					
15	B					
16	B					
17	B					
18	A					
19	B					
20	A					
Mean		4.60	4.77	-0.17	0.97	-0.0915
SD		1.78	0.91	1.52	0.33	0.3703
%RSD		38.8	19.1	914.69	33.99	
N		19	19	19	19	19

Sequence = Treatment sequence; A = Two 400-mg gabapentin capsules/one 800-mg gabapentin tablet; B = One 800-mg gabapentin tablet/two 400-mg gabapentin capsules.
Cmax = Maximum observed plasma gabapentin concentration (µg/mL).
Difference = Difference (tablet capsules) in Cmax values (µg/mL).
Ratio = Ratio (tablet capsules) of Cmax values.
ln(Ratio) = Natural logarithm of the ratio of Cmax values.
SD = Standard deviation.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations.

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TABLE D.5.2. Comparison of Individual Gabapentin AUC(0-∞) Values Following Administration of One 800-mg Gabapentin Tablet to Two 400-mg Gabapentin Capsules (Protocol 945-208)

Subject	Sequence	AUC(0-∞) Values by Formulation		Difference	Ratio	ln(Ratio)
		One 800-mg Tablet	Two 400-mg Capsules			
1	B					
2	A					
4	A					
5	A					
6	A					
7	B					
8	B					
9	B					
10	A					
11	A					
12	B					
13	A					
14	A					
15	B					
16	B					
17	B					
18	A					
19	B					
20	A					
Mean		47.2	49.9	-2.7	0.95	-0.0866
SD		16.3	11.9	12.4	0.26	0.2920
%RSD		34.4	23.8	464.3	27.7	
N		19	19	19	19	19

Sequence = Treatment sequence; A = Two 400-mg gabapentin capsules/one 800-mg gabapentin tablet; B = One 800-mg gabapentin tablet/two 400-mg gabapentin capsules.
AUC(0-∞) = Area under plasma concentration-time curve from time 0 extrapolated to infinite time (µg·hr/mL).
Difference = Difference (tablet capsules) in AUC(0-∞) values.
Ratio = Ratio (tablet/ capsules) of AUC(0-∞) values.
ln(Ratio) = Natural logarithm of the ratio of AUC(0-∞) values.
SD = Standard deviation.
%RSD = Relative standard deviation (% of mean value).
N = Number of observations.

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