

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-129

**CLINICAL PHARMACOLOGY and
BIOPHARMACEUTICS REVIEW(S)**

SEP 20 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

Gabapentin (Neurontin®)

250 mg/5 mL

NDA #21-129

Indication: _____

Reviewer: Z. Wahba, Ph.D.

Parke-Davis Pharmaceuticals

Ann Arbor, MI

Submission Date:

April 30, 1999

REVIEW OF AN NDA

OBJECTIVE

The sponsor seeks approval of an oral liquid dosage form for gabapentin in a strength of 250 mg/5 mL (50 mg/mL) (Attachment 1). The firm has conducted an in vivo bioavailability study (#945-201-0) to determine to bioequivalency of gabapentin 300 mg/6 mL to the reference drug product, Parke-Davis' gabapentin capsule, 300 mg.

BACKGROUND

The drug is indicated as an adjunctive therapy in the treatment of partial seizures with — without secondary generalization in adults with epilepsy.

The mechanism by which gabapentin exerts its anticonvulsant action is unknown, but in animal test systems designed to detect anticonvulsant activity, gabapentin prevents seizures as do other marketed anticonvulsants.

Gabapentin is structurally related to the neurotransmitter GABA (gamma-aminobutyric acid) but it does not interact with GABA receptors, it is not converted metabolically into GABA or a GABA agonist, and it is not an inhibitor of GABA uptake or degradation.

All pharmacological actions following gabapentin administration are due to the activity of the parent compound; gabapentin is not appreciably metabolized in humans.

Gabapentin bioavailability is not dose proportional; i.e., as dose is increased, bioavailability decreases. A 400-mg dose, for example, is about 25% less bioavailable than a 100-mg dose. Over the recommended dose range of 300 to 600 mg T.I.D., however, the differences in bioavailability are

not large, and bioavailability is about 60 percent. Food has no effect on the rate and extent of absorption of gabapentin.

Gabapentin circulates largely unbound (<3%) to plasma protein. The apparent volume of distribution of gabapentin after 150 mg intravenous administration is 58 ± 6 L (Mean \pm SD). In patients with epilepsy, steady-state predose (C_{min}) concentrations of gabapentin in cerebrospinal fluid were approximately 20% of the corresponding plasma concentrations.

Gabapentin is eliminated from the systemic circulation by renal excretion as unchanged drug. Gabapentin is not appreciably metabolized in humans.

Gabapentin elimination half-life is 5 to 7 hours and is unaltered by dose or following multiple dosing. Gabapentin elimination rate constant, plasma clearance, and renal clearance are directly proportional to creatinine clearance. In elderly patients, and in patients with impaired renal function, gabapentin plasma clearance is reduced. Gabapentin can be removed from plasma by hemodialysis.

RECOMMENDED DOSE INFORMATION

Neurontin® is given orally with or without food. The effective dose of Neurontin® is 900 to 1800 mg/day and given in divided doses (three times a day) using 300- or 400-mg capsules. The starting dose is 300 mg three times a day. To minimize potential side effects, especially somnolence, dizziness, fatigue, and ataxia, the first dose on Day 1 may be administered at bedtime. If necessary, the dose may be increased using 300- or 400-mg capsules three times a day up to 1800 mg/day. Dosages up to 2400 mg/day have been well tolerated in long-term clinical studies. Doses of 3600 mg/day have also been administered to a small number of patients for a relatively short duration, and have been well tolerated. The maximum time between doses in the T.I.D. schedule should not exceed 12 hours.

STUDY 945-201-0: Single-Dose Bioequivalence Study Comparing a Gabapentin Syrup Formulation to 300 mg Neurontin® Capsule.

Study design: Open-label, single-dose, randomized, 2-way crossover bioequivalence study in healthy subjects.

Number of subjects: 20 subjects (1 male and 19 females)

Treatments:

Test: one, 300 mg gabapentin syrup (300 mg/6 mL), Lot CZ 1191097, WL 87842-33.

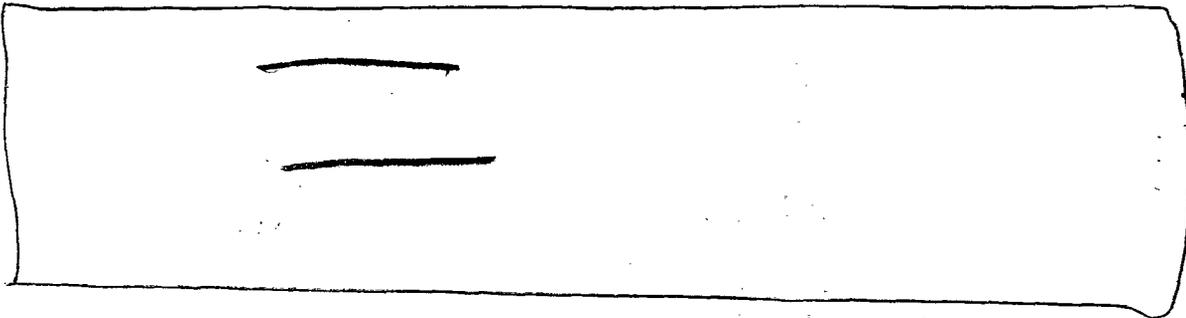
Reference: one, 300 mg Neurontin® Capsule (currently approved), Lot #006D6V

Dose: Single doses of 300 mg.

Washout: one week

Treatment Plan: On Days 1 and 8, each subject received a single AM dose following an overnight fast.

Withdrawn subject(s): none



BE Study Results: (also, please see attachments)

1. Figure #1 shows the mean plasma concentration-time profiles following administration of 300 mg gabapentin syrup and a 300 mg marketed gabapentin capsule to healthy subjects. Table #1 and #2 show the pharmacokinetic parameters for individual subjects for both treatments.

2. The mean pharmacokinetic parameter values, SD, ratios, and 90% confidence intervals are summarized in the following table.

Parameter	Mean Value Test Product (300 mg Syrup)	Mean Value Reference Product (300 mg Capsule)	Ratio	90%C.I.
C _{max} , µg/mL	2.8 (0.6)	2.9 (0.6)	97	89-105
AUC(0-t), µg.hr/mL	25.5 (5.2)	27.4 (5.4)	93	88-99
AUC(0-∞), µg.hr/mL	25.9 (5.1)	27.8 (5.4)	93	88-99
T _{max} , hr	2.7 (0.9)	3.3 (1.1)	81	NA
T _{1/2} , hr	5.7 (1.3)	5.4 (1.1)	106	NA

Comments on the PK parameters: The mean plasma gabapentin levels for the test and reference products were comparable to each other. The relative bioavailability of syrup to capsule was 93%. The 90% C.I. for the Lsmeans log-transformed AUC(0-t), AUC(0-∞) and Cmax were within the acceptable range of 80-125%.

GENERAL COMMENTS

The results of the bioequivalence study show that both the syrup and capsule formulations are bioequivalent at a dose of 300 mg.

LABELING COMMENT

Reference is made to the **CLINICAL PHARMACOLOGY/ Pharmacokinetics and Drug Metabolism** section of the firm's proposed labeling:

Under the Oral Bioavailability subsection:
The following statement should be added:

RECOMMENDATION

The study has demonstrated that gabapentin syrup formulation is bioequivalent to the marketed gabapentin capsules when administered at equal doses of 300 mg. The study is acceptable to OCPB.

This NDA for gabapentin — is approvable from an OCPB standpoint.

Please forward this Recommendation and the labelling Comment above to the sponsor.

Zakaria Z. Wahba, Ph.D. /S/
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. /S/

9/20/99.

Cc: NDA #21-129, HFD-120, HFD-860 (Wahba, Baweja, Mehta),
Central Documents Room

3.2.2. Components

The following components are used in the manufacture of the drug product.

Table 1. Components Used in Gabapentin Syrup

Component	Function
Gabapentin	Active
Glycerin	Solvent
Xylitol	Sweetener
Artificial Cool Strawberry Anise Flavor	Flavoring agent
Purified Water	Solvent

Drug Substance

Specifications and test methods for gabapentin are provided in approved NDA 20-235 for the 100-, 300-, and 400-mg capsules.

3.2.3. Composition

APPEARS THIS WAY
ON ORIGINAL

3.2.3.1. Quantitative Formulation

Formulation No.	
Label Claim	250 mg/5 mL
Ingredients	Quantity/5 mL
Gabapentin	250.00 mg
Glycerin	
Xylitol	
Artificial Cool Strawberry Anise Flavor	
Purified Water	
Total	

APPEARS THIS WAY
ON ORIGINAL

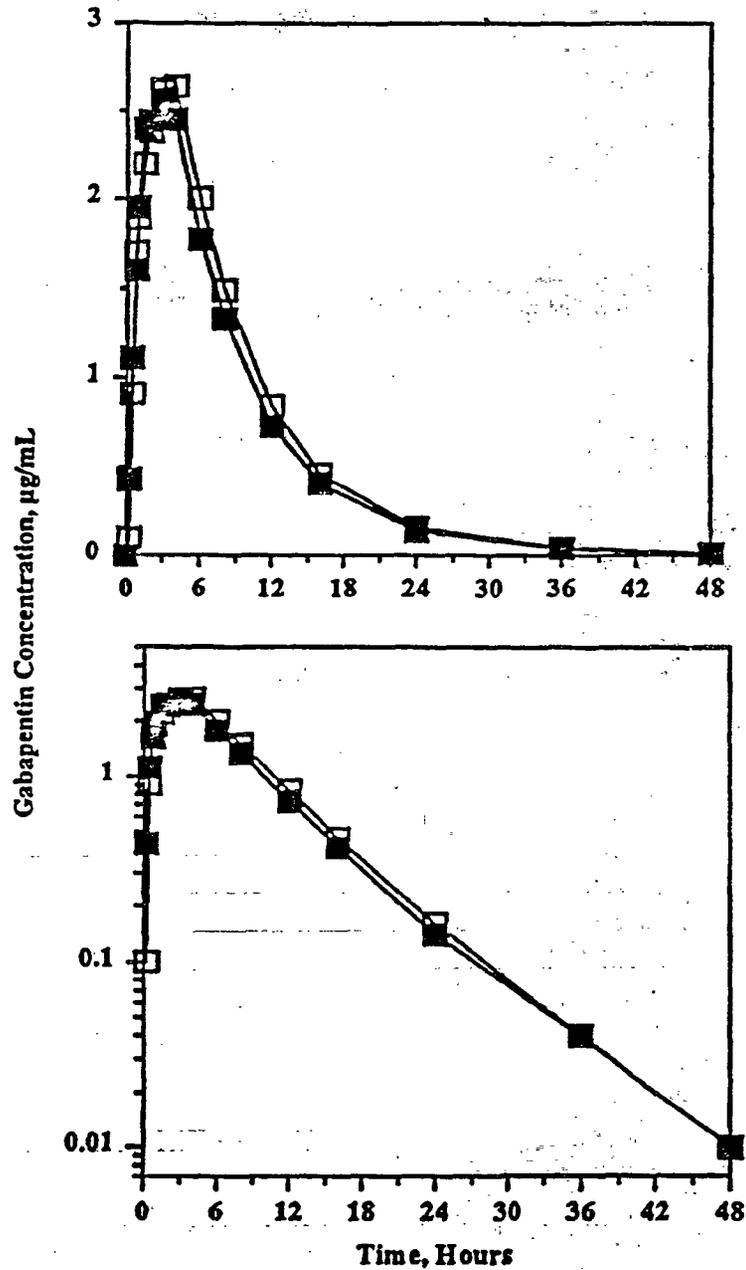


Figure 1. Mean Plasma Gabapentin Concentration-Time Profiles Following Administration of 300-mg Gabapentin (□) Manufactured in Litz, Pennsylvania and a 300-mg Marketed Gabapentin Capsule (■) to Healthy Subjects (Study 945-201-0).

Table # 1

Table E.3.2. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of Each Treatment: Protocol 945-201

----- TREATMENT=2: 300 mg Gabapentin -----

SUBJECT	PHASE	C _{max}	t _{max}	AUC (0-t _l dc)	AUC (0-inf)	% AUC(0-inf) Extrapolated	Lambda-z	Half-life
1	2							
2	1							
3	2							
4	1							
5	1							
6	2							
7	2							
8	1							
9	2							
10	1							
11	2							
12	1							
13	2							
14	2							
15	1							
16	1							
17	2							
18	1							
19	2							
20	1							
Mean		2.81	2.65	25.51	25.90	1.6	0.129	5.68
SD		0.62	0.90	5.17	5.11	1.8	0.029	1.32
%RSD		22.04	34.14	20.28	19.71	113.0	22.832	23.17
n		20.00	20.00	20.00	20.00	20.0	20.000	20.00
Median		2.71	3.00	25.16	25.43	1.0	0.124	5.61
Minimum								
Maximum								

C _{max}	▪ Maximum Plasma concentration (ug/mL)
t _{max}	▪ Time (Hours) for C _{max}
AUC(0-t _l dc)	▪ Area under Plasma curve from 0 Hours to time of last detectable concentration (Hours ug/mL)
AUC(0-inf)	▪ Area under Plasma curve from 0 Hours extrapolated to infinite time (Hours ug/mL)
Lambda-z	▪ Elimination rate constant (1/Hours)
Half-Life	▪ Elimination half-life (Hours)

Table #2

Table E.3.1. Individual and Mean Gabapentin Pharmacokinetic Parameter Values Following Administration of Each Treatment: Protocol 945-201

----- TREATMENT-1: 1 x 300-mg Neurontin Capsule -----

SUBJECT	PHASE	C _{max}	t _{max}	AUC (0-t _l dc)	AUC (0-inf)	% AUC(0-inf) Extrapolated	Lambda-z	Half-Life
1	1							
2	2							
3	1							
4	2							
5	2							
6	1							
7	1							
8	2							
9	1							
10	2							
11	1							
12	2							
13	1							
14	1							
15	2							
16	2							
17	1							
18	2							
19	1							
20	2							
Mean		2.91	3.25	27.40	27.76	1.4	0.135	5.36
SD		0.61	1.11	5.43	5.40	1.0	0.028	1.13
%RSD		20.92	34.04	19.83	19.44	71.0	20.425	21.16
n		20.00	20.00	20.00	20.00	20.0	20.000	20.00
Median		2.90	3.00	26.82	27.05	1.0	0.139	5.03
Minimum								
Maximum								

C _{max}	▪ Maximum Plasma concentration (ug/mL)
t _{max}	▪ Time (Hours) for C _{max}
AUC(0-t _l dc)	▪ Area under Plasma curve from 0 Hours to time of last detectable concentration (Hours ug/mL)
AUC(0-inf)	▪ Area under Plasma curve from 0 Hours extrapolated to infinite time (Hours ug/mL)
Lambda-z	▪ Elimination rate constant (1/Hours)
Half-Life	▪ Elimination half-life (Hours)

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Gabapentin
250 mg/5 mL**3.2.4.3. Summary of *in vivo* Bioavailability Study**

In order to determine if the inclusion of significant amounts of xylitol and glycerin in the formulation interferes with the bioavailability of the product, gabapentin 250 mg/5 mL (PDS Lot CZ-1191097; Lititz Lot 90107L) was tested for bioequivalence to Neurontin 300-mg commercial capsules (Lot 006D6V). The results (Protocol 945-201) summarized in Table 3 have confirmed the bioequivalency of gabapentin 250 mg/5 mL (Formulation 33) to the marketed capsule product.

Table 3. Summary (n = 20) of Gabapentin Pharmacokinetic Parameter Values Following Administration of Single 300-mg Doses as Syrup and 300-mg Neurontin Capsules (Protocol 945-201)

Parameter	Mean Values		Ratio	90% Confidence Interval
	300-mg Capsule	300-mg Syrup		
C_{max} , µg/mL	2.84	2.75	97	89% to 105%
T_{max} , hr	3.25	2.65	81	Not Applicable
AUC (0-t _{ldc}), µg·hr/mL	26.9	25.1	93	88% to 99%
AUC (0-∞), µg·hr/mL	27.3	25.5	93	88% to 99%
$t_{1/2}$, hr	5.36	5.68	106	Not Applicable

Ratio = Ratio of treatment mean values expressed as a percentage (100% × test/reference);

90% Confidence Interval = 90% confidence interval estimate for the ratio (test/reference) of treatment mean values, expressed as a percentage of the reference mean. *(log transformed data)*

3.2.5. Manufacturing**3.2.5.1. Manufacturing/Packaging/Testing Facilities**

Gabapentin, the active pharmaceutical ingredient (API) will be manufactured at:

Chemical Manufacturing
Parke-Davis Division of Warner-Lambert Company
188 Howard Avenue
Holland, MI 49423

or