CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022544Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	22-544
Supporting document/s:	000
Applicant's letter date:	March 30, 2010
CDER stamp date:	March 30, 2010
Product:	Gralise® (Gabapentin) ER tablets
Indication:	Management of postherpetic neuralgia (PHN)
Applicant:	Abbott Products, Inc.
Review Division:	Division of Anesthesia and Analgesia Products
Reviewer:	Armaghan Emami, Ph.D.
Supervisor/Team Leader:	Adam Wasserman, Ph.D.
Division Director:	Bob Rappaport, M.D.
Project Manager:	Allison Meyer

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 22-544 are owned by Abbott or are data for which Abbott has obtained a written right of reference.
Any information or data necessary for approval of NDA 22-544 that Abbott does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Abbott does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of NDA 22-544.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Sponsor is submitting this NDA under 505(b)(2) of the FD&C act, for an extended release formulation of gabapentin (G-ER) as tablets in 300 mg and 600 mg strengths for a maximal total daily dose of 1800 mg given once daily for the management of postherpetic neuralgia (PHN) in adults. The immediate release formulation of gabapentin is approved as Neurontin®, likewise for the management of postherpetic neuralgia, and in tablets at strengths of 600 mg and 800 mg administered in a titration regimen up to a daily maximal dose of 1800 mg (divided TID) if needed. Neurontin is also available in capsules containing 100, 300, 400 and 800 mg gabapentin or as an oral solution, and is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients. The maximum recommended human dose of Neurontin for seizures is 3600 mg/day.

G-ER 1800 mg administered once-daily demonstrated comparable bioavailability to Neurontin®, the immediate release product, administered 600 mg three times daily. The G-ER once-daily regimen (dosed with the evening meal) has a maximum concentration that exceeds the maximum concentration in the three times daily IR regimen but with similar AUC values. However, the C_{max} of G-ER 1800 mg once-daily is within the maximum human approved dose of Neurontin for the treatment of seizures (3600 mg/day).

1.2 Brief Discussion of Nonclinical Findings

The Sponsor is relying upon the Agency's prior finding of Safety and Efficacy for Neurontin® (NDA's 20-129, 20-235, 20-882, 21-397, 21-423, and 21-424) to support this application. The Sponsor conducted a 28-day repeat dose toxicity study in Beagle dogs (80-0014) using G-ER tablets (similar in formulation to those used in the clinical studies and material proposed for marketing) as well as including a separate Neurontin group for bridging purposes.

Gabapentin in the form of either G-ER tablet (at doses of 0, 600, 1200, or 2400 mg/day) or Neurontin® IR Tablets (comparative control article, at dose of 2400 mg/day) was administered orally to 3 beagle dogs/sex/group daily for 28 days. Decreased RBC (~ 13% for male and female received 2400 mg G-ER) and decreased hemoglobin (12% for male received 2400 mg G-ER) were recorded at the end of the dosing phase. However these changes were not seen in Neurontin groups. Gross necropsy of the dogs at the scheduled sacrifices revealed an increased testicular weight in dogs that received 2400 mg of G-ER tablets. These changes were dose dependent. However these findings were not seen in the Neurontin group. There were no clear treatment-related histopathology findings observed in this study. However, an increased severity of lymphocytic infiltrates in the prostates of males up to 2400 mg/day was seen. The incidence of the prostatic change was variable among treatment groups and was seen in control group therefore this it was considered to be unrelated to treatment. The

hematology effects and testicular weight values differences with G-ER compared to Neurontin is likely due to the excipients used and may be a formulation issue. Due to organ weight and hematology findings a dose level of 1200 mg/day was considered to be the NOAEL for G-ER. At 1200 mg/day on day 28, the exposure (AUC_{0-24}) was 492.5 and 598.4 µg.hr/mL and C_{max} was 32.8 and 41.7 µg/mL in males and females, respectively. The exposures to gabapentin after the administration of G-ER tablets at the NOAEL exceeds (by 3.9- fold for C_{max} and 4.1-fold for AUC) the exposure in humans dosed once daily with three 600 mg G-ER tablets, or 1800 mg/day, at steady state.

(b) (4) - also known as (b) (4) is a specified, identified impurity of the drug substance and the drug product. The Sponsor reduced the specification for (b) (4) from (b) (4) which at the maximum total daily intake of 1800 mg G-ER would represent (b) (4) mg/day (b) (4) impurity. This specification is above the ICH3B guidance. The total daily intake of this impurity in the nonclinical study with (b) (4) specification was (b) (4) mg. Therefore the nonclinical study in dogs does not support the proposed (b) (4) specification. However, upon referral to Janice Weiner in the Office of Regulatory Policy (ORP), the gabapentin (b) (4) impurity specification is consistent with FDA's finding of safety and effectiveness for the listed drug relied upon (Neurontin) and therefore additional studies are not needed to qualify the level of this impurity in the proposed specifications. The Sponsor is currently conducting an Ames assay, an *in vitro* Chromosomal aberration assay and a 1 month general toxicity study in rats to qualify the impurity. Summary reports were provided but the draft report has not been submitted yet to the NDA; these reports are not necessary now due to the ORP determination.

1.3 Recommendations

1.3.1 Approvability:

The route of administration, daily dosage, duration of use of G-ER and human AUC and C_{max} values at the MRHD is within the listed drug (LD). All excipients in the proposed formulation are within levels of other approved products. The (b) (4) impurity specification is consistent with FDA's finding of safety and effectiveness for the listed drug relied upon, while all other impurities are within acceptable levels. Additionally, a 28-dog repeat dose toxicity study provided supports the new formulation of G-ER.
Therefore from the non-clinical pharmacology toxicology perspective, this NDA may be approved.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling
Note the Applicant uses language from the Listed Drug Neurontin®. However the dose margin should be adjusted based on the lower total daily dose with Gabapentin ER for

the treatment of PHN. The final label may differ based on negotiations with Applicant and further internal discussion.

Sponsor's Proposed Labeling	Recommended Labeling	Rationale/ Comment
8.1 Pregnancy Pregnancy Category C: Gabapentin has been shown to be fetotoxic in rodents, causing delayed ossification of several bones in the skull, vertebrae, forelimbs, and hindlimbs. These effects occurred when pregnant mice received oral doses of 1000 or 3000 mg/kg/day during the period of organogenesis, (b) (4)	or approximately 3 to 8 times the maximum dose of 1800 mg/day given to PHN patients on a mg/m^2 basis. The no-effect level was 500 mg/kg/day representing approximately the maximum recommended human dose [MRHD] on a mg/m^2 body surface area (BSA) basis.	Correcting margin calculations as appropriate.
When rats were dosed prior to and during mating, and throughout gestation, pups from all dose groups (500, 1000 and 2000 mg/kg/day) were affected. These doses are equivalent to (b) (4) There was an increased incidence of hydroureter and/or hydronephrosis in rats in a study of fertility and general reproductive performance at 2000 mg/kg/day with no effect at 1000 mg/kg/day, in a teratology study at 1500 mg/kg/day with no effect at 300 mg/kg/day, and in a perinatal and postnatal study at all doses studied (500, 1000 and 2000 mg/kg/day). The doses at which the effects (b) (4) Other than hydroureter and hydronephrosis, the etiologies of which are unclear, the incidence of malformations was not increased compared to controls in offspring of mice, rats, or rabbits given doses (b) (4)	to approximately 3 to 11 times the MRHD on a mg/m^2 BSA basis. occurred are approximately 3 to 11 times the maximum human dose of 1800 mg/day on a mg/m^2 basis; the no-effect doses were approximately 5 times (Fertility and General Reproductive Performance study) and approximately equal to (Teratogenicity study) the maximum human dose on a mg/m^2 BSA basis. up to 100 times (mice), 60 times (rats), and 50 times (rabbits) the human daily dose on a mg/kg basis, or 8 times (mice), 10 times (rats), or 16 times (rabbits) the human daily dose on a mg/m^2 BSA basis.	
In a teratology study in rabbits, an increased incidence of postimplantation fetal loss occurred (b) (4)	in dams exposed to 60, 300, and 1500 mg/kg/day, or 0.6 to 16 times the maximum human dose on a mg/m^2 BSA	

(b) (4) There are no adequate and well controlled studies in pregnant women. This drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of in utero exposure to TRADENAME, physicians are advised to recommend that pregnant patients taking TRADENAME enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org/.	basis.	
8.3 Nursing Mothers Gabapentin is secreted into human milk following oral administration. A nursed infant could be exposed to a maximum dose of approximately 1 mg/kg/day of gabapentin. Because the effect on the nursing infant is unknown, TRADENAME should be used in women who are nursing only if the benefits clearly outweigh the risks.	No changes recommended	
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Gabapentin was given in the diet to mice at 200, 600, and 2000 mg/kg/day and to rats at 250, 1000, and 2000 mg/kg/day for 2 years. A statistically significant increase in the incidence of pancreatic acinar cell adenoma and carcinomas was found in male rats receiving the high dose; the no-effect dose for the occurrence of carcinomas was 1000 mg/kg/day. Peak plasma concentrations of gabapentin in rats receiving the high dose of 2000 mg/kg/day (b) (4) The pancreatic acinar cell carcinomas did not affect survival, did not metastasize and were not locally invasive. The relevance of this finding to carcinogenic risk in humans is unclear. Studies designed to investigate the mechanism of gabapentin-induced pancreatic carcinogenesis in rats indicate that gabapentin stimulates DNA synthesis in rat pancreatic	were more than 10 times higher than plasma concentrations in humans receiving 1800 mg per day and in rats receiving1000 mg/kg/day peak plasma concentrations were more than 6.5 times higher than in humans receiving 1800 mg/day.	Correcting margin calculations as appropriate.

acinar cells in vitro and, thus, may be acting as a tumor promoter by enhancing mitogenic activity. It is not known whether gabapentin has the ability to increase cell proliferation in other cell types or in other species, including humans. Gabapentin did not demonstrate mutagenic or genotoxic potential in 3 in vitro and 4 *in vivo* assays. It was negative in the Ames test and the in vitro HGPRT forward mutation assay in Chinese hamster lung cells; it did not produce significant increases in chromosomal aberrations in the *in vitro* Chinese hamster lung cell assay; it was negative in the *in vivo* chromosomal aberration assay and in the in vivo micronucleus test in Chinese hamster bone marrow; it was negative in the *in vivo* mouse micronucleus assay; and it did not induce unscheduled DNA synthesis in hepatocytes from rats given gabapentin. No adverse effects on fertility or reproduction were observed in rats at doses up to 2000 mg/kg (b) (4)	(approximately 11 times the maximum recommended human dose on an mg/m^2 basis).	

2 Drug Information

2.1 Drug

Gralise® (Gabapentin)

CAS Registry Number
60142-96-3

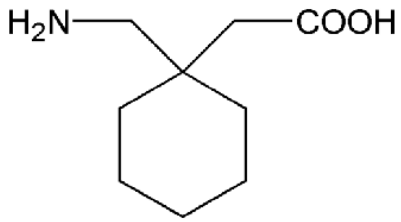
Generic Name
Gabapentin

Code Name
N/A

Chemical Name
γ-Amino-2-cyclohexyl-butyric acid

Molecular Formula/Molecular Weight
C9H17NO2/ 171.24

Structure



gamma (γ)-aminobutyric acid (GABA) analogue

2.2 Relevant IND/s, NDA/s, and DMF/s

Submission	Status/date	Drug	Dosage form	Indication	Sponsor	Division
NDA 020-235	Approved 12/30/1993	Neurontin	Capsule;	Treatment of epilepsy	Pfizer	DNP
NDA 020-882	Approved 10/09/1998	Neurontin	Tablet 600/800mg	Treatment of epilepsy	Pfizer	DNP
IND 021-129	Approved 03/02/2000	Neurontin	Solution 250mg/5ml syrup	Treatment of epilepsy	Parke davis	DNP
NDA 021-216	Approved 10/12/2000	Neurontin	Solution 250mg/5ml liquid	Treatment of epilepsy	Parke davis	DNP
NDA 021-397	Approved 05/24/2002	Neurontin	Tablet 600 mg	Postherpetic neuralgia (PHN)	Pfizer	DAAP
NDA 021-423			Capsule 800 mg			
NDA 021-424			Solution 250mg/5ml			
[redacted] (b) (4)						
[redacted] (b) (4)						
IND 71,439	Active 12/30/2004	Gabapentin	Gabapentin ER	PHN	Depomed	DAAP

2.3 Drug Formulation

Gabapentin ER is an extend release product. The compositional formulation of the ER tablets, 300 and 600-mg proposed for commercial manufacture are presented in Table 3 and Table 4 as provided by the Sponsor.

Table 3: Quantitative Composition of G-ER Tablets, 300 mg

Component[3]	Quantity [mg/tablet]	w/w [%]
	(b) (4)	
Gabapentin	300.00	(b) (4)
Polyethylene Oxide	(b) (4)	
Hydroxypropyl Methylcellulose (Hypromellose)		
Microcrystalline Cellulose		
Copovidone		
(b) (4		
Magnesium Stearate		
(b) (4)		
	(b) (4)	
(b) (4)		(b) (4)
Opadry® II White		
(b) (4)		
Total Coated Tablet		
(b) (4)		

[5] All excipients with the exception of Opadry® II White are tested according to the corresponding monographs in the current editions of the NF/USP/EP.

Table 4: Quantitative Composition of G-ER Tablets, 600 mg

Component[3]	Quantity [mg/tablet]	w/w [%]
	(b) (4)	
Gabapentin	600.00	(b) (4)
Polyethylene Oxide	(b) (4)	
Hydroxypropyl Methylcellulose (Hypromellose)		
Copovidone		
(b) (4)		
Magnesium Stearate		
(b) (4)		
	(b) (4)	
(b) (4)		(b) (4)
Opadry® II Beige		
(b) (4)		
Total Coated Tablet		
(b) (4)		

[3] All excipients with the exception of Opadry® II Beige are tested according to the corresponding monographs in the current editions of the NF/USP/EP.

2.4 Comments on Novel Excipients

Excipients in the proposed drug product are acceptable.

Reviewer's table:

ER formulation TDI for 600 mg tablet	Maximum potency in other approved product *
Polyethylene Oxide	(b) (4)
Hypromellose	
Copovidone	
Magnesium stearate	
Microcrystalline cellulose *(in 300 mg formulation)*	

* see Inactive Ingredient Guidance

** According to the FDA IIG, a maximum potency of Polyethylene oxide is 543.9 mg for a single oral administration. This reviewer identified an FDA approved drug for oral use that is currently marketed as Glumetza 500mg tables (NDA 021-748). Refer to the Glumetza label "in general, clinically significant responses are not seen at doses below 1500 mg per day" and each tablet contains of (b) (4) mg of polyethylene oxide. Therefore total daily dose would be (b) (4) mg/day (see appendix 2)

Noncompendial Opadry® II film-coating is used for film-coating.

(b) (4) (the DMF holder) has provided the quantitative composition of opadry II white (b) (4) and opadry II beige (b) (4) (DMF (b) (4)).

Reviewer's table

Product identification	**Polyvinyl alcohol** ***(%W/W)***	**Titanium Dioxide** ***(%W/W)***	**Macrogol/ PEG 3350** ***(%W/W)***	**Talc** ***(%W/W)***	**Iron oxide yellow** ***(%W/W)***	**Iron oxide red** ***(%W/W)***	**Lecithin (Soya)** ***(%W/W)***
Opadry II white (b) (4) (b) (4)	(b) (4)						
Opadry II beige (b) (4) (b) (4)							

(b) (4)

The highest quantities of polyvinyl alcohol, titanium dioxide, polyethlene glycol 3350, Talc and lecithin reported in approved solid oral dosage form listed in the Inactive Ingredient Guide are 34.0, 1387, 76.92, 220, and 54.0 mg respectively. These quantities are more than what the N022544 applicant is using as part of these Opadry II coating systems.

The amount of Iron oxide yellow and red is acceptable since it is below 5 mg/day (refer to 21 CFR 73.1200 part c, uses and restrictions, "The color additive synthetic iron oxide

may be safely used to color ingested or topically applied drugs generally subject to the restriction that if the color additive is used in drugs ingested by man the amount consumed in accordance with labeled or prescribed dosages shall not exceed 5 milligrams, calculated as elemental iron, per day.")

2.5 Comments on Impurities/Degradants of Concern

Table 1: Drug Substance and Drug Product Impurity Specifications

Gabapentin Related Compounds	Specifications	Qualification Threshold Exceeded[a]	Structural Alert for Mutagenicity or Genotoxicity[b]
(b) (4)			

Table 1: Drug Substance and Drug Product Impurity Specifications (Continued)

Gabapentin Related Compounds	Specification	Qualification Threshold Exceeded	Structural Alert for Mutagenicity or Genotoxicity[b]
(b) (4)			

(b) (4) - also known as (b) (4) is a specified, identified impurity of the drug substance and the drug product.

In the filling letter, the agency stated that from a regulatory legal perspective the 505(b)(2) pathway does not allow reliance on innovator data described in the Summary Basis of Approval for the Listed Drug to justify impurity specifications. The sponsor

proposed (b) (4)

In the Sponsor-Agency telephone conversation on July 13, 2010, the agency requested to reduce specifications or shorten the expiry or provide Ames assay and 1-month toxicology study to support the proposed specifications for (b) (4)

Note: PHN is not considered to represent chronic use therefore a shorter (1-month) qualification study is acceptable.

The Sponsor reduced the specification from (b) (4) which the total daily intake in human is (b) (4) mg/day (b) (4) impurity. The total daily intake impurity in the nonclinical study with (b) (4) specification was (b) (4) mg. Therefore the nonclinical study in dogs does not support proposed (b) (4) specification. See below the Sponsor's table.

Gabapentin Extended Release Tablets, 300 mg and 600 mg Solvay
2.6.7 Toxicology Tabulated Summary

2.6.7.4. Toxicology

		Drug Product		Test Article: Gabapentin ER Tablets, 600 mg	
Batch No.	**Assay (% label claim)**	**Specified Impurities (%)**		**Study Number**	**Type of Study**
PROPOSED SPECIFICATION:	(b) (4)				
04091501G3P				BASi: 795A-501-032-04 Depomed: 80-0014	28-day repeat dose toxicity

TDI in high dose dog with (b) (4) (b) (4) (b) mg/day (b) (4)
Maximum TDI in human with (b) (4) (b) (4) (b) (4) mg/day (b) (4)
Maximum TDI in human with (b) (4) (b) (4) (b) (4) mg/day (b) (4)

Note: the (b) (4) specification for gabapentin ER overlaps with Neurontin®.

The Sponsor provided the below response to the agency's request (August 6, 2010).

In view of the Sponsor position that the Agency should not be requesting repeat qualification studies given the results (and previous FDA findings of safety and efficacy that have been referenced to approve several ANDA's with similar (b) (4) contents) are deemed accessible under 505(b)(2), and that the Sponsor agrees to perform these studies, we request confirmation on the following request.

We request that the Agency proceed with the scientific review to the PDUFA date (30 January 2011) and allow a rolling submission of final reports for the qualification studies. The following schedule is estimated for the submission of these final reports:

Genetic toxicity studies (Bacterial Reverse Mutation Assay ('Ames' assay) and *in vitro* mammalian chromosome aberration assay in HPBL cells):

- Final Reports - December 1, 2010

30-day repeated dose toxicity study of up to 80 mg/kg gabapentin lactam in male and female Sprague-Dawley rats:

- Initiation of Study - September 01, 2010
- Draft Report - December 31, 2010
- Final Report - February 28, 2011

We propose that this is a reasonable position given the above and that the NDA review should otherwise proceed irrespective of the Agency position or the Sponsor position on the suitability of this request for repeat qualification testing. If this agreement can be reached, then the Sponsor will consider that there is no remaining point of contention related to the Sponsor's conduct or the Agency's timing for review for this qualification testing.

In the Sponsor-Agency telephone conversation on August 31, 2010, the agency advised the Sponsor:

1. The studies (Ames and general toxicity studies) may not be needed to qualify the level of the impurity in the Sponsor's proposed specifications since the level of impurity is consistent with FDA's finding of safety and effectiveness for the listed drug. However this decision depends on the agency's conclusion and is not confirmed yet. The Sponsor was told it was their risk whether conduct the study or not and submit without this data.
2. Another option was to compare their formulation at the end of shelf-life to that of the innovator at end of shelf-life and show they have cleaner specs.
3. All other drug substance specifications are above the ICH3A guidance and need to be reduced or qualified.

With the exception of the (b) (4) impurity, the Sponsor reduced the specifications for drug substance impurities to below the ICH3A limits for qualification which is acceptable, see below table from the October 29, 2010 submission.

Related Compound	Proposed Limits	Justification
		(b) (4)

Upon referral to Janice Weiner in the Office of Regulatory Policy (ORP), the level of (b) (4) impurity is consistent with FDA's finding of safety and effectiveness for the listed drug relied upon and additional studies are not needed to qualify the level of this impurity in Abbott's proposed specifications (see appendix 5). However, the Sponsor conducted an Ames assay, an *in vitro* Chromosomal aberration assay and a 1 month general toxicity study in rats to qualify the impurity. Summary reports were provided but the draft report has not been submitted yet to the NDA. These reports are not necessary now due to the ORP determination.

2.6 Proposed Clinical Population and Dosing Regimen

The Sponsor is submitting this NDA for an extended release formulation of gabapentin as tablets in 300 mg and 600 mg strengths at a maximal total daily dose of 1800 mg given once daily for the management of postherpetic neuralgia (PHN) in adults.

2.7 Regulatory Background

Gabapentin (Neurontin®) was originally approved in December, 1993 (NDA 20-235) as adjunctive therapy in the treatment of partial seizures and was subsequently approved for the management of PHN in adults (May 2002, NDA 21-424). NDAs are held by Pfizer, Inc.

The present applicant (Abbott) is submitting this New Drug Application for gabapentin ER tablets under Section 505(b)(2) of the FD&C Act, and reference is made to the Division's findings of safety in NDA's 20-129, 20-235, 20-882, 21-397, 21-423, and 21-

424 for Neurontin® to support this application. The related IND 71,439 (Gabapentin ER) originally submitted by Depomed Inc., is active since 12/30/2004.

3 Studies Submitted

3.1 Studies Reviewed: a 28-Day Oral Toxicity Bridging Study in Beagle Dogs with Gabapentin ER Tablets

			Overview			Test Article: Gabapentin ER Tablet, 600 mg	
Type of Study	**Species and Strain**	**Method of Administration**	**Duration of Dosing**	**Doses (mg/day)**	**GLP Compliance**	**Testing Facility**	**Study Number**
Single-Dose Toxicity	ND						
Repeat-Dose Toxicity	Canine Beagle	Oral Tablet	28 days	0, 600, 1200, & 2400 mg/day	YES	(b) (4)	BASi 795A-501-032-04 Depomed: 80-0014
Genotoxicity	ND						
Carcinogenicity	ND						
Reproductive and Developmental Toxicity	ND						
Local Tolerance	ND						
Other Toxicity Studies	ND						

ND = Not Done

3.2 Studies Not Reviewed: N/A

3.3 Previous Reviews Referenced: The Sponsor is submitting this NDA as a 505(b) (2) application and is relying on prior Agency determination of safety and efficacy of Neurontin® (NDA's 20-129, 20-235, 20-882, 21-397, 21-423, and 21-424) to support this application.

In the following sections, available studies from the literature on the pharmacology, pharmacokinetics (ADME) of gabapentin will be briefly reviewed.

4 Pharmacology

Gabapentin is a structural analogue of the neurotransmitter gamma (γ)-aminobutyric acid (GABA). Even though gabapentin is a synthetic analog of GABA, it does not interact with either GABAA or GABAB receptors (Hwang and Yaksh 1997). Gabapentin binds to the α2δ subunit of voltage-dependent calcium channels in neuronal tissue (Gee, Brown et al. 1996) and to inhibit calcium currents in dorsal root ganglion cells, mediators of pain perception (Alden and Garcia 2001). Recently, gabapentin, at therapeutic concentrations, has been shown to block thrombospondin-induced synapse formation (Eroglu, et al. 2009).

In animal models of inflammatory and neuropathic pain gabapentin possess antiallodynic and antihyperalgesic actions (Field, Holloman et al. 1997; Field, Oles et al. 1997; Hwang and Yaksh 1997; Takasaki, Andoh et al. 2001). In rats allodynia was produced by ligation of the L5-6 nerve roots, and a catheter was placed in the lumbar region of the spinal cord for administration of compounds. Injection of gabapentin resulted in a dose-dependent decrease in the pain response at doses that had no effect on motor function. Injection of GABAA or GABAB antagonists had no effect on the response to gabapentin. This study indicates that gabapentin attenuates nerve injury induced allodynia through spinal mechanisms not involving GABA receptors.
The effect of gabapentin on nociceptive behavior was tested in a mouse model of herpetic pain by Takasaki et al (Takasaki, Andoh et al. 2001). Infection with herpes simplex virus type-1 (HSV-1) resulted in tactile allodynia and mechanical hyperalgesia of the infected paw upon replication of HSV-1 in the dorsal root ganglion and skin eruption on the infected paw. Oral administration of gabapentin, 10-100 mg/kg, resulted in a dose-dependent inhibition of both allodynic and hyperalgesic response to von Frey hair stimulation. Intrathecal injection of gabapentin, 10-100 µg/animal, also dose-dependently attenuated the response to von Frey hair stimulation. However, intraplantar, intracisternal and intracerebroventricular injection had no effect on these responses. Pretreatment with naltrexone had no effect on gabapentin's action but blocked the inhibition of hyperalgesia and allodynia by morphine. Locomotor activity was not affected by oral gabapentin at doses up to 300 mg/kg. These data indicate that gabapentin may be an effective treatment for herpetic pain and that its site of action is at the spinal cord level by a non-opiate mechanism. Additionally, at a dose effective for pain relief there was no effect of gabapentin on locomotor activity.

5 Pharmacokinetics/ADME

Gabapentin is well absorbed from the gastrointestinal tract and is primarily eliminated by renal mechanisms in the animal species studied, as is the case in human. However, absorption is less than dose proportional indicating possible saturable absorption. It is not metabolized in the mouse and monkey, slightly in the rat and more extensively in the dog. In humans there is no evidence of metabolism.

Tables below copied from NDA submission:

Table 1: PK Parameters (mean ±SD) of Gabapentin, 50 mg/kg IV or PO in the Rat

PK parameter	IV	PO
$AUC_{0-\infty}$ (µg·hr/mL)	92.4 ± 16.0	73.1 ± 9.9
C_{max} (µg/mL)	NA	16.4 ± 21
t_{max} (hr)	NA	1.7 ± 0.6
$t_{½}$ (hr)	1.7 ± 0.3	1.7 ± 0.8
CL (mL/min/kg)	9.3 ± 1.9	NA
V_d (L/kg)	1.44 ± 0.50	NA
F (%)	NA	79.0 ± 11.0

NA= Not applicable

Table 2: PK Parameters (mean ±SD) of Gabapentin 50 mg/kg IV or PO in the Dog

PK Parameter	IV	PO
$AUC_{0-\infty}$ (µg·hr/mL)	367	242
C_{max} (µg/mL)	NA	56.3
t_{max} (hr)	NA	1.1
$t_{½}$ (hr)	2.9	2.2
CL (mL/min/kg)	2.27	NA
V_d (L/kg)	0.16	NA
F (%)	NA	67

NA= Not applicable

Table 3: Mean PK Parameters of Gabapentin Following PO Administration at Doses of 10, 25 and 50 mg/kg in the Monkey

	Dose		
PK Parameter	**10**	**25**	**50**
C_{max} (µg/mL)	5.7	8.1	12.0
nC_{max} (µg/mL)	5.7	3.3	2.4
t_{max} (hr)	2.0	1.8	2.5
$t_{½}$ (hr)	3.7	5.8	7.5
$AUC_{0-\infty}$ (µg·hr/mL)	49.3	65.1	100.0
$nAUC_{0-\infty}$ (µg·hr/mL)	49.3	26.0	20.0

nC_{max} and $nAUC_{0-\infty}$ are normalized to a dose of 10 mg/kg

6 General Toxicology

The Sponsor is relying on the division's findings of safety in the original Neurontin® NDAs 20-129, 20-235, 20-822, 21-397, 21-423 and 21-424. The Sponsor conducted only a 28-Day Oral Toxicity Bridging Study in Beagle Dogs with Gabapentin ER Tablets.

6.1 Single-Dose Toxicity

None

6.2 Repeat-Dose Toxicity

Study title: **Gabapentin Extended Release Tablets: A 28-Day Oral Toxicity Bridging Study in Beagle Dogs.**

Study no.:	80-0014
Study report location:	(b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	17 September 2004
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	1. Gabapentin ER 600 mg coated tablet lot # 04091501-G3P %Purity: 98.7% - 100.5% 2. Neurontin 600 mg lot # 14584U % Purity: N/A

Key Study Findings

- This study was conducted to characterize the potential toxicity of gabapentin extended-release (G-ER) tablets and to evaluate systemic exposure to the active ingredient in the test articles (G-ER) and comparative control articles (Neurontin®) by measuring gabapentin concentrations in plasma when administered orally to Beagle dogs.

- Gabapentin in the form of either G-ER tablets or Neurontin tablets was administered orally to 3 Beagle dogs/sex/group. G-ER was administered at doses of 0 (G-ER Placebo tablets), 600, 1200, or 2400 mg/day for 28 days. Neurontin was administered at 2400 mg/day for 28 days.

- The 600 mg dose was given in the AM, the 1200 mg and 2400 mg dose consisted of one or two 600 mg tablet(s) twice daily, respectively, given approximately 7 hours apart. Neurontin was given as two 600 mg tablets BID as described above.
- Shortened QT intervals were recorded during the final week of dosing for male dogs receiving either 1200 or 2400 mg of the Gabapentin ER tablets or 2400 mg of Neurontin®. However these changes were not toxicologically significant and were not seen in the opposite sex compared to control group. These changes appear equivalent between G-ER and Neurontin groups.
- At the end of the dosing phase, decreased RBC (13% and 12% for male and female receiving 2400 mg G-ER, respectively) and Hemoglobin (12% for male receiving 2400 mg G-ER) were recorded. However these changes were not seen in Neurontin male and female dogs.
- Increased absolute (38%) and relative to body weight (28%) testicular (TE) weight values were recorded for male dogs that received 2400 mg of gabapentin ER tablets. These changes were dose-dependent and are considered treatment related. However no testicular histopathology changes were recorded in this study and these changes were not seen in Neurontin group.
- An increased severity of lymphocytic infiltrates in the prostates of males up to 2400 mg/day was seen. The incidence of the prostatic change was variable among treatment groups and was seen in control group therefore this it was considered to be unrelated to treatment.
- Due to organ weight and hematology findings a dose level of 1200 mg/day is considered to be NOAEL by this reviewer. At 1200 mg/day on day 28, the exposure (AUC_{0-24}) was 492.5 and 598.4 µg.hr/mL and C_{max} was 32.8 and 41.7 µg/mL in males and females, respectively.
- The exposures to gabapentin after the administration of G-ER tablets at the NOAEL exceeded (by 3.9- fold for C_{max} and 4.1-fold for AUC) the exposure to humans dosed once daily with three G-ER tablets, 1800 mg/day, at steady state (Study Report: 81-0049, appendix 1).
- The exposure to gabapentin, as measured by AUC_{0-24} was somewhat higher following administration of G-ER Tablets (957 µg.hr/mL) than after Neurontin IR tablets (906 µg.hr/mL) receiving 2400 mg/day. The hematology effects and testicular weight values differences with G-ER compared to Neurontin is likely due to the excipients used and may be a formulation issue.

Methods

Doses: Gabapentin ER: 0, 600, 1200 and 2400 mg/day

Neurontin®: 2400 mg/day

Frequency of dosing:

Group Number	Group Name	Test Article Identification	Gabapentin Dose Level (mg/day)	Dose (#/tablets/day)*		Total No. of Animals
				AM	PM	
CFV1	Placebo	Gabapentin Extended Release Placebo Tablet	0	2	2	6
CFV2	Test Article	Gabapentin Extended Release Tablet	600	1	0	6
CFV3	Test Article	Gabapentin Extended Release Tablet	1200	1	1	6
CFV4	Test Article	Gabapentin Extended Release Tablet	2400	2	2	6
CFV5	Comparative Control	Neurontin® (gabapentin) Tablet	2400	2	2	6

* Animals dosed twice daily received their doses approximately 7 hr apart. Animals were fed half their daily food ration before the AM dosing and half before the PM dosing. Although no dose was given to Group CFV2 animals in the PM, the feeding schedule was the same as for the remainder of the study animals.

Route of administration: Oral

Dose volume: Tablets

Formulation/Vehicle:

1. 600 mg Gabapentin + Excipients (Polyethylene oxide, NF; Hydroxypropyl Methylcellulose, USP; Magnesium Stearate, NF, and Opadry II white)

Note: the toxicology formulation is similar (not same) with the proposed formulation (see appendix 3)

2. 600 mg Neurontin®

Species/Strain: Beagle dogs

Number/Sex/Group: 3/Sex/Group

Age: Approximately 11-12 months

Weight: 8-14 kg male, 7-11 kg female

Satellite groups: N/A

Unique study design: N/A

Deviation from study protocol: N/A

Dogs were offered food twice daily for 1 hour intervals and each dose was administered approximately 30 minutes after the food was offered to the dogs. Parameters for evaluation included daily clinical observations, daily food consumption, weekly body weights, periodic ophthalmoscopic and physical examinations, electrocardiogram recordings, and hematology, clinical chemistry, and urinalysis determinations. Organ weights and gross necropsy observations were recorded at necropsy and tissues were collected for histopathologic examination. Plasma samples for evaluation of systemic exposure were collected from each dog in the Gabapentin ER Tablets treated groups and the comparator group.

Observations and Results

Mortality: All animals were observed for mortality at least twice daily. No animals died or were sacrificed in moribund condition during this evaluation

Clinical Signs: All animals were observed daily for pharmacological effect, toxicological effect, behavioral effect, and general appearance**.** No treatment-related clinical observations were recorded during this study.

Body Weights: Body weights were recorded Pretest, on Day -1, then weekly throughout the study. No-treatment related changes were recorded during this study.

Feed Consumption: Food consumption was recorded after each feeding session throughout the study and reported as g/day. On Days 1 and 24, food consumption was reported as the grams consumed during each feeding session (i.e., AM and PM feedings). Statistically significant increased food consumption was seen in the Group CFV5 (Neurontin, positive control) female dogs during the morning feeding on Day 1 and the total amount consumed during Day 28. These changes are considered inconsistent across dose groups, and the opposite sex was not similarly affected**.**

Ophthalmoscopy: All dogs were examined pretest and again once during the last week of dosing. No-treatment related changes were recorded.

ECG: ECG were taken once prior to initiation and once prior to the end of dosing. Shortened QT intervals were recorded during the final week of dosing for male dogs receiving either 1200 or 2400 mg of the Gabapentin ER tablets or 2400 mg of Neurontin®. However these changes were slight and were not seen in the opposite sex compared to control group. These changes appear equivalent between G-ER and Neurontin groups.

Male

Group Number		QRS Pretest	QRS Day 28	QT Pretest	QT Day 28	QTc Pretest	QTc Day 28
Ç CFV1M	Mn:	43.3	47.2	197.8	233.3	55.2	63.4
Ç	SD:	5.8	14.0	3.9	15.3	1.7	2.8
Ç	N:	3	3	3	3	3	3
CFV2M	Mn:	46.7	48.9	221.1	223.3	60.6	62.4
	SD:	5.8	24.6	25.3	20.8	5.4	4.7
	N:	3	3	3	3	3	3
CFV3M	Mn:	42.2	26.7	207.8	202.8*	59.7	58.9
	SD:	2.5	11.5	13.9	.9	6.9	5.6
	N:	3	3	3	3	3	3
CFV4M	Mn:	42.2	40.0	213.3	204.4*	58.4	56.1
	SD:	2.5	.0	13.4	5.1	2.2	.2
	N:	3	3	3	3	3	3
CFV5M	Mn:	47.2	48.9	198.9	195.6*	58.2	57.5
	SD:	6.7	8.4	1.9	5.1	2.6	2.1
	N:	3	3	3	3	3	3

Group Number		HR Pretest	HR Day 28	RR Pretest	RR Day 28	PR Pretest	PR Day 28
Ç CFV1M	Mn:	101.5	97.0	592.2	681.1	92.2	78.9
Ç	SD:	1.5	9.1	35.6	105.9	21.2	5.1
Ç	N:	3	3	3	3	3	3
CFV2M	Mn:	99.1	116.2	656.7	585.6	95.5	80.0
	SD:	24.2	9.2	164.7	90.5	6.9	.0
	N:	3	3	3	3	3	3
CFV3M	Mn:	119.8	99.5	533.3	657.8	86.7	77.8
	SD:	22.8	13.1	167.6	115.5	3.4	3.9
	N:	3	3	3	3	3	3
CFV4M	Mn:	93.8	92.3	656.6	642.2	73.3	78.9
	SD:	18.8	9.7	144.7	72.4	8.8	1.9
	N:	3	3	3	3	3	3
CFV5M	Mn:	129.7	130.3+	476.7	455.6*	87.8	80.0
	SD:	34.5	9.3	124.1	35.6	3.9	.0
	N:	3	3	3	3	3	3

Female

Group Number		QRS Pretest	QRS Day 28	QT Pretest	QT Day 28	QTc Pretest	QTc Day 28
Ç CFV1F	Mn:	53.3	40.0	213.3	195.6	59.3	56.1
Ç	SD:	11.5	.0	20.3	7.7	6.9	2.7
Ç	N:	3	3	3	3	3	3
CFV2F	Mn:	65.6	40.0	202.2	208.9	56.2	58.1
	SD:	9.6	.0	3.9	15.4	2.3	3.6
	N:	3	3	3	3	3	3
CFV3F	Mn:	56.7	53.9	208.9	200.0	56.5	55.9
	SD:	20.8	28.5	15.4	.0	4.3	2.0
	N:	3	3	3	3	3	3
CFV4F	Mn:	46.7	40.0	215.6	197.8	59.8	54.1
	SD:	11.5	20.0	13.9	3.9	3.8	2.1
	N:	3	3	3	3	3	3
CFV5F	Mn:	53.3	45.6	200.0	200.0	56.6	55.7
	SD:	23.1	9.6	.0	.0	.3	2.5
	N:	3	3	3	3	3	3

Group Number		HR Pretest	HR Day 28	RR Pretest	RR Day 28	PR Pretest	PR Day 28
Ç CFV1F	Mn:	100.4	115.0	612.2	516.7	80.0	90.0
Ç	SD:	7.7	8.7	78.6	32.8	20.0	26.5
Ç	N:	3	3	3	3	3	3
CFV2F	Mn:	100.2	101.1	610.0	603.3	61.7	77.8
	SD:	5.1	8.6	74.2	61.2	20.9	3.9
	N:	3	3	3	3	3	3
CFV3F	Mn:	88.7	103.0	688.9	593.3	64.4	80.0
	SD:	4.9	18.3	34.2	102.0	21.4	.0
	N:	3	3	3	3	3	3
CFV4F	Mn:	132.9	90.6	608.9	654.4	74.4	82.2
	SD:	59.6	7.3	35.6	65.5	2.0	3.9
	N:	3	3	3	3	3	3
CFV5F	Mn:	107.7	102.5	550.0	611.1	68.9	87.8
	SD:	3.6	22.9	17.3	131.7	19.2	13.9
	N:	3	3	3	3	3	3

Hematology:

Following an overnight fast, blood was collected from each animal once pretest and again during the final week of dosing. Blood was collected from the jugular vein into the proper tubes. Selected group mean hematology data for pretest and during the final week of dosing are summarized in below tables:

Group	0 (placebo)		600 (G-ER)		1200 (G-ER)		2400 (G-ER)		2400 (Neurontin)	
Males	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4
WBC K/µL	7.15	7.29	9.17	10.00	6.85	7.13	7.35	9.03	6.60	9.11
NE percent	56	58	64	63	57	57	62	59	62	63
EOS Cells/µL	99	21	174	142	69	431	200	355	42	210
RBC M/ µL	6.67	6.57	6.92	6.52	7.02	6.03	6.59	5.85 13%↓	6.57	6.44
HB g/dL	15.6	15.2	16.1	15.4	16.9	14.6	15.2	13.5 12%↓	15.3	15.5
HCT Percent	41.5	43.6	44.1	44.3	44.2	41.5	41.0	38.3	41.1	43.4

Group	0 (placebo)		600 (G-ER)		1200 (G-ER)		2400 (G-ER)		2400 (Neurontin)	
Females	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4	Pretest	Week 4
WBC K/µL	8.79	7.89	8.05	7.99	9.15	10.08	5.50	6.78	8.61	8.11
NE	60	54	52	58	60	68	55	62	66	60
EOS Cells/µL	32	104	399	465	53	159	0	113	69	224
RBC M/ µL	7.17	6.79	6.50	6.33	6.59	6.36	7.38	6.49 12%↓	6.55	6.06
HB g/dL	16.7	16.2	15.6	15.0	15.8	15.5	15.4	15.3	15.7	14.5
HCT Percent	47.9	45.5	42.9	42.4	44.1	43.1	49.2	43.0	44.1	41.1

At the end of the dosing phase, higher eosinophil (EOS) count values were recorded for MD male dogs. This change was not dose dependent and was not seen in female. These changes appear equivalent between G-ER and Neurontin groups.

At the end of the dosing phase, decreased RBC (13% and 12% for HD male and HD female G-ER) and HB (12% for HD G-ER male) were recorded. However these changes were not seen in Neurontin male and female dogs.

At pretest, lower mean white blood cell counts were recorded for the HD G-ER females. This finding was attributed to higher mean white blood cell count values for the control group at pretest and was not meaningful.

Clinical Chemistry:
Serum samples were obtained from all dogs once pretest and again during the final week of dosing. Lower serum potassium concentrations (~10%) for MD and HD female

dogs compared to pretest. However these changes were not seen in opposite sex and Neurontin groups. This reviewer agrees with the Sponsor that the differences in clinical chemistry are considered slight and within the expected range of normal.

Urinalysis:
Urine samples for urinalyses were obtained via catheterization from all dogs once pretest and again within the final week of the dosing. Minimal decreased urine specific gravity was recorded for the male dogs that received 2400 mg of Neurontin®/day. The evaluation of the urine samples did not reveal any treatment effect.

Post-Mortem Evaluation
A complete postmortem examination was performed on all dogs were euthanized at the scheduled necropsies. All surviving dogs were fasted overnight, euthanized, and necropsied the day after their last dose. Terminal body weights were taken after an overnight fast.

Gross Pathology:
At the end of dosing necropsy, most animals in each group had no gross lesions. There was a few gross observations : dogs with instances of the following: colon - reddened mucosa [one in HD female], cranium - cyst [one in LD male], mass - axillary region [one in HD Neurontin female], pituitary - cystic structure [one in control], and stomach - reddened mucosa [one in MD male]. These findings are not considered to be treatment-related.

Organ Weights:
Increased absolute (38%) and relative to body weight (28%) testicular (TE) weight values were recorded for male dogs that received 2400 mg of gabapentin ER (G-ER) tablets. These changes were dose dependent. However these findings were not seen in Neurontin group.

Group	0 (placebo)	600 (G-ER)	1200 (G-ER)	2400 (G-ER)	2400 (Neurontin)
Mean absolute testicular weight (g)	11.49	13.07 *14%*↑	13.19 *15%*↑	15.92 ***38%***↑	12.89 *12%*↑
Mean organ weights relative to body weight (g/kg)	0.106	0.112 *6%*↑	0.116 *9%*↑	0.136 ***28%***↑	0.109 *3%*↑

No-treatment related changes for other organs (adrenals, brain, heart, kidneys, liver, pituitary, spleen, thyroids/parathyroid, testis and ovaries).

Histopathology:

Adequate Battery

The following tissues were collected from all dogs, fixed in 10% neutral buffered formalin for subsequent processing and light microscopic examination for histopathologic findings:

Adrenals	Ileum	Sciatic Nerve with skeletal muscle
Aorta (thoracic)	Jejunum	Skin
Brain	Kidneys	Spinal Cord (cervical, thoracic, lumbar)
Cecum	Lacrimal Glands	Spleen
Cervix	Liver	Sternum & Marrow
Colon	Lungs & Bronchi	Stomach
Diaphragm	Mammary Gland	Testes
Duodenum	Mesenteric Lymph Node	Thymus
Epididymides	Mandibular Lymph Node	Thyroids/parathyroids
Esophagus	Ovaries	Tongue
Eyes (optic nerve)	Pancreas	Trachea
Proximal femur (including joint surface)	Pituitary	Urinary Bladder
Gallbladder	Prostate	Uterus
Heart	Salivary Gland (mandibular)	Vagina
Lesions (to include apparently normal contiguous tissue)		

For mammary gland, a section of skin containing a nipple and the underlying subcutaneous tissue was collected; however, the Consultant Study Pathologist determined the presence or absence of mammary tissue during microscopic examination since specimens collected from the mammary region at necropsy may not contain mammary tissue.

Reviewer Note: Normally eyes and testes are fixed in special fixatives such as Bouin's Fluid or modified/unmodified Davidson's Fluid. This is sub-optimal considering the observed gross effects (weight change) on testes.

Peer Review

All tissues collected from animals at the scheduled necropsy and all gross lesions were examined microscopically by a board-certified veterinary pathologist (ACVP).

Histological Findings

Histomorphologic findings were graded from one to five depending upon severity or were indicated as not remarkable (X). No treatment-related changes were seen in this study. The selected findings were summarized by sex and treatment group in tables below (copied from the NDA submission).

An increased severity of lymphocytic infiltrates in the prostates of males up to 2400 mg/day was seen. The Sponsor stated that the incidence of the prostatic change was variable among treatment groups and, as this is a common background finding, it was considered to be unrelated to treatment.

795A-501-032-04
28-Day Sacrifice
Male Dog

ANIMAL	GROUP CFV1			GROUP CFV2			GROUP CFV3			GROUP CFV4			GROUP CFV5		
	CFV1M1	CFV1M2	CFV1M3	CFV2M4	CFV2M5	CFV2M6	CFV3M7	CFV3M8	CFV3M9	CFV4M10	CFV4M11	CFV4M12	CFV5M13	CFV5M14	CFV5M15
LACRIMAL GLAND	X	X	X							X	X		X	X	
Infiltrate, Lymphocytic							2								
Infiltrate, Lymphoid, Conjuctiva				3	3	2	2	3	3			2			2
PROSTATE				X	X					X			X		
Fibrosis, Interstitial															1
Infiltrate, Mononuclear Cell	1	3	1			2	1	3	3		3	4		2	1

795A-501-032-04
28-Day Sacrifice
Female Dog

ANIMAL	GROUP CFV1			GROUP CFV2			GROUP CFV3			GROUP CFV4			GROUP CFV5		
	CFV1F16	CFV1F17	CFV1F18	CFV2F19	CFV2F20	CFV2F21	CFV3F22	CFV3F23	CFV3F24	CFV4F25	CFV4F26	CFV4F27	CFV5F28	CFV5F29	CFV5F30
INTESTINE-LARGE, COLON	X	X	X	X	X	X	X	X	X		X	X	X	X	X
Congestion, Mucosal/Submucosal										3					
LACRIMAL GLAND	X	X	X	X	X	X		X				X		X	X
Infiltrate, Lymphocytic											2				
Infiltrate, Lymphoid, Conjuctiva							2		2	2			2		

Special Evaluation: N/A

Toxicokinetics:
Groups of 3 male and 3 female beagle dogs received daily doses of either G-ER placebo, G-ER or G-IR as outlined in the below Table.

Table 1: Group Identification and Dose Levels

Group Number	Group Name	Test Article Identification	Gabapentin Dose Level (mg/day)	Dose (#/tablets/day)*		Total No. of Animals
				AM	PM	
CFV1	Placebo	Gabapentin Extended Release Placebo Tablet	0	2	2	6 (3M, 3F)
CFV2	Test Article	Gabapentin Extended Release Tablet	600	1	0	6 (3M, 3F)
CFV3	Test Article	Gabapentin Extended Release Tablet	1200	1	1	6 (3M, 3F)
CFV4	Test Article	Gabapentin Extended Release Tablet	2400	2	2	6 (3M, 3F)
CFV5	Comparative Control	Neurontin® (gabapentin) Tablet	2400	2	2	6 (3M, 3F)

* Animals dosed twice daily received their doses approximately 7 hr apart. Animals were fed half their daily food ration 30 min before the AM dosing and half 30 min before the PM dosing. Although no dose was given to Group CFV2 animals in the PM, the feeding schedule was the same as for the remainder of the study animals.

The daily exposure to gabapentin, as measured by AUC_{0-24}, increased nearly proportional to increasing doses following administration of G-ER Tablets for both male and female dogs. C_{max} also increased nearly proportional to increased dose. The gabapentin plasma concentration time profiles subsequent to administration of G-ER Tablets were characteristic of an extended release formulation on both days, whereas the profiles obtained after administration of Neurontin tablets were characteristic of an immediate release formulation. The exposure to gabapentin, as measured by AUC_{0-24} was somewhat higher following administration of G-ER Tablets than after Neurontin tablets. On day 1, C_{max} was similar after administration of G-ER Tablets to that of Neurontin tablets in males, while in the females the C_{max} was higher after G-ER Tablets compared to Neurontin tablets. On Day 24 the C_{max} was lower after administration of G-ER Tablets compared to Neurontin tablets in the male dogs, while in the females they were similar. There was no evidence for any substantial differences based on sex, duration of dosing or dose level with the G-ER Tablets. Nor was there any evidence of accumulation of gabapentin, based on dose-normalized AUC values during administration of G-ER Tablets (see table below, the exposure values are from the steady state values)

2.6.7.3. Toxicokinetics

Test Article:		Overview of Toxicokinetics Data AUC_{0-24} (µg•hr/mL)			Overview of Toxicokinetics Data C_{max} (µg/mL)		
Name	Daily Dose (mg/day)	Canine		Human	Canine		Human
		Male	Female		Male	Female	
G-ER[a]	600 mg/day	192.3	192.2		23.3	24.3	
G-ER	1200 mg/day	492.5	598.4		32.8	41.7	
G-ER	1800 mg/day			132.8[b]			9.6[b]
G-ER	2400 mg/day	943.0	972.0		65.6	73.3	
Neurontin	2400 mg/day	919.3	893.1		77.4	74.7	

[a] G-ER = Gabapentin Extended Release Tablets, 600 mg
[b] Data from Depomed Study 81-0049, QD administration of 1800 mg

The exposure for dogs was several folds higher than for humans administered the same dose. (Study Report: 81-0049, appendix 1).

7 Genetic Toxicology

None

8 Carcinogenicity

None

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development:
None

9.2 Embryonic Fetal Development:
None

9.3 Prenatal and Postnatal Development:
None

10 Special Toxicology Studies

None

11 Integrated Summary and Safety Evaluation

The Sponsor is submitting this NDA under 505(b)(2) of FD&C act, for an extended release formulation of gabapentin (G-ER) as tablets in 300 mg and 600 mg strengths at a maximal total daily dose of 1800 mg given once daily for the management of postherpetic neuralgia (PHN) in adults. The immediate release formulation of gabapentin is approved as Neurontin®, likewise for the management of postherpetic neuralgia, and in tablets at strengths of 600 mg and 800 mg administered in a titration regimen up to a daily maximal dose of 1800 mg (divided TID) if needed. Neurontin is also available in capsules containing 100, 300, 400 and 800 mg gabapentin or as an oral solution, and is also indicated as adjunctive therapy in the treatment of partial seizures in pediatric patients. The maximum recommended human dose for Neurontin is 3600 mg/day.

G-ER 1800 mg once-daily demonstrated comparable bioavailability to Neurontin®, the immediate release product, administered 600 mg three times daily. The G-ER once-daily regimen (dosed with the evening meal) has a maximum concentration that exceeds the maximum concentration in the three times daily IR regimen but with similar AUC values. However, the C_{max} of G-ER 1800 mg once-daily is within the maximum human approved dose of Neurontin in the treatment of seizures (3600 mg/day).

The Sponsor is relying on the prior Agency determination of safety and efficacy for Neurontin® (NDA's 20-129, 20-235, 20-882, 21-397, 21-423, and 21-424) to support

this application. The Sponsor conducted a 28-day repeat dose toxicity study in Beagle dogs (80-0014) using G-ER tablets which were similar in formulation to those used in the clinical studies.

Gabapentin in the form of either Gabapentin ER tablet (at doses of 0, 600, 1200, or 2400 mg/day) or Neurontin® Tablets (comparative control article, at dose of 2400 mg/day) was administered orally to 3 beagle dogs/sex/group daily for 28 days.

The daily exposure to gabapentin increased nearly proportional to dose with Gabapentin ER Tablets. There was no evidence of accumulation, or differences between sexes. For the same dose exposure was somewhat higher for Gabapentin ER Tablets compared to Neurontin tablets. The exposure for dogs was several folds higher than for humans administered the same dose. There were no unscheduled deaths or other clinical signs of toxicity and no meaningful differences in body weight or body weight changes noted between the placebo, test article, and comparative control treated groups. Evaluation of physical and ophthalmic examination, hematology, coagulation, clinical chemistry, and urinalysis data revealed no changes that were attributable to the administration of test article or the comparative control article. Gross necropsy of the dogs at the scheduled sacrifices revealed an increased absolute (38%) and relative to body weight (28%) testicular weight values for male dogs that received 2400 mg of gabapentin ER (G-ER) tablets. These changes were dose dependent. However these findings were not seen in Neurontin group. There were no treatment-related histopathology findings observed in this study. However, an increased severity of lymphocytic infiltrates in the prostates of males up to 2400 mg/day was seen. The incidence of the prostatic change was variable among treatment groups and was seen in control group therefore this it was considered to be unrelated to treatment. Due to histopathology, organ weight and hematology findings a dose level of 1200 mg/day was considered to be NOAEL. At 1200 mg/day on day 28, the exposure (AUC_{0-24}) was 492.5 and 598.4 µg.hr/mL and C_{max} was 32.8 and 41.7 µg/mL in males and females, respectively. The exposures to gabapentin after the administration of G-ER tablets at the NOAEL exceeded (by 3.9- fold for Cmax and 4.1-fold for AUC) the exposure to humans dosed once daily with three G-ER tablets, 1800 mg/day, at steady state (Study Report: 81-0049, appendix 1).

Safety margin for G-ER

	Dose (mg/day)	C_{max} (µg/mL)	$AUC_{0\ 24}$ (µg.hr/mL)	Human SM Based on Cmax	Human SM Based on AUC
Human G-ER MRHD	1800	9.6	132.8		
Dogs 28 days					
	600	23.8	192	2.5	1.4
NOAEL	1200	37.25	545	3.9	4.1
	2400	69.45	957	7.2	7.2

In the 28-day repeat dose toxicity study in dogs, the exposure to gabapentin, as measured by AUC_{0-24} was somewhat higher following administration of G-ER Tablets (957 µg.hr/mL) than after Neurontin IR tablets (906 µg.hr/mL) receiving 2400 mg/day. The hematology effects and testicular weight values differences with G-ER compared to Neurontin is likely due to the excipients used and may be a formulation issue.

In a PK study using healthy humans subjects (Depomed Protocol 81-0008), the mean AUC_{0-24} after administration of one G-ER tablet 600 mg was 42.2 µg.hr/mL, while the mean C_{max} was 3.1 µg/mL. The mean AUC_{0-24} on Day 24 for male and female dogs receiving one G-ER tablet, 600 mg/day, were 192.3 and 192.2 µg hr/mL, respectively, indicating approximately 4-5-fold higher daily exposures for the animals at the same daily dose. Likewise C_{max} was also approximately 7- 8-fold higher.

(b) (4) - also known as (b) (4) is a specified, identified impurity of the drug substance and the drug product. The Sponsor reduced the specification for (b) (4) from (b) (4) which at the MRHD the total daily intake in human is (b) (4) mg/day of the (b) (4) impurity. This specification is above the ICH3B guidance. The total daily intake impurity in the nonclinical study with (b) (4) specification was (b) (4) mg. Therefore the nonclinical study in dogs does not support proposed (b) (4) specification. However, the level of (b) (4) impurity specification is consistent with FDA's finding of safety and effectiveness for the listed drug relied upon and additional studies are not needed to qualify the level of this impurity in the proposed specifications.

12 Reference

Gee, N. S., J. P. Brown, et al. (1996). "The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel." J Biol Chem 271(10): 5768-76.

Alden, K. J. and J. Garcia (2001). "Differential effect of gabapentin on neuronal and muscle calcium currents." J Pharmacol Exp Ther 297(2): 727-35.

Eroglu, C., et al. (2009). "Gabapentin receptor α2δ-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis." Cell 139: 1-13.

Hwang, J. H. and T. L. Yaksh (1997). "Effect of subarachnoid gabapentin on tactileevoked allodynia in a surgically induced neuropathic pain model in the rat." Reg Anesth 22(3): 249-56.

Takasaki, I., T. Andoh, et al. (2001). "Gabapentin antinociception in mice with acute herpetic pain induced by herpes simplex virus infection." J Pharmacol Exp Ther 296(2): 270-5.

Field, M. J., E. F. Holloman, et al. (1997). "Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain." J Pharmacol Exp Ther 282(3): 1242-6.

Field, M. J., R. J. Oles, et al. (1997). "Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents." Br J Pharmacol 121(8): 1513-22.

13 Appendix/Attachments

Appendix 1

Table 1: Gabapentin PK Parameters in Study 81-0044

PK Parameter	Geometric Mean (%CV) Arithmetic Mean ± SD			
	600 mg	1200 mg	1800 mg	2400 mg
$AUC_{0-\infty}$ (ng·hr/mL)	35698 (32) 37624 ± 11910	63209 (33) 66383 ± 21806	90894 (31) 95147 ± 29755	108572 (29) 113334 ± 32397
C_{max} (ng/mL)	2840 (26) 2962 ± 775	4826 (21) 4933 ± 1051	6478 (26) 6686 ± 1748	7598 (27) 7847 ± 2102
T_{max} (hr)[a]	6.0 (4.0 -10.0)	6.0 (3.0-12.0)	6.0 (4.0-12.0)	7.0 (3.0-10.0)
$t_{1/2}$ (hr)	6.4 ± 1.3	6.7 ± 1.2	7.2 ± 1.6	7.3 ± 1.6

[a] Median (min - max)

Results of the study 81-0049 (Table 2) suggest time-independent pharmacokinetics for gabapentin after both G-ER regimens and IR formulation, evident by similar values of $AUC_{0-\infty}$ after a single day dose (Day 1) and AUC_{0-24} at steady state (Day 8, five days of consecutive dosing).

Table 2: Gabapentin Pharmacokinetics after Single and Multiple Days of Dosing (5 Consecutive Days) with BID G-ER (600 mg AM +1200 mg PM), QD G-ER (1800 mg PM), and TID Neurontin (3 x 600 mg)

Pharmacokinetic Parameter	Day 1	Day 8 (5 consecutive dosing days)
G-ER BID (600 mg AM, 1200 mg PM)		
AUC[1] (ng·hr/mL)	144491 ± 28619	144605 ± 31171
C_{max} (ng/mL)	6997 ± 1480	8048 ± 1819
G-ER QD (1800 mg PM)		
AUC[1] (ng·hr/mL)	124008 ± 32144	132808 ± 34701
C_{max} (ng/mL)	7974 ± 2157	9585 ± 2326
Neurontin TID (600 mg x 3)		
AUC[1] (ng·hr/mL)	139010 ± 32206	141301 ± 29459
C_{max} (ng/mL)	7455 ± 1496	8536 ± 1715

[1] AUC denotes 0-∞ on Day 1 and 0-24 hr on Day 8.

Appendix 2

2. Composition

The complete composition of GLUMETZA 500 mg tablets is shown in Table 1.

Table 1: Composition of GLUMETZA 500 mg Tablets

Raw Material	Composition		Function
	Wt/Tab	%w/w	
Metformin Hydrochloride, EP	500 mg	(b) (4)	Active ingredient
Polyethylene Oxide, NF	(b) (4)		
Hypromellose, USP			
Microcrystalline Cellulose, NF			
Hypromellose, USP			
Magnesium Stearate, NF			
TOTAL COATED TABLET:	(b) (4)		

Appendix 3

DEPOMED, INC.
Enhancing Pharmaceuticals

Document number: 20-0116f
Type: Master Formula
Revision: 0
Effective Date: 19 AUG 04

"Gabapentin Extended Release Tablets, 600 mg"

Product Description

(b) (4)

[redacted]

Appendix 4

From: Regulatory Submissions [mailto:Regulatory.Submissions@solvay.com]
Sent: Friday, June 25, 2010 12:40 PM
To: Meyer, Allison
Subject: FW: NDA 22544- Gabapentin

This message is sent of behalf of Naran Patel, Manager, Regulatory Affairs.
Dear Ms. Meyer,

As a follow up to our phone call on Monday seeking clarification of items in the 9 June 2010 Filing Communication Letter, this message is to request a discussion with the Agency prior to submitting our response to item 1 (below). Additionally, we would also like to discuss (b) (4)

Discussion Question 1- Clarity on Impurity Specifications/Adequacy of USP Qualification
Abbott would like to seek for clarification with the reviewer regarding the following item 1 from the letter:

Item 1: *Utilization of the 505(b)(2) approval pathway only allows reliance on the Agency's finding of safety and/or effectiveness as it is reflected in the approved labeling of the referenced Listed Product. You cannot rely on innovator studies or specifications described in the Summary Basis of Approval for the RLD to support your proposed drug product specifications. Additionally, the specifications that need to be in compliance with ICHQ3B (drug product) are those at the end of the shelf-life of the product. Your stability data showed that the qualification threshold (0.2% or 3 mg total daily intake [TDI], whichever is lower) is exceeded for multiple impurities on the basis of TDI. Reduced specifications to comply or you will need to provide impurity qualification studies to support the proposed specifications.*

A review of the room temperature (25 ºC/60 RH) stability data for registration batches reported in the section 3.2.P.8.3 shows only two impurities that are above ICH qualification limits. The two impurities are USP (b) (4)) and (b) (4) For the (b) (4), the results for the 36 month test station were analyzed using a relative response factor correction (RRF (b) (4) in relation to Gabapentin). This represents the worst case scenario as the impurity is at its highest level for each batch and demonstrates that the (b) (4) does not exceed the ICH qualification limits and supports our proposed specifications.

Based on our assessment of the proposed specification (module 3.2.P.5.1), only (b) (4) exceeds the ICH Q3B threshold on the basis of TDI -- 0.2% or 0.167% (which is lower and calculated based on 1800 mg TDI of active – (b) (4)/1800mg = 0.167%). All unidentified compounds/impurities have a specification of (b) (4).

Therefore, we would like to discuss a specification for USP (b) (4) of (b) (4) to meet the limit specified in the USP monograph. Qualification studies would therefore not be necessary. Does the Agency agree?

To aid in our discussion, a detailed summary table can be provided to the Agency on request to outline each impurity, the range of stability results, proposed specifications, and justification for the specifications (including toxicological considerations).

Appendix 5

From: Weiner, Janice
Sent: Friday, August 27, 2010 2:27 PM
To: Mellon, Dan
Cc: Emami, Armaghan; Wasserman, Adam; Meyer, Allison; Roca, Rigoberto A; Dickinson, Elizabeth; Dettelbach, Kim; Hayes, Nancy; Quaintance, Kim M; Duvall Miller, Beth A; Ripper, Leah W; Stevens, Jennifer
Subject: FW: More background on Abbotts impurity qualification claim

Dan,

Thank you again for the additional background information. A 505(b)(2) applicant may rely on FDA's finding that Neurontin (which contains the (b) (4) impurity at "x" level) is safe and effective and, from a regulatory perspective, need not conduct studies to qualify a level of this impurity above the ICH threshold but below the level found in the listed drug relied upon. Although we do not agree with all of the sponsor's interpretive comments regarding the 505(b)(2) pathway, OCC and I agree that this type of reliance is acceptable and also is consistent with OGD's longstanding practice for ANDAs.

This approach does not involve reliance on the SBA or disclosure of the innovator's specifications, but rather reflects that FDA has found a drug product with certain characteristics (including certain levels of impurities) safe and effective. The approved labeling for the listed drug reflects FDA's finding of safety and effectiveness; however, FDA's finding may include certain characteristics that are not described in product labeling.

It is my understanding that Abbott intends to initiate a nonclinical study in rats on September 1, 2010, to qualify the (b) (4) impurity contained in its drug product currently under review (goal date: January 30, 2011). From a regulatory perspective, there is no need to repeat qualification of an impurity that is below the level approved for the listed drug relied upon for a 505(b)(2) application. If the Division's request for the study is based only on the perceived inability to rely on FDA's finding of S&E for Neurontin, we recommend that the Division advise Abbott (without disclosing the specifications approved for Neurontin) that, upon reflection, a study is not needed to qualify the level of the impurity in Abbott's proposed specifications. It is not necessary to engage Abbott in a discussion regarding Abbott's interpretation of the statute and regulations for 505(b)(2) applications.

With respect to addressing the (b) (4) impurity in a review, you may wish to consider noting that the level of impurity is consistent with FDA's finding of safety and effectiveness for the listed drug (and, if scientifically appropriate in the Division's judgment, consistent with the USP monograph).

Should you have any questions, please feel free to contact me. Thank you.

-- Janice

APPEARS THIS WAY ON ORIGINAL.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARMAGHAN EMAMI
12/01/2010

ADAM M WASSERMAN
12/02/2010

I concur with Dr. Emami that this 505(b)(2) NDA application may be approved from the nonclinical standpoint.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 22-544 **Applicant:** Abbott **Stamp Date:** March 30, 2010

Drug Name: Gabapentin ER **NDA/BLA Type:** 505(b2) **DAAP/OND/CDER/FDA**

On **initial** overview of the NDA application for Refuse to File (RTF):

	Parameters	Yes	No	Comment
1	On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin?	+		
2	Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin?	+		
3	On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin?	+		
4	Are all required (*) and requested BBIND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA/BLA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)?	+		

5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation?	+		• The Sponsor conducted a 28-day multiple-dose study (Study Report: 80-0014) in Beagle dogs administered up to four 600 mg G-ER tablets per day (2400 mg/day gabapentin total, approximate dosage on a weight basis 200 mg/kg/day for males and 260 mg/kg/day for females).
6	Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)?	+		• The total daily exposure to the excipients was less than the maximum potency limits as listed in the IIG. • Similar ER formulation of Glumetza® and Proquin® have been approved by the FDA
7	On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted a rationale to justify the alternative route?	+		
8	Has the sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	+		
9	Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor?	+		
10	Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?	+		
11	Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues.	+		• Overall, there are five identified gabapentin-related compounds (b) (4)

				• Using the DEREK software, no Structural alert reported by the Sponsor for mutagenicity or genotoxicity for these five related compounds. • For the drug substance, qualification threshold (b) (4) exceeded on the basis of total daily intake. According to the Sponsor, the specifications refer to the USP monograph, and further reference is made to Neurontin® NDA's for qualification of impurities in the drug substance. • For drug product, qualification threshold (b) (4) exceeded on the basis of total daily intake. The Sponsor is incorrectly relying on the Division's findings of preclinical toxicology and safety conducted on Neurontin® (NDAs).
12	Has the sponsor addressed any abuse potential issues in the submission?			N/A
13	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			N/A
14	From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not.	+		

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comments to Sponsor:
You cannot rely on innovator studies or specifications described in the Summary Basis of Approval for the RLD to support your proposed drug product specifications. Additionally, the specifications that need to be in compliance with ICHQ3B (drug product) are those at the end of the shelf-life (i.e. from stability). Your stability data showed that the qualification threshold (0.2% or 3 mg TDI) is exceeded for multiple impurities on the basis of total daily intake. Reduce specifications to comply or you will need to provide supportive qualification studies to support proposed specifications.

Reviewing Pharmacologist: Armaghan Emami 04-28-2010

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22544	ORIG-1	ABBOTT PRODUCTS INC	GABAPENTIN E-R TABLETS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARMAGHAN EMAMI
05/17/2010

ADAM M WASSERMAN
05/17/2010