

Table 6.30 Summary of Patient and Clinician Global Impression of Change

	Patient Global Impression			Clinician Global Impression		
	Placebo N= 105	Gabapentin 1800 mg N=107	Gabapentin 2400 mg N=98	Placebo N= 107	Gabapentin 1800 mg N=108	Gabapentin 2400 mg N=103
Very much improved	7 (7)	18 (17)	12 (12)	6 (6)	14 (13)	12 (12)
Much improved	17 (16)	26 (24)	30 (31)	14 (13)	34 (31)	33 (32)
Minimally improved	23 (22)	22 (21)	21 (21)	30 (28)	16 (15)	26 (25)
No Change	45 (43)	34 (32)	27 (28)	46 (43)	37 (34)	25 (24)
Minimally worse	7 (7)	3 (3)	3 (3)	8 (7)	5 (5)	4 (4)
Much worse	3 (3)	3 (3)	5 (5)	3 (3)	1 (1)	3 (3)
Very much worse	3 (3)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)
Mean (SD)	3.5 (1.3)	2.9 (1.3)	2.9 (1.3)	3.4 (1.1)	2.9 (1.3)	2.9 (1.2)
Median	No change	Minimally improved	Minimally improved	No change	Minimally improved	Minimally improved

Based on 1 =very much improved; 2=much improved; 3=minimally improved; 4=no change; 5=minimally worse; 6=much worse; 7=very much worse.

Source: Sponsor's Table 12 and 13, Vol. 1.95, P. 35 and 36.

#### Quality of Life

The results of the SF-36 did not reveal any meaningful statistically significant differences between the gabapentin treatment groups and placebo. Of the eight domains, the vitality domain scores were statistically significant different from placebo for gabapentin 1800 mg ( $p=0.03$ ) and gabapentin 2400 mg ( $p=0.01$ ). The bodily pain subscale was statistically significantly different for gabapentin 1800 mg compared to placebo ( $p=0.008$ ), but not for gabapentin 2400 mg. With no corrections for multiple comparisons, these findings can not be considered substantial evidence for a meaningful effect on quality of life.

#### Mean Paracetamol Consumption

Although a planned secondary analysis, analysis of the mean paracetamol consumption was not performed by the sponsor. According to the sponsor, the units for daily dosing were collected as grams in some cases, number of tablets in other cases, and without units specified in others. Many combination products were also used concurrently during the study, some of which contained paracetamol.

APPEARS THIS WAY  
ON ORIGINAL

## **SECTION 7 INTEGRATED REVIEW OF SAFETY**

### **SECTION 7.1 SAFETY FINDINGS - SUMMARY**

The safety database consisted of 1357 patients in double-blind, placebo-controlled and open label studies of gabapentin in neuropathic pain. The postherpetic neuralgia studies enrolled 563 patients. A total of 820 patients received gabapentin, primarily over a period of 6-8 weeks. Additional safety information for deaths, serious adverse events (SAEs), and discontinuations due to adverse events was obtained from four ongoing studies in diabetic neuropathy and mixed etiology neuropathic pain, and from combinations studies with naproxen and hydrocodone in non-neuropathic pain.

Patients were evenly distributed across gender, but more than 80% of patients were Caucasian. Twenty five percent of patients were over the age of 75. In the PHN trials, 50% of the patients were over the age of 75.

Of the 11 deaths reported, there was only one death for which there was any reason to suspect even a small contributory roll of study medication. The patient had widely metastatic prostate cancer, and died following the onset of sleepiness, 3 days after beginning gabapentin. The patient had been receiving concomitant morphine which can increase the bioavailability of gabapentin, possibly contributing to CNS depression. The investigator attributed the cause of death due to progression of the underlying cancer.

There were few serious adverse events for which a contributory role could be assigned to gabapentin. In the neuropathic pain studies, gabapentin may have played a role in one case of peripheral edema with subsequent cellulitis, and likely contributed to the somnolence seen following an intentional overdose. There was one case of angioedema in a patient on no concomitant medications, but the study drug assignment had not been unblinded at the time of the report.

Adverse events were fairly common and occurred in more gabapentin-treated patients than placebo treated patients. PHN patients who were older, had greater proportion of discontinuations due to adverse events. It may be that older patients have a greater bioavailability of gabapentin which is excreted exclusively by the kidney, and so are more susceptible to adverse events. However, other unidentified factors may also have contributed.

The nature of the adverse events were consistent with the adverse event profile known from study of gabapentin in other patient populations. The most common adverse events were dizziness and somnolence, followed by peripheral edema and dry mouth. There was less ataxia, fatigue, and nystagmus compared with the epilepsy population.

### **SECTION 7.2 ADEQUACY OF SAFETY EXPOSURE**

The original ISS submitted August 6, 2001, included information from the studies presented in Table 7.1. The safety data was provided in separate datasets for each of the

five completed clinical neuropathy studies. A dataset combining the individual datasets was submitted on October 4, 2001. A dataset including dose at onset for the integrated safety data was submitted on November 30, 2001. The ISS was broken down to include an analysis of safety among patients with PHN in the submission dated December 20, 2001 based on the data from the original ISS.

Table 7.1 Overview of Studies Included in ISS

Studies Contained in ISS <sup>a</sup>	Number of Subjects/Patients	Information Included in this ISS
<b>CLINICAL PHARMACOLOGY STUDIES</b>		
2 Studies 945-190, 1032-015	32	AEs, Deaths, Serious AEs, Withdrawals Due to AEs, Clinical Laboratory Parameters
<b>CLINICAL NEUROPATHIC PAIN STUDIES</b>		
<b>Placebo-Controlled Clinical Studies Neuropathic Pain Associated With PHN</b>		
2 Controlled Studies 945-211, 945-295	563	Demographics, Drug Exposure, AEs, Deaths, Serious AEs, Withdrawals Due to AEs, Other Safety Measures
<b>Placebo-Controlled Clinical Studies Neuropathic Pain Associated With DPN, Diverse Etiologies</b>		
3 Controlled Studies 945-210, 945-224, 945-306	794	Demographics, Drug Exposure, AEs, Deaths, Serious AEs, Withdrawals Due to AEs, Other Safety Measures
Total:	1357	
<b>Uncontrolled Clinical Study</b>		
1 Open-Label Extension Phase of Placebo-Controlled Study in DPN 945-224 OL	67 <sup>a</sup>	Demographics, Drug Exposure, AEs, Deaths, Serious AEs, Withdrawals Due to AEs
<b>Ongoing Clinical Studies</b>		
3 Placebo-Controlled and 1 Uncontrolled Studies 945-271, 945-276, 945-429, 945-411	529 Enrolled	Deaths, Serious AEs, Withdrawals Due to AEs
<b>NON-NEUROPATHIC PAIN STUDIES (COMBINATION STUDIES)</b>		
<b>Combination Therapy Studies <sup>b</sup></b>		
3 Controlled and 1 Uncontrolled Studies in CI-1032 (GBP + NPN)	607	Deaths, Serious AEs, Withdrawals Due to AEs
3 Controlled Studies in CI-1035 (GBP+HC)	464	Deaths, Serious AEs, Withdrawals Due to AEs

AE = Adverse event(s), NPN = Naproxen-sodium; HC= Hydrocodone.

a. Fourteen of these 67 patients received placebo during the double-blind phase and gabapentin for the first time during the open-label phase.

b. Does not include patients who received NPN or HC alone.

Source: Table 1, P. 10, Vol. 3, 12-20-01

The 120-day safety update was submitted on December 6, 2001. The table below details the material provided in this submission. The sponsor provided an integrated update of deaths, SAEs, and withdrawals due to adverse events from ongoing trials, but study drug assignment remains blinded for many of the reported events. This was the only additional adverse event data was from Study 945-411, a foreign open-label study completed subsequent to the cutoff date for the original ISS. This data was submitted separate from the prior adverse event reporting without an integrated dataset.

Table 7.2. Overview of Clinical Studies Summarized in the Original ISS and SU1

Type and Study Number	Safety Data in Original ISS	Study Status for Original ISS	New Data in SU1	Cutoff Date for SU1
<b>Clinical Pharmacology Studies</b>				
945-190	All	Study Completed	No	NA
1032-015	All	Study Completed	No	NA
<b>Clinical Studies in Neuropathic Pain</b>				
<b>Pivotal Placebo-Controlled Studies</b>				
945-210 (DPN)	All	Study Completed	No <sup>a</sup>	NA
945-211 (PHN)	All	Study Completed	No	NA
945-224 (DPN)	All	Study Completed	No	NA
945-295 (PHN)	All	Study Completed	No <sup>b</sup>	NA
945-306 (MNP)	All	Study Completed	No	NA
<b>Uncontrolled Open-Label Extension</b>				
945-224 (DPN)	All	Study Completed	No	NA
<b>Dose-Controlled Open-Label Study</b>				
945-411 (DPN)	D, S, W	Data Being Summarized	Yes	NA
<b>Other Controlled Studies</b>				
945-271 (Post-traumatic, post-operative neuralgia)	D, S, W	Study Ongoing	D, S W	31 Oct01 01 Oct01
<b>945-429 (DPN)</b>				
	D, S, W	Study Ongoing	D, S W	31 Oct01 01 Oct01
<b>Non-neuropathic Pain Studies</b>				
<b>Gabapentin/Naproxen Combination</b>				
1032-001	D, S, W	Study Completed	No	NA
1032-002	D, S, W	Study Completed	No	NA
1032-003	D, S, W	Data being summarized <sup>c</sup>	No <sup>d</sup>	NA
1032-004	D, S, W	Study Completed	No	NA
1032-010	D, S, W	Study Completed	No	NA
<b>Gabapentin/Hydrocodone Combination</b>				
1035-001	D, S, W	Study Completed	No	NA
1035-002	D, S, W	Study Completed	No	NA
1035-003	D, S, W	Study Completed	No	NA

D, S, W = Deaths, Serious Adverse Events, Withdrawals Due to Adverse Events; NA = Not Applicable; DPN = Diabetic Peripheral Neuropathy; PHN = Postherpetic Neuralgia; MNP = Mixed Neuropathic Pain.  
a A new SAE is discussed in Section 3.2, narrative is in Appendix 13.4 (Patient 210\_006001).  
b Updated death information discussed in Section 3.1, narrative is in Appendix 13.4 (Patient 295\_017046). Study c Report Issued 27Sep2001  
d Updated SAE discussed in Section 3.2, narrative is in Appendix 13.4 (Patient 008018, Study 1032-003).  
Source: Table 2, P. 5, Vol. 1, 12-06-01

### SECTION 7.2.1 Extent of Exposure

There were five, completed, controlled neuropathic pain studies (Studies 945-211, -295, -210, -224, and -306) and the open-label extension of Study 945-224 in which 834 patients were treated with gabapentin, and 537 patients treated with placebo at the time of original NDA submission. These studies will be referred to the “original five completed neuropathy studies” to distinguish them from the ongoing studies, Study 945-411 which

was completed subsequent to the original NDA submission, and the combination studies for non-neuropathic pain. Included in these five were the two pivotal studies (Studies 945-211 and -295) of neuropathic pain associated with postherpetic neuralgia in which 336 patients were treated with gabapentin, and 227 patients treated with placebo.

Table 7.3 Overview of Original Five Completed Neuropathy Studies: Number of Patients in Each Gabapentin Treatment Group (ITT Population)

Study (Patient Population)	Duration of Double-Blind Phase			Number of Patients								
	Titration	Fixed Dose	Overall Duration	Placebo	Gabapentin Treatment Group, mg/day					Any GBP	All Patients	
945-210(DPN)	4 weeks	4 weeks	8 weeks	81						84	84	165
945-211 (PHN)	4 weeks	4 weeks	8 weeks	116						113	113	229
945-224 <sup>a</sup> (DPN)	3 weeks	4 weeks	7 weeks	77	82	82		83			247	324
945-295(PHN)	3 weeks	4 weeks	7 weeks	111			115	108			223	334
945-306 (MNP)	4 weeks	4 weeks	8 weeks	152				153			153	305
<b>Total Patients</b>				<b>537</b>	<b>82</b>	<b>82</b>	<b>115</b>	<b>344</b>	<b>197</b>	<b>820</b>	<b>1357</b>	

DPN = Diabetic peripheral neuropathy; PHN = Postherpetic neuralgia; MNP = Mixed neuropathic pain; GBP = gabapentin. ITT Population = All randomized patients who took at least one dose of study medication.

a Open-label extension phase added 14 gabapentin-treated patients (these patients received placebo during double-blind phase of study)

Source: Table 2, P. 11, Vol. 1.52

Non-neuropathic pain studies (combination therapy studies) have been completed and exposed 804 subjects and patients to gabapentin alone or in combination, and 267 subjects to placebo.

The planned duration of exposure to gabapentin varied according to study design. The original five completed neuropathy studies were designed to last seven or eight weeks, plus an optional 12 week open-label extension in study 945-224. During the double-blind phase of the studies, 83.7% of gabapentin-treated patients remained on gabapentin for up to 6 weeks across all assigned treatment groups (Table 7.4). This table overestimates exposure however, because not all patients within an assigned treatment groups completed titration to the full dose.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 7.4 Summary of Exposure to Study Medication During Double-Blind Phase of 5 Pivotal Controlled Studies, by Assigned Treatment Group, Number (%) of Patients

	Gabapentin Treatment Group (mg/day)						Any Gabapentin
	Placebo	600	1200	1800	2400	3600	
Total Exposure	N = 537	N = 82	N = 82	N = 115	N = 344	N = 197	N = 820
≥1 day	537 (100.0)	82 (100.0)	82 (100.0)	115 (100.0)	344 (100.0)	197 (100.0)	820 (100.0)
≥1 week	524 (97.6)	79 (96.3)	81 (98.8)	110 (95.7)	328 (95.3)	192 (97.5)	790 (96.3)
>2 weeks	507 (94.4)	76 (92.7)	81 (98.8)	102 (88.7)	312 (90.7)	184 (93.4)	755 (92.1)
>4 weeks	468 (87.2)	73 (89.0)	80 (97.6)	96 (83.5)	293 (85.2)	172 (87.3)	714 (87.1)
>6 weeks	447 (83.2)	70 (85.4)	78 (95.1)	94 (81.7)	281 (81.7)	163 (82.7)	686 (83.7)
>8 weeks	243 (45.3)	0 (0)	0 (0)	1 (0.9)	125 (36.3)	135 (68.5)	261 (31.8)
>10 weeks	10 (1.9)	0 (0)	0 (0)	0 (0)	1 (0.3)	4 (2.0)	5 (0.6)
>12 weeks	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Source: Table 4, P. 17, Vol. 1.52

By examining the actual time spent receiving gabapentin in a specific dosing range as displayed in Table 7.5, it can be seen that many patients did not receive the full dose of their respective assigned treatment group for the duration possible according to the study protocols. The protocols each specified a 4-week double-blind period on the final titrated dose. For example, of a possible 344 patients assigned to 2400 mg/day, only 230 patients remained on study drug at a dose from 2400 mg up to 3600 mg for the full 4 week double-blind period. This is due to the inability of some patients to titrate to the full dose or remain on the full titrated dose due to dose-related adverse events and early study discontinuations. The majority of patients received any dose of gabapentin for 6 to 10 weeks.

Table 7.5 Duration of Exposure to Gabapentin by Received Dosage Range during the Original Five Completed Neuropathy Studies

Exposure	Gabapentin Dosage Range (mg/day)					
	>0 to <900	900 to <1200	1200 to <1800	1800 to <2400	2400 to <3600	3600
≥ 1 day to <1 week	687	570	546	119	25	6
≥1 week to <2 weeks	51	132	21	332	127	3
≥2 weeks to <4 weeks	13	18	19	30	41	9
≥ 4 weeks to <6 weeks	3	7	23	55	230	106
≥ 6 weeks to <8 weeks	53	4	64	66	11	0
≥ 8 weeks to <10 weeks	14	4	2	0	0	0
≥ 10 weeks to <12 weeks	3	0	1	1	2	0
≥12 weeks to <16 weeks	0	5	6	7	15	0
≥ 16 weeks to <20 weeks	3	2	1	1	6	0
≥ 20 weeks to <24 weeks	2	0	0	0	0	0
≥ 24 weeks to <36 weeks	0	0	0	0	0	0
Total Patient-Days	7119	4788	7293	9857	12475	3750
Total Patient-Weeks	1017.00	684.00	1041.86	1408.14	1782.14	535.71
Total Patient-Years	19.49	13.11	19.97	26.99	34.15	10.27

Note: Each patient is counted in only 1 row within a column, but patients who received more than 1 dose of gabapentin will appear in multiple columns.

Source: Table 5, P. 19, Vol. 1.52

### Exposure in PHN

Table 7.6 demonstrates the exposure to gabapentin during the two PHN trials by gabapentin treatment group assignment, any gabapentin, and placebo. Based on study design, double-blind exposure durations of 7 and 8 weeks were planned which included titration periods. Overall, nearly 15% of patients did not remain on study drug for more than 4 weeks and this was comparable across the three different gabapentin treatment arms.

Table 7.6 Summary of Exposure, Double-Blind Phase of Studies 945-211 and 945-295

Total Exposure	Placebo N = 227	Gabapentin 1800 mg/day N = 115	Gabapentin 2400 mg/day N = 108	Gabapentin 3600 mg/day N = 113	Any Gabapentin N = 336
1 Day	227 (100.0)	115 (100.0)	108 (100.0)	113 (100.0)	336 (100.0)
>1 Week	221 (97.4)	110 (95.7)	103 (95.4)	110 (97.3)	323 (96.1)
>2 Weeks	218 (96.0)	102 (88.7)	99 (91.7)	103 (91.2)	304 (90.5)
>4 Weeks	206 (90.7)	96 (83.5)	92 (85.2)	97 (85.8)	285 (84.8)
>6 Weeks	198 (87.2)	94 (81.7)	89 (82.4)	90 (79.6)	273 (81.3)
>8 Weeks	81 (35.7)	1 (0.9)	4 (3.7)	75 (66.4)	80 (23.8)
>10 Weeks	5 (2.2)	0	0 (0.0)	3 (2.7)	3 (0.9)
>12 Weeks	0	0	0 (0.0)	0	0 (0.0)

Source: Table 4, P. 20, Vol. 3, 12-20-01

### SECTION 7.2.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics are displayed below. The gabapentin and placebo treatment groups were comparable across age, gender, race, and mean baseline pain scores.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 7.7. Patient Characteristics: Original Five Completed Neuropathy Studies (ITT)

	Gabapentin mg/day							All Neuropathic Pain Patients N=1357
	Placebo N=537	600 N=82	1200 N=82	1800 N=115	2400 N=344	3600 N=197	Any GPN N=820	
<b>Gender, n (%)</b>								
Male	268 (49.9)	45 (54.9)	52 (63.4)	46 (40.0)	158 (45.9)	112 (56.9)	413 (50.4)	681 (50.2)
Female	269 (50.1)	37 (45.1)	30 (36.6)	69 (60.0)	186 (54.1)	85 (43.0)	407 (49.6)	676 (49.8)
Not Specified	57 (21.2)	0 (0.0)	0 (0.0)	0 (0.0)	70 (37.6)	0 (0.0)	70 (17.2)	127 (18.8)
<b>Race, n (%)</b>								
White	238 (44.3)	67 (81.7)	74 (90.2)	0 (0.0)	72 (20.9)	166 (84.3)	379 (46.2)	617 (45.5)
Black	10 (1.9)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (7.6)	17 (2.1)	27 (2.0)
Hispanic	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	11 (5.6)	11 (1.3)	18 (1.3)
Asian/Pac. Islander	4 (0.7)	3 (3.7)	2 (2.4)	0 (0.0)	2 (0.6)	5 (2.5)	12 (1.5)	16 (1.2)
American Indian	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Other	2 (0.4)	3 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	5 (0.4)
Not Specified	275 (51.2)	7 (8.5)	6 (7.3)	115 (100) <sup>a</sup>	270 (78.5) <sup>a</sup>	0 (0.0)	398 (48.5)	673 (49.6) <sup>a</sup>
<b>Age (Years)</b>								
Mean	63.3	60.4	60.8	72.8	62.8	63.2	63.9	63.6 <sup>a</sup>
(SD)	14.1	9.9	10.0	9.4	14.3	13.7	13.3	13.6
Median	64	62	61	74	64	65	65	65
Min, Max	20,94	34,84	37, 83	22, 88	23,90	25,90	22,90	20,94
<b>Age Categories, n (%)</b>								
18 to 64 Years	272 (50.7)	53 (64.6)	50 (61.0)	21 (18.3)	179 (52.0)	98 (49.7)	401 (48.9)	673 (49.6)
65 to 74 Years	130 (24.2)	24 (29.3)	27 (32.9)	37 (32.2)	76 (22.1)	47 (23.9)	211 (25.7)	341 (25.1)
75 + Years	135 (25.1)	5 (6.1)	5 (6.1)	57 (49.6)	89 (25.9)	52 (26.4)	208 (25.4)	343 (25.3)
<b>Baseline Mean Pain Score</b>								
Mean	6.6	6.3	6.1	6.5	6.7	6.4	6.5	6.6
(SD)	1.6	1.5	1.6	1.7	1.6	1.6	1.6	1.6
Median	6.6	6.1	6.1	6.3	6.7	6.4	6.4	6.4
Min, Max								

<sup>a</sup> Only study 945-295 contributed 1800 mg/d and 2400 mg/d treatment arms to this table and race was not recorded for this study.

Source: Table 6, P. 21, Vol. 1.52

#### Baseline Characteristics in PHN

The demographic characteristics of patients in Studies 945-211 and 945-295 were similar across treatment groups. Race characteristics were not reported in Study 945-295. Study 945-211 had slightly more male patients. Approximately half of the patients were age 75 or greater and roughly one fifth were 64 years of age and younger. This group representing a subset of the entire neuropathic pain group, was on average, older than the entire neuropathic pain group.

Table 7.8 Demographics of Postherpetic Neuralgia Trial Patients, Studies 945-211 and 945-295

	Placebo N=227	Gabapentin Treatment Group, mg/day			Any Gabapentin N=336	All PHN Patients N=563
		1800 N=115	2400 N=108	3600 N=113		
<b>Gender, n (%)</b>						
Male	102 (44.9)	46 (40.0)	46 (42.6)	63 (55.8)	155 (46.1)	257 (45.6)
Female	125 (55.1)	69 (60.0)	62 (57.4)	50 (44.2)	181 (53.9)	306 (54.4)
<b>Race, a (%)</b>						
White	109 (48.0)	0 (0.0)	0 (0.0)	99 (87.6)	99 (29.5)	208 (36.9)
Black, Hispanic, Asian	7 (3.1)	0 (0.0)	0 (0.0)	14 (12.4)	14 (4.2)	13 (2.3)
Not Specified	111 (48.9)	115 (100.0)	108 (100.0)	0 (0.0)	223 (66.4)	334 (59.3)
<b>Age (Years)</b>						
Mean	72.5	72.8	73.7	70.8	72.4	72.4
(SD)	10.7	9.4	10.1	10.5	10.0	10.3
Min, Max	28, 94	22, 88	36, 90	36, 90	22, 90	22, 94
<b>Age Categories, n (%)</b>						
18 to 64 Years	45 (19.8)	21 (18.3)	19 (17.6)	26 (23.0)	66 (19.6)	111 (19.7)
65 to 74 Years	70 (30.8)	37 (32.2)	27 (25.0)	38 (33.6)	102 (30.4)	172 (30.6)
75 or Greater Years	112 (49.3)	57 (49.6)	62 (57.4)	49 (43.4)	168 (50.0)	280 (49.7)
<b>Baseline Mean Pain Score</b>						
Mean	6.4	6.5	6.5	6.3	6.4	6.4
(SD)	1.7	1.7	1.6	1.7	1.7	1.7
Min, Max						

a Only study 945-295 contributed the 1800 mg/d and 2400 mg/d treatment arms in this table and race was not recorded for this study.

Source: Table 6, P. 22, Vol. 3, 12-20-01

### SECTION 7.2.3 Disposition

The most common reason for early discontinuation from participation in a neuropathy pain study was the occurrence of adverse events for both placebo- (10.8%) and gabapentin-treated (13.2%) patients.

Table 7.9. Summary of Withdrawals in the Original Five Completed Neuropathy Studies Number (%) of Patients

	Placebo N = 537	Any Gabapentin N = 820
Completed Study	431 (80.3)	670 (81.7)
Withdrawn	106 (19.7)	150 (18.3)
Adverse Event <sup>a</sup>	58 (10.8)	108 (13.2)
Lack of Compliance	11 (2.0)	13 (1.6)
Lack of Efficacy	17 (16.0)	9 (1.1)
Lost to Follow-up	1 (0.2)	0 (0)
Personal Reasons	2 (0.4)	1 (0.1)
Other	17 (3.2)	19 (2.3)

a Includes withdrawals for both treatment emergent and non-treatment emergent adverse events; 3 placebo-treated patients and 4 gabapentin-treated patients withdrew due to non-treatment emergent adverse events.

The end of study status for 1 placebo-treated patient who discontinued study medication (withdrew) due to an adverse event was recorded as "noncompliant". This patient is included in the withdrawal due to adverse event summary (including a narrative in Appendix B).

Source: Table 20, P. 54, Vol. 1.52, Original ISS, 8-06-01

Adverse events lead to early discontinuation of study participation more often among gabapentin-treated patients in the PHN trials (55 out of 336, 16.3%) compared with the entire neuropathy population (108 out of 820, 13.2%). This was not reflected in the placebo treated patients, (9% for PHN group, 10.8% for entire neuropathy group).

Table 7.10 Patient Disposition PHN Trials

	Study 945-211		Study 945-295		
	Placebo	Gabapentin 3600 mg/d	Placebo	Gabapentin 1800 mg/d	Gabapentin 2400 mg/d
Randomized	116	113	111	115	108
Completed Study	95 (81.9%)	89 (78.8%)	94 (84.7)	93 (80.9)	85 (78.7)
Premature Discontinuation:	21(18.1%)	24 (21.2%)	17 (15.3)	22 (19.1)	23 (21.3)
Reasons for Discontinuation:					
Adverse Event	14 (12.1%)	21(18.6%)	7 (6.3) <sup>a</sup>	15 (13.0)	19 (17.6)
Lack of Compliance with Protocol	2 (1.7%)	1 (0.9%)	3 (2.7) <sup>a</sup>	2 (1.7)	1 (0.9)
Treatment Failure	2 (1.7%)	0 (0.0%)	4 (3.6)	2 (1.7)	1 (0.9)
Lost to Follow-up	1 (0.9%)	0 (0.0%)			
Personal Reasons	2 (1.7%)	1 (0.9%)			
Other	0 (0.0%)	1 (0.9%)	3 (2.7)	3 (2.6)	2 (1.9)

Source: Sponsor's Table 9, Vol. 1.77, P. 88, Table 5, Vol. 1.95, P. 22

### SECTION 7.3 SAFETY ASSESSMENT

Table 7.11 presents an overview of the discontinuations due to adverse events, SAEs and deaths by assigned treatment group for patients in the five original, completed neuropathy trials.

Table 7.11 Overview of Discontinuations, SAEs, and Deaths, Original Five Completed Neuropathy Studies

Adverse Event Category	Gabapentin Treatment Group, mg/day						Any Gabapentin N = 820
	Placebo N = 537	600 N = 82	1200 N = 82	1800 N = 115	2400 N = 344	3600 N = 197	
Adverse Event Category	N = 537	N = 82	N = 82	N = 115	N = 344	N = 197	N = 820
Number (%) of Patients Withdrawn due to AEs <sup>a</sup>	58 (10.8)	8 (9.8)	3 (3.7)	15 (13.0)	54 (15.7)	28 (14.2)	108 (13.2)
Number (%) of Patients With Non-Fatal SAEs <sup>a,b</sup>	16 (3.0)	5 (6.1)	2 (2.4)	4 (3.5)	8 (2.3)	13 (6.6)	32 (3.9)
Number (%) of Patients Withdrawn due to SAEs <sup>a</sup>	6 (1.1)	3 (3.7)	0 (0.0)	1 (1.9)	3 (0.9)	3 (1.5)	10 (1.2)
Number (%) of Patients Who Died <sup>a,b</sup>	4 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)

<sup>a</sup> Includes both treatment emergent (TESS) and non-TESS adverse events

<sup>b</sup> 3 placebo-treated patients [Patients 211-008093, 211-009034, and 306-028050] had serious adverse events (SAEs) that resulted in death. These 3 placebo-treated patients are included only in the row, "Number of Patients Who Died". Thus, this table (Table 6) has 16 placebo-treated patients with "Serious Non-Fatal Adverse Events", whereas, the "Summary of Serious Adverse Events" (Table 14) includes these 3 patients for a total of 19 placebo-treated patients with SAEs. One additional placebo-treated patient [Patient 306-0333781 who had an SAE had another SAE that resulted in death. This patient is included in both "Number of Patients with Non-Fatal Serious Adverse Events" and "Number of Patients Who Died".

Source: Table 7, P. 24, Vol. 1.52

There were no discontinuations due to adverse events, deaths, or serious adverse events during the two clinical pharmacology studies.

The ISS submitted in the 12-20-01 submission was used for the safety review from the postherpetic neuralgia subgroup.

Table Deaths, SAEs and Withdrawals due to AEs, Postherpetic Neuralgia Trials

	Placebo N=227	Gabapentin Treatment Group, mg/day			Any Gabapentin N=336
		1800 N=115	2400 N=108	3600 N=113	
Patients Withdrawn Due to AEs, N (%)					
All AEs	21 (9.3)	15 (13.0)	19 (17.6)	21 (18.6)	55 (16.4)
Patients with non-fatal Serious AEs <sup>a</sup> , N (%)					
All AEs	5 (2.2)	4 (3.5)	1 (0.9)	10 (8.8)	15 (4.5)
Patients Withdrawn due to SAEs, N (%)					
All AEs	2 (0.9)	1 (0.9)	1 (0.9)	3 (2.7)	5 (1.5)
Patients Who Died, N (%) <sup>a,b</sup>					
All Deaths	3 (1.3)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.3)

Source: Table 7, p. 27, Vol. 3, 12-20-01

a 2 placebo-treated patients [Patients 211-008093 and 211-009034] had serious adverse events (SAEs) that resulted in death. These 2 placebo-treated patients are included only in the row, "Number of Patients Who Died". Thus, this table (Table 7) has 5 placebo-treated patients with "Serious Non-Fatal Adverse Events", whereas, the Summary of Serious Adverse Events" (Table 19) includes these 2 patients for a total of 7 placebo-treated patients with SAEs

b Includes both treatment emergent (TESS) and non-TESS adverse events

### SECTION 7.3.1 Deaths

There were 11 deaths reported, nine in the original ISS, and two in the 120-day safety update submitted on 12-6-01. The ISS submitted in the 12-20-01 submission was used for this review which incorporated the data from the original ISS and the 120-day ISS. The deaths described in this section represent those events occurring from all of the studies submitted in support of safety in this application. These studies contributing information were:

- 5 completed, controlled neuropathic pain studies (Studies 945-211, -295, -210, -224, and -306) and the open-label extension of Study 945-224 in which 834 patients were treated with gabapentin, and 537 patients treated with placebo
- completed non-neuropathic pain studies (combination therapy studies) with 804 subjects and patients who were exposed to gabapentin alone or in combination, and 267 subjects to placebo.

Table 7.12 Deaths

Patient ID <sup>a</sup>	Study Medication	Reason for Death Preferred Term/INVESTIGATOR TERM	Study Day	Age/Gender
<b>Reported Since the Original ISS (SU1)</b>				
276_007109	Gabapentin 600 mg/day	/INTERACTION WITH OPIOIDS; HEPATIC METASTASIS	3	48/M
276_007110	Blinded	/PROGRESSION OF TUMOR; MALAISE (SAE); INTESTINAL OCCLUSION (SAE)	15 (4 days post-study)	51/M
<b>Previously Reported in Original ISS</b>				
<b>Original Five Completed Neuropathy Studies in Neuropathic Pain</b>				
211_008093	Placebo	Apnea; Lung Disorder; Acc. Injury/ RESP. FAILURE; COPD; BROKEN HIP (SAE)	89 (33 days post-study)	75/M
211_009034	Placebo	Myocardial Infarct/ SUSPECTED MI	84 (27 days post-study <sup>b</sup> )	84/F
211_017258	Placebo	Myocardial Infarct/ MI	84 (29 days post-study)	73/M
295_017046	Gabapentin 2400 mg/day	CHF; Pneumonia; Heart Arrest/ CHF, RLL PNEUMONIA; CARDIAC ARREST	91 (41 days post-study <sup>c</sup> )	89/M
306_028050	Placebo	Myocardial Ischemia/ ISCHEMIC HEART DISEASE	88 (31 days post-study)	83/M
306_033378	Placebo	Heart Failure/ HEART FAILURE	48 (22 days posttreatment)	85/M
<b>Ongoing Clinical Studies in Neuropathic Pain</b>				
276_002014	Blinded	Heart Arrest; Hepatic Failure/ CARDIAC ARREST; ACUTE LIVER FAILURE	9 (1 day posttreatment)	58/F
276_009121	Blinded	Subarachnoid Hemorrhage/ SUBARACHNOID HEMORRHAGE	14 (12 days posttreatment)	61/F
<b>Studies In Non-Neuropathic Pain, (Combination Studies, Gabapentin/Hydrocodone, CI-1035)</b>				
002_002131 (1035-002)	Placebo	Heart Arrest/ CARDIAC ARREST	2 (1 day posttreatment)	73/M

a Study Number\_Center and patient number (3 digits each)

b This patient received placebo during Study 945-211. Per study narrative, she received marketed gabapentin post-study.

c Received marketed gabapentin post-study.

d Assessed by sponsor medical reviewer

Source: Table 6, P. 12, Vol. 1, 12-6-01

The narratives for the first nine deaths reported were reviewed from Appendix B.5.1 from the original submission, (Vol. 1.52) and for the two deaths reported in the 120-day safety update, Appendix B.4.1 (Vol. 1).

Patient 211\_008093 was a 75 year old man with PHN who died 33 days following his last dose of placebo. As the patient died long after completing the study and had received placebo, the conditions of the patient's death are not considered further.

Patient 211\_009034 was an 84 year old woman with PHN who died 27 days following her last dose of placebo. As the patient died long after completing the study and had received placebo, the conditions of the patient's death are not considered further.

Patient 211\_017258 was a 73 year old man with PHN who died 29 days following his last dose of placebo. As the patient died long after completing the study and had received placebo, the conditions of the patient's death are not considered further.

Patient 295\_017046, an 89 year old man with PHN who died 41 days after study termination. The patient had received gabapentin in the 2400 mg/day treatment arm. The patient had a history of heart disease and died of cardiac arrest. There is no circumstances surrounding the patient's death that suggests a contributory role of the study medication.

Patient 306\_028050 was an 83 year old man with PHN who died 31 days following study termination, having received placebo. As the patient died long after completing the study and had received placebo, the conditions of the patient's death are not considered further.

Patient 306\_033378 was an 85 year old man with PHN who died 22 days following study termination, having received placebo. The patient was hospitalized with worsening heart failure on Day 25. The patient had a history of cardiac disease and failure.

Patient 276\_002014 was a 58 year old woman with neuropathic pain due to malignant melanoma. On Day 5, the patient developed hypotension, somnolence and asthenia and she died from a cardiac arrest and acute liver failure on Day 9. Study drug was terminated on Day 8. The blind was not broken and it is unknown if the patient received placebo or gabapentin 1800 mg/d. The patient had metastases to the liver and impaired liver function at study onset. Given the patient's advanced metastatic disease, the conditions surrounding do not suggest any contributory role due to study drug, even if the patient was receiving gabapentin.

Patient 276-009121 was a 61 year old woman with neuropathic pain due to malignancy who experienced a subarachnoid hemorrhage on Day 2 of the study, and died following a re-hemorrhage on Day 14. The study is still blinded, the patient received either placebo or gabapentin 600 mg/day. The patient had also been receiving indomethacin. There were no circumstances reported to suggest that study drug contributed to the cause of death, even if the patient was receiving gabapentin.

Patient 276\_007109 was a 48 year old man with neuropathic pain due to prostate cancer. The patient had hepatic, renal, and ganglionic metastasis with severe hepatic dysfunction. The patient had received gabapentin 600 mg/day for 3 days. The patient died following the onset of increased sleepiness. The narrative suggests there may have been an interaction between the gabapentin and the concomitant use of morphine sulfate.

Patient 276-007110 was a 51 year old man with neuropathic pain due to malignancy. The patient had a history of metastatic bladder cancer. the patient was hospitalized with malaise on Day 5, developed intestinal occlusion on Day 8, and study medication was discontinued on Day 11 following completion of the study. The patient died on Day 15,

4 days after discontinuing study medication and cause of death was attributed to progression of the underlying malignancy. The study blind was not broken. There were no circumstances reported to suggest that study drug, gabapentin or placebo, contributed to the cause of death.

Patient 1035\_002131 was a 73 year old man with pain due to a total knee arthroplasty who died of a cardiac arrest after a single dose of placebo. There were no circumstances reported to suggest that study drug contributed to the cause of death.

In summary, based on the narratives provided, of the 11 deaths reported, there was only one death for which there was any reason to suspect even a small contributory roll of study medication. Patient 276\_007109 was a patient suffering from widely metastatic prostate cancer. The patient died following the onset of sleepiness, 3 days after beginning gabapentin. While gabapentin has little effect on hydrocodone, hydrocodone increases the bioavailability of gabapentin as demonstrated by the sponsor. Literature submitted by the sponsor demonstrates that morphine can also increase the bioavailability of gabapentin, although the effects of gabapentin on morphine have not been explicitly explored. Patient 276\_007109 was also receiving morphine. Whether a possible drug interaction between gabapentin and morphine may have contributed to the patient's cause of death cannot be ascertained with the information provided.

### SECTION 7.3.2 Serious Adverse Events

There were 74 SAEs reported in the original ISS (08-06-01), and 5 additional SAEs were reported in the 120-day safety update (12-06-01). Some patients had more than one SAE and more than one SAE per Body System. In the controlled trials, there were 32 patients treated with gabapentin who reported SAEs representing approximately 4% of the group. These 32 patients experienced 44 SAEs. There were 19 patients treated with placebo also representing approximately 4% of the group, who reported SAEs, with a total of 23 SAEs among them. So, while a similar proportion of patients in the controlled trials treated with gabapentin and placebo experienced SAEs, the gabapentin group described a greater number of SAEs per patient. The SAEs described in this section represent those events occurring from all of the studies submitted in support of safety in this application

Table 7.13 Serious Adverse Events, Five Original, Completed, Controlled Studies

	5 Completed Controlled Studies		945-224	945-411 <sup>b</sup>	Ongoing Studies, GBP	Ongoing Studies, Blinded	GBP Combo Studies
	Placebo N=537	GPN N=820	OL N=67 <sup>a</sup>	OL N=339			
	Number (%) of Patients				Number of Patients		
Original ISS	19 <sup>c</sup> (3.5)	32 (3.9)	4 (6.0)	5	1	6	6 GPN/ 1 pl
New In 120-Day Safety Update	0	1		1		3	0
Total # Patients With SAEs	19 (3.5%)	33 (4.0)	4 (6.0)	6 (1.8%)	1	9	6 GPN/ 1 pl
Total # of SAEs by Body System	20	38					
Total # of SAEs by Event	23	44		17		15	6

- a Includes patients rolled over from double-blind period of 945-224.
  - b Study completed after original ISS cut-off date
  - c Two of these patients died. Narratives were included among deaths not SAEs.
- Source: Table 7, p. 15, Vol. 1, 12-06-01; p. 49, Vol. 1.52, 8/06/01

When SAEs were counted from the five clinical trials included in dataset AELISTP submitted on the 11-30-01, 74 SAEs were found occurring in 55 patients. This dataset reflects information from the original ISS combined into one dataset with dose at onset of adverse events included. Twenty of the SAEs were in patients in the placebo treatment group (including four patients who died), 35 in the combined gabapentin treatment group. A count of the narratives of the SAEs submitted in the original ISS submission reveals 52 reports of SAEs, 17 in placebo patients (none of whom died) and 35 in patients who had received gabapentin. Appendix B.3.1 of the original ISS (p. 244, Vol. 1.52) reveals one placebo-treated patient missing that was present in the narratives, Patient 295\_024096, for a total of 17 SAEs not resulting in death and 35 SAEs not resulting in death among the gabapentin-treated patients.

Among the 17 placebo-treated patients from the 5 controlled neuropathy trials with SAEs, six patients were in the PHN trials, eight in the diabetic neuropathy trials, and three in the mixed neuropathy trial. Among the PHN trials, out of a total of 227 placebo treated patients the six patients with SAEs result in an incidence of 2.6%.

The sponsor was asked to explain why there were a greater number of narratives (35) for patients with SAEs than there were patients reported in the original ISS table (Table 18, p. 50, Vol. 1.52) and the safety update. In a faxed response dated May 13, 2001, the sponsor provided a breakdown. Thirty-two of 820 gabapentin-treated patients had SAEs. Of the 35 narratives for patients assigned to receive gabapentin, two patients had events during baseline before study drug was begun. They are counted in the table under Gabapentin, but their narratives report study drug as "none". Four patients with SAEs during the open label phase of Study 945-224 have Gabapentin in the header of the narratives but were not counted in Table 18 under gabapentin. One patient with a narrative that references gabapentin, was actually off study drug following study termination when the event occurred and so was not included in Table 18.

Of the 35 narratives for gabapentin-treated patients, 15 patients were enrolled in the PHN trials, 16 in the diabetic neuropathy trials, and 4 in the mixed neuropathy trial. Among the PHN trials, out of a total of 336 gabapentin-treated patients, the 15 patients with SAEs result in an incidence of 4.5%, nearly twice as many as among the placebo treated patients.

All of the narratives of SAEs were reviewed and Table 7.14 below lists all of the SAEs. In the 5 controlled neuropathy trials, there was one occurrence of a SAE for which gabapentin may have played a contributory role. Patient 211\_014246 was a 76 year old woman with PHN at the time of the study. The patient experienced increasing edema in her legs and cellulitis following 27 days of treatment. Dose at onset was 1800 mg/day. The patient responded to diuretic and intravenous antibiotic treatment and remained in the study. Gabapentin is known to cause peripheral edema in some patients. That this

patient remained in the study subsequent to treatment of the SAE suggests that the investigator did not attribute causality, but does not exclude the possibility of a contributory effect by gabapentin.

The one additional SAE added to the 5 controlled trials was Patient 210\_006001. This patient had experienced chest pain, initially reported as an AE. The sponsor reports that a site audit revealed that this chest pain required hospitalization, so the event was reclassified as an SAE.

There were 27 SAEs from the open-label studies, ongoing trials, and non-neuropathic pain trials. Among the in the ongoing studies, Patient 271\_011,5019, a 69 year old man with post-surgical neuralgia, developed angioedema on Day 6. The symptoms of edema of eyelids, eye area, and tongue, paresthesia and palpitations lasted 2 to 3 hours. The study drug was discontinued. It is unknown whether the patient received gabapentin 2400 mg/day or placebo. As the patient was on no concomitant medication, it is possible this reaction was due to study drug, likely gabapentin.

Patient 271\_042,5158, a 34 year old woman with post-traumatic neuralgia of the ulnar nerve and a history of chronic myeloid leukemia developed blurred vision in her right eye on Day 12. Neurological exam, labs, Ophthalmological exam, MRI and lumbar puncture were all normal except for a pleocytosis of mononuclear cells in the CSF. The study blind was broken, the patient had been receiving gabapentin 2400 mg/d, which was discontinued on Day 16. The event had not resolved at the time of the report. It is possible that gabapentin had a contributory role in this event.

Patient 411\_001018, a 36 year old woman with diabetic neuropathy, intentionally overdosed in a suicide attempt. She ingested 4500 mg of gabapentin and developed somnolence. Attempts to empty her stomach were unsuccessful and the patient recovered the following day. The somnolence was attributed to the gabapentin.

Patient 007013 from combination study 1032-002, was a 74 year old man with osteoarthritis of the knee, who developed a duodenal ulcer which hemorrhaged on two occasions requiring hospitalization. The patient had received gabapentin in combination with naproxen. The investigator and sponsor have designated this event as related to study medication, but it is the naproxen, and not the gabapentin, that is believed to have played a contributory role.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 7.14 Summary of Nonfatal Serious Adverse Events, All Studies, from 120-day Update

	5 Pivotal Original Controlled Studies		945-224 OL, 945-411, & Ongoing Studies	Ongoing Studies	GBP Combo Studies
	Number (%) of Patients		Number of Patients		
<b>Body System</b>	Placebo N = 537	GBP N = 820	GBP	Blinded	GBP/ NPN
<b>Preferred Term</b>					
<b>Body as a Whole</b>	<b>4 (0.7)</b>	<b>13 (1.6)<sup>a</sup></b>			
Accidental Injury	2 (0.4)	4 (0.5)	1		x <sup>b</sup>
Cellulitis	0 (0.0)	2 (0.2)	1		
Chest Pain <sup>a</sup>	1 (0.2)	3 (0.4) <sup>a</sup>	1		
Abscess	0 (0.0)	1 (0.1)			1
Back Pain	0 (0.0)	1 (0.1)	1		
Fever	0 (0.0)	1 (0.1)		1	
Infection	0 (0.0)	1 (0.1)			1 <sup>c</sup>
Abdominal Pain	1 (0.2)	0 (0.0)		1	
Asthenia	1 (0.2)	0 (0.0)			
Headache	0 (0.0)	0 (0.0)	1		
Intentional Overdose	0 (0.0)	0 (0.0)	1		
Lymphoma-Like Reaction	0 (0.0)	0 (0.0)	1		
Suicide Attempt	0 (0.0)	0 (0.0)	1		
Pelvic Pain	0 (0.0)	0 (0.0)			1
<b>Cardiovascular System</b>	<b>8 (1.5)</b>	<b>9 (1.1)</b>			
Myocardial Infarct	1 (0.2)	2 (0.2)			
Syncope	2 (0.4)	2 (0.2)	1		
Cardiovascular Disorder	0 (0.0)	1 (0.1)			
Cerebrovascular Accident	1 (0.2)	1 (0.1)	1		
Congestive Heart Failure	0 (0.0)	1 (0.1)			
Hypertension	0 (0.0)	1 (0.1)			
Retinal Vein Thrombosis	0 (0.0)	1 (0.1)			
Angina Pectoris	1 (0.2)	0 (0.0)	1		
Heart Failure	1 (0.2)	0 (0.0)			
Myocardial Ischemia	1 (0.2)	0 (0.0)			
Thrombosis	1 (0.2)	0 (0.0)			
Peripheral Vascular Disorder	0 (0.0)	0 (0.0)		1	1
Angioedema	0 (0.0)	0 (0.0)		1	
<b>Digestive System</b>	<b>2 (0.4)</b>	<b>3 (0.4)</b>			
Nausea	0 (0.0)	2 (0.2)			
Vomiting	1 (0.2)	2 (0.2)			
Cholecystitis	0 (0.0)	1 (0.1)			
Cholelithiasis	0 (0.0)	1 (0.1)			
GGT Increased	0 (0.0)	1 (0.1)			
Gastrointestinal Disorder	0 (0.0)	1 (0.1)			
Intestinal Obstruction	0 (0.0)	1 (0.1)			
Malabsorption Syndrome	1 (0.2)	0 (0.0)			
Pancreatitis	1 (0.2)	0 (0.0)			
Stomach Atony	1 (0.2)	0 (0.0)			
Duodenal Ulcer	0 (0.0)	0 (0.0)			1
<b>Hemic &amp; Lymphatic System</b>	<b>0 (0.0)</b>	<b>1 (0.1)</b>			
CLL	0 (0.0)	1 (0.1)			
<b>Metabolic, Nutritional Dis</b>	<b>0 (0.0)</b>	<b>1 (0.1)</b>			

Table 7.14 continues

Table 7.14 continued

<u>Body System</u> Preferred Term	Number (%) of Patients		Number of Patients		
	Placebo N = 537	GBP N = 820	GBP	Blinded	GBP/ NPN
Alk Phos Increased	0 (0.0)	1 (0.1)			
Ketosis	0 (0.0)	0 (0.0)	1		
<b>Musculoskeletal System</b>	<b>1 (0.2)</b>	<b>2 (0.2)</b>			
Arthritis	0 (0.0)	1 (0.1)			
Myasthenia	0 (0.0)	1 (0.1)			
Arthrosis	1 (0.2)	0 (0.0)	1		
Bone Neoplasm	0 (0.0)	0 (0.0)		1	
<b>Nervous System</b>	<b>3 (0.6)</b>	<b>1 (0.1)</b>			
Vertigo	0 (0.0)	1 (0.1)			
Depression	2 (0.4)	0 (0.0)			
Dizziness	1 (0.2)	0 (0.0)			
Somnolence	0 (0.0)	0 (0.0)	1		
Subarachnoid Hemorrhage	0 (0.0)	0 (0.0)			
<b>Respiratory System</b>	<b>2 (0.4)</b>	<b>5 (0.6)</b>			
Pneumonia	0 (0.0)	3 (0.4)			1
Dyspnea	0 (0.0)	1 (0.1)			
Hemoptysis	0 (0.0)	1 (0.1)		1	
Asthma	1 (0.2)	0 (0.0)			
Carcinoma of Lung	1 (0.2)	0 (0.0)			
Sinusitis	0 (0.0)	0 (0.0)	1		
Cough	0 (0.0)	0 (0.0)		1	
<b>Skin and Appendages</b>	<b>0 (0.0)</b>	<b>3 (0.4)</b>			
Maculopapular Rash	0 (0.0)	1 (0.1)			
Skin Carcinoma	0 (0.0)	1 (0.1)			
Skin Ulcer	0 (0.0)	1 (0.1)			
<b>Special Senses</b>	<b>0 (0.0)</b>	<b>0 (0.0)</b>			
Otitis Media	0 (0.0)	0 (0.0)	1		
Abnormal Vision	0 (0.0)	0 (0.0)	1		
<b>Not Yet Mapped</b>					
probable brain infarction				1	
depressed breathing				1	
consciousness decreased				1	
opiate withdrawal syndrome				1	
bilateral hands rigidity, numbness				1	
loss of proprioception				1	
bilat. foot weakness, paresthesia				1	
degenerative joint disease				1	

GBP = gabapentin; NPN = naproxen sodium

a Includes chest pain newly classified as serious due to hospitalization as reported in SU1.

b X = 1 patient in a combination therapy study had an accidental injury while receiving placebo.

c Updated preferred term

Source: Table 7, p. 15, Vol. 1, 12-06-01

### Summary

While SAEs were more common among gabapentin-treated patients, than placebo-treated patients, there were few serious adverse events for which a contributory role could be assigned to gabapentin. In the neuropathic pain studies, gabapentin may have played a role in one case of peripheral edema with cellulitis, and likely contributed to the somnolence seen following an intentional overdose. It is unknown if gabapentin

contributed to blurred vision in one patient. The angioedema that occurred in a patient in an ongoing study which has not yet been unblinded, is likely due to study drug in the absence of concomitant medications and one would suspect that the patient had received active drug, gabapentin. The duodenal ulcer and hemorrhage in one patient in a non-neuropathic pain study were likely related to the naproxen that was combined with the gabapentin.

### **SECTION 7.3.3 Discontinuations Due to Adverse Events**

The sponsor provided a table describing discontinuations due to adverse events in the original ISS with an update for study 411 and ongoing studies in the 120-day update submitted on 12-06-01, but failed to integrate the two submissions. The discontinuations due to adverse events described in this section represent those events occurring from all of the studies submitted in support of safety in this application.

Table 7.15 depicts the AEs leading to discontinuation that occurred in at least 5 patients during the 5 clinical neuropathy studies. The table represents the data found in sponsor's Table 21 (P. 56, Vol. 1.52, Original ISS 08-06-01), modified with seven additional events detected in DATASET AELISTP (11-30-01). According to the sponsor, these seven patients had their events during the open-label phase of study 945-295, and so were not counted among the double-blind studies.

In the original five completed neuropathy studies, there were 173 patients who discontinued study participation due to adverse events, 113 (13.8%) of these patients were treated with gabapentin and 60 (11.7%) with placebo. Those adverse events occurring in more than one patient in either treatment group are presented in Table. The full listing of AEs leading to study discontinuation are presented in Appendix A.

Among the most frequent AEs leading to study discontinuation were nausea, somnolence and dizziness, although nausea was comparable in both placebo and gabapentin treated patients. Headache and dyspepsia were more common among the placebo-treated patients.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 7.15 Adverse Events Leading to Discontinuation in at Least 5 Patients, Original Five Completed Neuropathy Studies .

Body System Preferred Term	Placebo N = 537	Any GBP N = 820
Number of Patients Withdrawn Due to AEs	60 (11.7)	113 (13.8)
Body as a Whole	16 (3.0)	24 (2.9)
Asthenia	2 (0.4)	6 (0.7)
Accidental injury	2 (0.4)	4 (0.5)
Pain	2 (0.4)	5 (0.6)
Headache	5 (0.9)	1 (0.1)
Cardiovascular System	5 (0.9)	5 (0.6)
Digestive System	21 (3.9)	25 (3.0)
Nausea	6 (1.1)	12 (1.3)
Diarrhea	5 (0.9)	6 (0.7)
Vomiting	1 (0.2)	6 (0.7)
Gastrointestinal disorder	2 (0.4)	3 (0.4)
Flatulence	3 (0.6)	2 (0.2)
Dyspepsia	5 (0.9)	1 (0.1)
Metabolic and Nutritional Disorders	3 (0.6)	4 (0.5)
Peripheral edema	3 (0.6)	2 (0.2)
Musculoskeletal System	3 (0.6)	4 (0.5)
Nervous System	22 (4.1)	73 (8.9)
Dizziness	7 (1.3)	36 (4.4)
Somnolence	6 (1.1)	26 (3.2)
Thinking abnormal	0 (0.0)	5 (0.6)
Depression	4 (0.7)	3 (0.4)
Skin and Appendages	3 (0.6)	3 (0.4)
Special Senses	2 (0.4)	5 (0.6)
Amblyopia	1 (0.2)	4 (0.5)

1. Includes withdrawals due to non-TESS and TESS adverse events; 3 placebo-treated patients (constipation, dyspepsia, flatulence; dyspepsia; diarrhea), and 4 gabapentin-treated patients (twitching, accidental injury, depression, and hyperglycemia) withdrew due to non-TESS adverse events.
2. Numbers in italics include one additional report found in dataset AELISTP, not previously reported by the sponsor.

Source: Table 21, P. 56, Vol. 1.52, Original ISS 08-06-01 Dataset AELISTP, 11-30-01

Among the open label study 945-411, the three ongoing blinded studies, and the eight combination studies, there were 69 patients who discontinued due to AEs in the original ISS, and an additional 12 patients in the 120-day safety update for a total of 81. The AEs leading to these discontinuations are summarized in Table 7.16 by study drug. Many patients had multiple complaints. Dizziness, somnolence, and dyspepsia were the most common among patients treated with gabapentin alone or with naproxen.

APPEARS THIS WAY  
ON ORIGINAL

Table 7.16 AEs Leading to Study Discontinuation, Open Label Study 945-411, Ongoing Blinded Studies, and Combination Studies

	GBP/NPN	GBP	NPN	Placebo	GBP/HC or HC	Blinded
Abnormal Stools	1					
Angioedema						1
Aggressiveness						1
Amblyopia/ Diplopia	1	1				2
Amnesia						1
Anemia	1					
Anorexia	1					
Asthenia/ Malaise	2					5
Ataxia						1
Cardiac arrest						1
Cellulitis		1				
Consciousness decreased						1
Constipation				1		
Cutaneous allergy/ rash/ itching	1	1		1		2
Degen. Joint Disease						1
Diarrhea	2	1				
Dizziness	1	4				4
Duodenal Ulcer/ Gastric ulcer	2					
Dysarthria						1
Elevated LFTs/	1		1			
Epigastric / Abdominal pain	1	1				
Epistaxis	1	1				
Extrem. paresthesia, weakness						2
Falling down						1
Flatulence				1		
Flu-like symptoms/fever		2			6	2
GI disorder (GERD)/dyspepsia	5					1
Headache/Migraine	2	1	1	1		1
Hypotension						1
Interaction with opioids		1				
Liver failure						1
Memory disturbance						1
Metrorrhagia/abdominal pain			2			
Nausea	1	1				2
Neoplasm						2
Opiate withdrawal						1
Pain (Knee, Back)	3	1				
Peripheral edema	4	3				
Pneumonia	1					
PVD						1
Pyuria	1					
Respiratory depression						1
Somnolence	4	4				1
Suicide attempt/ intentional OD		2				
Tremor		1				1
Urinary incontinence						1
Varicose Vein		1				
Vertigo		1				1
Vomiting	1		1			1

Worsened Neurop/ Neuralgia		1				2
----------------------------	--	---	--	--	--	---

Source: Appendix B.4.2, P. 318, and B4.3, P. 320, Vol. 1.52 Original ISS, Appendix B.3.3, P. 68 Vol. 1, 120-day Safety Update,12-6-01

Review of the patients narratives from all of the clinical trials revealed that the investigators often attributed the adverse event leading to study discontinuation to study drug. This was particularly true of dizziness, nausea, and somnolence. Exceptions included neuropathy and numbness which were more likely related to the underlying neuropathy resulting in study eligibility. Pyuria, infection, pneumonia, back or knee pain were also unlikely to be attributed to study medication. Several patients on gabapentin and naproxen or naproxen alone had abdominal pain or dyspepsia likely related to the use of the naproxen.

#### **SECTION 7.3.4 Adverse Events**

Adverse events were fairly common during the clinical trials. Among all patients in the neuropathic pain trials, 67% experienced at least one adverse event, compared to 57% of placebo-treated patients. AEs were a little more common among patients with PHN, 72%. Table 7.17 highlights adverse events that were either more common among gabapentin-treated or placebo-treated patients. A full listing of AEs from the neuropathic pain studies is presented in Appendix B.

Among the entire neuropathic pain study population, the most common AEs occurred much more frequently among the gabapentin-treated patients, dizziness (21% gabapentin group vs. 7% placebo group) and somnolence (16% gabapentin group vs. 5% placebo group). These AEs demonstrated a sensitivity to dose, increasing from the 1200 mg/day dose group to the 1800 mg/day dose group, but similarly among the 1800 mg/d, 2400 mg/day and 3600mg/day groups. Peripheral edema and dry mouth were more common among the gabapentin group (5.5% and 3.3%, respectively) compared to placebo (3.0% and 0.9%, respectively).

**APPEARS THIS WAY  
ON ORIGINAL**

Table 7.17. Treatment Emergent Adverse Events in  $\geq 1\%$  of patients, Original Five Completed Neuropathy Studies

	Gabapentin dose, mg/day										All Neuropathy GPN N=820		All PHN GPN N=336		All Neuropathy Placebo N=537	
	600 mg/d N=82		1200 N=82		1800 N=115		2400 N=344		3600 N=197		n	%	n	%	n	%
Patients with AEs	40	48.8	35	42.7	80	69.6	237	68.9	154	78.2	546	66.6	242	72.0	306	57.0
Total # of AEs											1410		601		679	
AEs/patient											1.7		1.9		1.3	
Dizziness	7	8.5	4	4.9	33	28.7	77	22.4	47	23.9	168	20.5	95	28.3	35	6.5
Somnolence	4	4.9	3	3.7	20	17.4	54	15.7	51	25.9	132	16.1	72	21.4	26	4.8
Headache	7	8.5	2	2.4	2	2.4	20	5.8	15	7.6	46	5.6	11	3.3	32	6.0
Diarrhea	2	2.4	3	3.7	8	7.0	19	5.5	15	7.6	47	5.7	19	5.7	26	4.8
Infection	2	2.4	4	4.9	4	3.5	21	6.1	15	7.6	46	5.6	17	5.1	45	8.4
Peripheral edema	4	4.9	1	1.2	5	4.3	18	5.2	15	7.6	43	5.2	28	8.3	15	2.8
Asthenia	5	6.1	4	4.9	6	5.2	15	4.4	11	5.6	41	5.0	19	5.7	24	4.5
Acc. injury	3	3.7	2	2.4	1	0.9	18	5.2	4	2.0	28	3.4	11	3.3	17	3.2
Pain	2	2.4	4	4.9	6	5.2	11	3.2	3	1.5	26	3.2	9	2.7	30	5.6
Dry mouth	1	1.2	1	1.2	7	6.1	9	2.6	9	4.6	27	3.3	16	4.8	5	0.9
Abdominal pain	2	2.4	0	0.0	3	2.6	14	4.1	4	2.0	23	2.8	9	2.7	18	3.4
Constipation	4	4.9	0	0.0	4	3.5	6	1.7	6	3.0	20	2.4	13	3.9	9	1.7
Back pain	0	0.0	2	2.4	1	0.9	8	2.3	7	3.6	18	2.2	4	1.2	8	1.5
Ataxia	1	1.2	1	1.2	1	0.9	4	1.2	12	6.1	19	2.3	11	3.3	0	0.0
Weight gain	3	3.7	1	1.2	4	3.5	6	1.7	1	0.5	15	1.8	6	1.8	0	0.0
Amblyopia	0	0.0	0	0.0	3	2.6	8	2.3	4	2.0	15	1.8	9	2.7	2	0.4
Flatulence	2	2.4	0	0.0	1	0.9	3	0.9	9	4.6	15	1.8	7	2.1	6	1.1
Amnesia	1	1.2	0	0.0	1	0.9	11	3.2	1	0.5	14	1.7	4	1.2	3	0.6
Thinking abnormal	0	0.0	0	0.0	4	3.5	4	1.2	6	3.0	14	1.7	9	2.7	0	0.0
Confusion	0	0.0	1	1.2	1	0.9	4	1.2	8	4.1	14	1.7	3	0.9	4	0.7
Rash	2	2.4	1	1.2	1	0.9	9	2.6	1	0.5	14	1.7	4	1.2	4	0.7
Abnormal gait	0	0.0	0	0.0	2	1.7	8	2.3	1	0.5	11	1.3	5	1.5	0	0.0
Hypesthesia	0	0.0	0	0.0	1	0.9	5	1.5	5	2.5	11	1.3	4	1.2	4	0.7
Depression	0	0.0	1	1.2	0	0.0	7	2.0	3	1.5	11	1.3	2	0.6	12	2.2
Dyspnea	1	1.2	0	0.0	2	1.7	4	1.2	2	1.0	9	1.1	4	1.2	3	0.6
Hyperglycemia	1	1.2	1	1.2	0	0.0	3	0.9	4	2.0	9	1.1	4	1.2	2	0.4
Vertigo	1	1.2	2	2.4	0	0.0	3	0.9	3	1.5	9	1.1	1	0.3	2	0.4

Source: Table 7, P. 24, Vol. 1.52, Source: Database: aelistp.xpt, 11-30-01

Among the PHN studies, the AEs occurring in at least 1% of any treatment group are presented in Table 7.18. The full AE table is present in Addendum. The most common AEs experienced during these clinical trials were dizziness, somnolence, peripheral edema, asthenia, diarrhea, and infection which all occurred in more than 5% of gabapentin-treated patients.

There was a small increase in the overall incidence in adverse events based on treatment group assignment, with 69.6% of patients in the 1800 mg/day group, 72.2% of patients in the 2400 mg/day group, and 74.3% of patients in the 3600 mg/day group experiencing

adverse events. (Table 7, P. 25, Vol. 3, 12-20-01) While the placebo and 1800 mg/day groups had a similar number of AEs per patient, this increased across the 2400 mg/day and 3600 mg/day treatment groups.

As highlighted in Table 7.18, dizziness, somnolence, and peripheral edema were the three most common AEs, and were much more common among the gabapentin treated patients than placebo. Dry mouth, accidental injury, ataxia, amblyopia (referring to blurred vision), thinking abnormal, abnormal gait, and incoordination were all more common among the gabapentin treated patients. Pain, depression, and anorexia were more common among the placebo-treated patients.

Table 7.18 Treatment Emergent Adverse Events in  $\geq 1\%$  of Any Treatment Group, PHN Studies

	Gabapentin, mg/day									
	Placebo N=227		1800 N=115		2400 N=108		3600 N=113		All Gabapentin N=336	
No of AEs	245		167		181		253		601	
No of pts with AE	113	49.8%	80	69.6%	78	72.2%	84	74.3%	242	72.0%
No of AEs/pt	2.17		2.09		2.32		3.01		2.5	
	N	%	N	%	N	%	N	%	N	%
<b>Dizziness</b>	17	7.5	33	28.7	35	32.4	27	23.9	95	28.3
<b>Somnolence</b>	12	5.3	20	17.4	21	19.0	31	27.4	72	21.4
<b>Peripheral edema</b>	6	2.6	5	4.4	12	11.1	11	9.7	28	8.3
Asthenia	11	4.9	6	5.2	6	5.6	7	6.2	19	5.7
Diarrhea	7	3.1	8	7.0	5	4.6	6	5.3	19	5.7
Infection	8	3.5	3	2.6	5	4.6	9	8.0	17	5.1
<b>Dry mouth</b>	3	1.3	7	6.1	5	4.6	4	3.5	16	4.8
Constipation	4	1.8	4	3.5	4	3.7	5	4.4	13	3.9
Nausea	7	3.1	1	0.9	6	5.6	6	5.3	13	3.9
<b>Accidental injury</b>	2	0.9	1	0.9	7	6.5	3	2.7	11	3.3
<b>Ataxia</b>	0	0.0	1	0.9	2	1.9	8	7.1	11	3.3
Headache	7	3.1	2	1.7	4	3.7	5	4.4	11	3.3
Vomiting	4	1.8	4	3.5	3	2.8	4	3.5	11	3.3
Abdominal pain	6	2.6	3	2.6	3	2.8	3	2.7	9	2.7
<b>Amblyopia</b>	2	0.9	3	2.6	3	2.8	3	2.7	9	2.7
Pain	12	5.3	6	5.2	2	1.9	1	0.9	9	2.7
<b>Thinking abnormal</b>	0	0.0	4	3.5	2	1.9	3	2.7	9	2.7
Flatulence	4	1.8	1	0.9	0	0.0	6	5.3	7	2.1
Tremor	4	1.8	2	1.7	3	2.8	1	0.9	6	1.8
<b>Weight gain</b>	0	0.0	4	3.5	1	0.9	1	0.9	6	1.8
<b>Abnormal gait</b>	0	0.0	2	1.7	2	1.9	1	0.9	5	1.5
<b>Incoordination</b>	0	0.0	2	1.7	0	0.0	3	2.7	5	1.5
Neuralgia	4	1.8	0	0.0	1	0.9	4	3.5	5	1.5
Amnesia	2	0.9	1	0.9	3	2.8	0	0.0	4	1.2
Back pain	6	2.6	1	0.9	1	0.9	2	1.8	4	1.2
Conjunctivitis	0	0.0	1	0.9	1	0.9	2	1.8	4	1.2

Table 7.18 continues

Table 7.19. Dose at Onset for AEs Occurring in > 2% of Gabapentin-Treated Patients in 2 Pivotal Studies of PHN, Number (%) of Patients (ITT)

Adverse Event	Any GBP N=336 N (%)	Gabapentin Dosage Range (mg/day)						Unknown N (%)
		0 N (%)	1 to 600 N (%)	601 to 1200 N (%)	1201 to 1800 N (%)	1801 to 2400 N (%)	2401 to 3600 N (%)	
Dizziness	94 (28.0)	0 (0.0)	34 (36.2)	28 (29.8)	21 (22.3)	7 (7.4)	4 (4.3)	0 (0.0)
Somnolence	72 (21.4)	0 (0.0)	29 (40.3)	17 (23.6)	17 (23.6)	3 (4.2)	6 (8.3)	0 (0.0)
Peripheral Edema	28 (8.3)	0 (0.0)	1 (3.6)	3 (10.7)	9 (32.1)	10 (35.7)	5 (17.9)	0 (0.0)
Asthenia	19 (5.7)	0 (0.0)	6 (31.6)	4 (21.1)	5 (26.3)	2 (10.5)	1 (5.3)	1 (5.3)
Diarrhea	19 (5.7)	2 (10.5)	0 (0.0)	5 (26.3)	6 (31.6)	1 (5.3)	5 (26.3)	0 (0.0)
Infection	17 (5.1)	1 (5.9)	2 (11.8)	2 (11.8)	3 (17.6)	3 (17.6)	6 (35.3)	0 (0.0)
Dry mouth	16 (4.8)	0 (0.0)	3 (18.8)	3 (18.8)	7 (43.8)	2 (12.5)	0 (0.0)	1 (6.3)
Constipation	13 (3.9)	0 (0.0)	2 (15.4)	8 (61.5)	1 (7.7)	1 (7.7)	0 (0.0)	1 (7.7)
Nausea	13 (3.9)	0 (0.0)	7 (53.8)	2 (15.4)	1 (7.7)	0 (0.0)	3 (23.1)	0 (0.0)
Vomiting	11 (3.3)	1 (11.1)	2 (18.2)	3 (27.3)	1 (9.1)	1 (9.1)	3 (27.3)	0 (0.0)
Accidental Injury	11 (3.3)	1 (9.1)	0 (0.0)	1 (9.1)	5 (45.5)	4 (36.4)	0 (0.0)	0 (0.0)
Ataxia	11 (3.3)	0 (0.0)	6 (54.5)	1 (9.1)	3 (27.3)	0 (0.0)	1 (9.1)	0 (0.0)
Headache	11 (3.3)	0 (0.0)	1 (9.1)	2 (18.2)	3 (27.3)	3 (27.3)	2 (18.2)	0 (0.0)
Abdominal Pain	9 (2.7)	0 (0.0)	1 (11.1)	4 (44.4)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)
Amblyopia	9 (2.7)	0 (0.0)	3 (33.3)	2 (22.2)	3 (33.3)	1 (11.1)	0 (0.0)	0 (0.0)
Pain	9 (2.7)	1 (11.1)	0 (0.0)	0 (0.0)	5 (55.6)	3 (33.3)	0 (0.0)	0 (0.0)
Thinking Abnormal	9 (2.7)	0 (0.0)	3 (33.3)	0 (0.0)	5 (55.6)	0 (0.0)	1 (11.1)	0 (0.0)
Flatulence	7 (2.1)	0 (0.0)	0 (0.0)	3 (42.9)	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)

Source Table 12, P. 36, Vol. 3, 12-20-01

#### Clinical Pharmacology Studies

Thirteen of 14 healthy volunteers in study 945-190 experienced total of 172 treatment emergent adverse events. Twelve of 18 healthy volunteers in Study 1032-015 experienced 28 treatment emergent adverse events. The most common events were dizziness, somnolence and dry mouth. A table listing all of the AEs occurring in at least 2 patients is provided in Appendix C. There were no unexpected or serious adverse events during these studies.

#### Comparison with Epilepsy Trials

The sponsor provided two tables to compare the more common treatment emergent adverse events occurring during the original five completed neuropathy trials and epilepsy add-on trials. The two tables were merged below into Table 7.20. The two populations differed, in age and treatment. The epilepsy patients averaged 34 years of age and were treated with dosages up to 1800 mg/day compared with the neuropathic pain patients who averaged 634 years of age and dosages up to 3600 mg/day. The adverse events that occurred during the neuropathic pain trials were consistent with what is known about gabapentin from the add-on studies in epilepsy. The epilepsy patients had more ataxia, nystagmus, fatigue, somnolence, tremor, but this may have been related to the fact that the gabapentin was added to a regimen of other anticonvulsants that are as a group, known to cause these adverse events.

Table 7.20 Percent of Treatment Emergent AEs in  $\geq 3\%$  of Patients, Neuropathy and Epilepsy Add-on Studies

	All Neuropathy GPN N=820	PHN GPN N=336	Neuropathy Placebo N=537	Epilepsy GPN (N=543%)	Epilepsy Placebo (N=378)
Abdominal pain	3.0	2.7	3.9		
Abnormal gait	1.3	1.5	0.0		
Acc. injury	3.9	3.3	3.2	1.3	0.0
Amblyopia	1.8	2.7	0.4	4.2	1.1
Amnesia	1.8	1.2	0.6	2.2	0
Asthenia/fatigue	5.2	5.7	4.7	11.0	5.0
Ataxia	2.3	3.3	0.0	12.5	5.6
Back pain	2.4	1.2	1.7	1.8	0.5
Confusion	1.7	0.9	0.7		
Conjunctivitis	0.9	1.2	0.0		
Constipation	2.6	3.9	1.9	1.5	0.8
Cough increased	0.9	0.9	1.1	1.8	1.3
Depression	1.3	0.6	2.2	1.8	1.1
Diarrhea	5.9	5.7	4.8		
Diplopia	0.7	1.2	0.2	5.9	1.9
Dizziness	21.3	28.3	7.1	17.1	6.9
Dry mouth	3.3	4.8	0.9	1.7	0.5
Dyspepsia	2.1	1.2	2.2		
Dyspnea	1.1	1.2	0.6		
Flatulence	1.8	2.1	1.3		
Flu syndrome	2.8	1.2	3.0		
Headache	6.1	3.3	6.7		
Hyperglycemia	1.1	1.2	0.4		
Hypesthesia	1.3	1.2	0.7		
Impotence	0.4	0.3	0.0	1.5	1.1
Incoordination	0.9	1.5	0.0	1.1	0.3
Increased appetite	0.7	0.6	0.2	1.1	0.8
Infection	5.6	5.1	8.4		
Leukopenia				1.1	0.5
Myalgia	0.7	0.6	0.4	2.0	1.9
Nausea	5.6	3.9	5.6		
Nervousness	0.9	0.3	0.6	2.4	1.9
Nystagmus	0.4	0.9	0.0	8.3	4.0
Otitis media	1.0	1.2	0.7		
Pain	3.7	2.7	6.5		
Peripheral edema	5.5	8.3	3.0	1.7	0.5
Pharyngitis	2.2	1.2	1.9	2.8	1.6
Pruritus	0.5	0.9	1.5	1.3	0.5
Rash	1.7	1.2	0.7		
Rhinitis	0.9	0.6	0.7	4.1	3.7
Somnolence	16.3	21.4	5.4	19.3	8.7
Thinking abnormal	1.7	2.7	0.0	1.7	1.3
Tooth disorder	0.4	0.6	0.2	1.5	0.3
Tremor	1.1	1.8	1.1	6.8	3.2
Vasodilatation	0.2	0.3	0.2	1.1	0.3
Vertigo	1.1	0.3	0.4		
Vomiting	2.1	3.3	2.6		
Weight gain	1.8	1.8	0.0	2.9	1.6

### **SECTION 7.3.5 Vital Signs and Labs**

#### **Vital Signs**

Blood pressure and heart rate were measured in 4 of 5 neuropathic pain studies. The sponsor notes that there were no clinically important effects of gabapentin on these parameters. No data was provided for review in the ISS. Vital sign data were reviewed from the individual study reports. No clinically meaningful trends or changes were noted.

#### **Labs**

Clinical laboratory parameters were only collected during Study 945-211. There were eight patients with lab abnormalities recorded as clinically significant changes from baseline. Five of these patients were gabapentin-treated, three placebo-treated. The abnormalities are listed below.

Table 7.21 Clinically Significant Laboratory Abnormalities, Study 945-211

	Placebo	Gabapentin
Glucose Elevated	1	1
BUN Elevated	1	
AST/ALT Elevated	1	1
Hematocrit Decreased		1
LDH Elevated		1
GGT and Alk. Phos. elevated		1

**APPEARS THIS WAY  
ON ORIGINAL**

## SECTION 8 GABAPENTIN DOSING

The two pivotal clinical trials, Study 945-211 and Study 945-295 evaluated were designed with different treatment arms. Study 945-211 titrated patients to 3600 mg/day. Study 945-295 titrated patients to either 1800 mg/day or 2400 mg/day. While both studies demonstrated efficacy as gabapentin treated patients having statistically significantly greater pain reduction at study completion compared to placebo treated patients, the lack of replicated dosing arms in the two studies leaves the open the question of whether adequate replication of the effective dose was demonstrated. Two approaches have been reviewed to determine if there is adequate data from the two pivotal trials to determine if there is adequate information to describe appropriate dosing of gabapentin for neuropathy associated with PHN.

First, an attempt was made to glean information from the titration period of Study 945-211 to replicate the 1800 mg/day and 2400 mg/day doses. Theoretically, had the titration schedule been followed very closely, all subjects in the active treatment arm would have been titrated to 1800 mg/day by Day 13 and 2400 mg/day by Day 20 and on these doses or close to a week. The sponsor reports that this approach contributes to the finding of a dose response. However, a review of the duration of time patients were on these doses revealed that this duration was very variable between patients, and that the median duration at these titration points was 2 days for both treatment arms. Furthermore few patients were on these doses for more than 2-4 days. The variability in duration on each titration step between patients means the effects of different doses could not be reliably determined by looking at efficacy results from Day 13 or Day 20. Across the study, patients would be on many different doses at these specific timepoints. The effects of gabapentin is believed to require from several days to weeks to fully manifest. The duration of time on the intermediate doses during the titration period was too brief to provide meaningful data reflective of the effects of those doses on pain.

Second, the size of the treatment effect was examined in both studies. The absolute pain scores from the End of Study are so similar across the studies for all gabapentin treated groups as to suggest comparable efficacy of the three doses of gabapentin that were studies. This needs to be viewed in the context of a slightly greater placebo effect in study 945-295. This difference in placebo effect was taken into account in the modeling of simulation expectations performed by the Biopharmaceutics reviewer. The reader is referred to the detailed discussion of this analysis and a full description of the methods in the Biopharmaceutics review.

Table 8.1

Statistics	Study 945-211		Study 945-295		
	Placebo N=116	Gabapentin 3600 mg N=109	Placebo N=111	Gabapentin 1800 mg N=115	Gabapentin 2400 mg N=108
Average Weekly Diary Pain Score, Mean (SD)					
Baseline	6.5 (1.7)	6.3 (1.7)	6.4 (1.6)	6.5 (1.7)	6.5 (1.6)
Week 8 (or last visit)	6.0 (2.4)	4.2 (2.3)	5.3 (2.3) <sup>a</sup>	4.3 (2.5) <sup>a</sup>	4.2 (2.1) <sup>a</sup>
Responder rate (>50% change)	12%	31%	14%	32%	34%

The results of a responder analysis from Study 945-295 demonstrated responder rates of 32% for the 1800 mg/day treatment group and 34% for the 2400 mg/day treatment group. The responder rate from the gabapentin treated patients in Study 945-211, was calculated from the efficacy dataset to be 31% for the gabapentin 3600 mg group. Thus the responder rates were similar for all three gabapentin treatment groups.

The findings of quantitatively similar efficacy findings from the two studies supports the efficacy of the 1800 mg/day dose, with little additional benefit from the higher doses. This is further supported by the appearance of pain scores from the gabapentin treated groups separating from placebo during titration, prior to reaching the final titrated doses.

These results demonstrate the efficacy of gabapentin, 1800 mg/day, in the treatment of PHN. Patients should begin titration with a single 300-mg dose on Day 1, 600 mg/day on Day 2 (divided BID), and 900 mg/day on Day 3 (divided TID). Gradual titration should proceed to 1800 mg/day (divided TID). Although an acceptable safety profile has been demonstrated up to a dose of 3600 mg/day, little additional benefit is expected from titration beyond 1800 mg/day.

**APPEARS THIS WAY  
ON ORIGINAL**

## SECTION 9 SPECIAL POPULATIONS

### SECTION 9.1 Summary

There was a larger treatment effect in patients  $\geq 75$  years. This finding is attributed to a greater bioavailability and exposure due to age-related reductions in renal function, although other unidentified factors may also be contributing to this effect.

Adverse events were overall, more frequent among patients over the age of 75. The only individual adverse events that were notably more common in this group were dizziness and peripheral edema. There were no effects of gender on the distribution of adverse events. There was too little racial diversity to evaluate the effects of race on the adverse event profile.

### SECTION 9.2 Integrated Efficacy Analyses - Subgroups

To increase the power of subgroup analyses, the sponsor performed these on a combined group of patients, all of those in the two pivotal neuropathic pain trials (ISE, Vol. 10, 12-20-01). The characteristics of this combined population from Studies 945-211 and 945-295 are presented in Table 7.31.

Table 9.1 Patient Characteristics, ITT Population: 2 Pivotal Studies of PHN

	Gabapentin					All Patients N 563
	Placebo N=227	GBP 1800 mg/day N=115	GBP 2400 mg/day N=108	GBP 3600 mg/day N=113	Any GBP N=316	
Gender, n (%)						
Men	102 (44.9)	46 (40.0)	46 (42.6)	63 (55.8)	155 (46.1)	257 (45.6)
Women	125 (55.1)	69 (60.0)	62 (57.4)	50 (44.2)	181 (53.9)	306 (54.4)
Race, n (%)						
White	109 (48.0)	NA	NA	99 (87.6)	99 (29.5)	208 (36.9)
Black	3 (1.3)	NA	NA	10 (8.8)	10 (3.0)	13 (2.3)
Hispanic	3 (1.3)	NA	NA	2 (1.8)	2 (0.6)	5 (0.9)
Asian/Pacific Islander	1 (0.4)	NA	NA	2 (1.8)	2 (0.6)	3 (0.5)
Not Specified	111 (48.9)	115 (100.0)	108 (100.0)	0 (0.0)	223 (66.4)	334 (59.3)
Age (Years)						
Mean	72.5	72.8	73.7	70.8	72.4	72.4
(SD)	10.7	9.4	10.1	10.5	10.0	10.3
Median	74	74	76	72	74.5	74
Min, Max	28,94	22,88	36,90	36,90	22,90	22,94
Age Categories, n (%)						
18 to 64 Years	45 (19.8)	21 (18.3)	19 (17.6)	26 (23.0)	66 (19.6)	111 (19.7)
65 to 74 Years	70 (30.8)	37 (32.2)	27 (25.0)	38 (33.6)	102 (30.4)	172 (30.6)
75 or greater Years	112 (49.3)	57 (49.6)	62 (57.4)	49 (43.4)	168 (50.0)	280 (49.7)
Baseline Mean Pain Score						
Mean	6.4	6.5	6.5	6.325	6.4	6.4
(SD)	1.7	1.7	1.6	1.667	1.7	1.7
Median	6.3	6.3	6.2	6.429	6.3	6.3
Min, Max						

ITT = Intent-to-Treat; SD = Standard Deviation.

Source: Sponsor's Table 7, P. 28, Vol. 10, 12-20-01

### Age

There was a large proportion of patients in the over 75 age category in the two pivotal studies supporting efficacy, 945-211 and 945-295, 49.9%, reflective of the population afflicted with PHN. Using an ANCOVA model adjusted for study with baseline score as a covariate to evaluate the effects of age on primary efficacy, a greater treatment effect was found for patients  $\geq 75$  years of age. A second ANCOVA model including age, treatment group, protocol, baseline pain, and treatment group-by-age found a statistically significant interaction between age and treatment group ( $p < 0.01$ ). This finding supported a larger treatment effect in patients  $\geq 75$  years. The finding of a greater treatment effect in this population is attributed to a greater bioavailability and exposure due to age-related reductions in renal function.

### Gender

The sponsor evaluated the effects of gender on primary efficacy using an ANCOVA model adjusted for study with baseline score as a covariate. This analysis found efficacy did not differ in a meaningful way across gender groups. A second ANCOVA model including gender, treatment group, protocol, baseline pain, and treatment group-by-gender found no statistically significant interactions between gender and treatment group.

### Race

Data on race was not collected in study 945-295. There was a very small number of non-Caucasian subjects in 945-211, 14, compared with Caucasian patients, 95, limiting the value of statistical comparisons.

## **SECTION 9.3 Safety - Subgroups**

### Age

Patients over the age of 75 were well represented in this safety database. This is due to the demographics of patients with PHN who tend to be older. Nearly half of the patients enrolled in the PHN trials were over 75, and this group represented approximately one quarter of the entire neuropathy population.

Among all of the completed neuropathy trials, dizziness and somnolence were the most common individual AEs, and while notably different from placebo, did not demonstrate a consistent difference across the age groups. Peripheral edema was more common among the over 75 gabapentin treated group compared to the younger gabapentin treated groups and compared to the over 75 placebo group.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 9.2 Adverse Events that Occurred in >\_5%<sup>a</sup> of Patients Number (%) of Patients by Age in Original Five Completed Neuropathy Trials (ITT)

Adverse Event	Placebo			Any Gabapentin		
	18 to 64	65 to 74	>75	18 to 64	65 to 74	≥75
	N=272	N=130	N=135	N=401	N=211	N=208
Dizziness	15 (5.5)	6 (4.6)	14 (10.4)	69 (17.2)*	43 (20.4)*	56 (26.9)*
Somnolence	13 (4.8)	7 (5.4)	6 (4.4)	56 (14.0)*	39 (18.5)*	37 (17.8)*
Peripheral Edema	10 (3.7)	2 (1.5)	3 (2.2)	13 (3.2)	11 (5.2)	19 (9.1)*
Infection	28 (10.3)	6 (4.6)	5 (3.7)	22 (5.5)	2 (0.9)	14 (6.7)
Diarrhea	15 (5.5)	7 (5.4)	2 (1.5)	28 (7.0)	9 (4.3)	10 (4.8)
Nausea	21 (7.7)	4 (3.1)	3 (2.2)	25 (6.2)	10 (4.7)	8 (3.8)
Asthenia	18 (6.6)	1 (0.8)	5 (3.7)	24 (6.0)	9 (4.3)	8 (3.8)
Pain	16 (5.9)	5 (3.8)	9 (6.7)	11 (2.7)	7 (3.3)	8 (3.8)
Headache	27 (9.9)	3 (2.3)	2 (1.5)	35 (8.7)	7 (3.3)	1.9)

a Includes placebo- or gabapentin-treated (any gabapentin) patients in any age group; sorted by gabapentin ≥75 years

\* Statistically significant compared with placebo (odds ratio confidence interval does not include 1 or p <0.05 from Fisher's exact test)

Source: Table 14, P. Vol. 1.52

Among the PHN patients, the findings were similar. Gabapentin-treated patients over 75 years of age had a somewhat greater incidence of adverse events (76%) than those under 75 (68%). This difference in gabapentin-treated patients was more notable given that placebo-treated patients less than 65 experienced more adverse events (60%) than either of the 65-74 and over 75 placebo age groups (44% and 49%, respectively). As with the entire neuropathy population, dizziness and somnolence were the most common individual AEs, although they did not demonstrate a consistent difference across the age groups. Peripheral edema was more common among the over 65 and over 75 gabapentin treated group compared to the younger gabapentin treated group and compared to the over 65 and over 75 placebo groups. Ataxia was also more common in the over 75 gabapentin group. Asthenia, dry mouth, and headache more common in the both placebo and gabapentin-treated patients under 65.

**APPEARS THIS WAY  
ON ORIGINAL**

Table 9.3 AEs in  $\geq 4^a$  of Patients by Age (Years) in PHN Studies, Number (%) of Patients (ITT)

Adverse Event	Placebo			Any Gabapentin		
	18 to 64 N=45	65 to 74 N=70	$\geq 75$ N=112	18 to 64 N=66	65 to 74 N=102	$\geq 75$ N=168
Number of Patients with AEs	27 (60.0)	31 (44.3)	55 (49.1)	45 (68.2)	70 (68.6)	127 (75.6)
Dizziness	3 (6.7)	1 (1.4)	13 (11.6)	22 (33.3)	25 (24.5)	47 (28.0)
Somnolence	1 (2.2)	5 (7.1)	6 (5.4)	11 (16.7)	27 (26.5)	34 (20.2)
Peripheral Edema	1 (2.2)	1 (1.4)	3 (2.7)	1 (1.5)	9 (8.8)	18 (10.7)
Infection	3 (6.7)	2 (2.9)	3 (2.7)	5 (7.6)	1 (1.0)	11 (6.5)
Diarrhea	0 (0.0)	5 (7.1)	2 (1.8)	4 (6.1)	5 (4.9)	10 (6.0)
Constipation	2 (4.4)	0 (0.0)	2 (1.8)	1 (1.5)	4 (3.9)	8 (4.8)
Ataxia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.0)	8 (4.8)
Asthenia	5 (11.1)	1 (1.4)	5 (4.5)	6 (9.1)	6 (5.9)	7 (4.2)
Pain	2 (4.4)	1 (1.4)	9 (8.0)	0 (0.0)	2 (2.0)	7 (4.2)
Vomiting	0 (0.0)	1 (1.4)	3 (2.7)	0 (0.0)	4 (3.9)	7 (4.2)
Dry mouth	2 (4.4)	0 (0.0)	1 (0.9)	6 (9.1)	4 (3.9)	6 (3.6)
Nausea	2 (4.4)	2 (2.9)	3 (2.7)	3 (4.5)	4 (3.9)	6 (3.6)
Amblyopia	0 (0.0)	1 (1.4)	1 (0.9)	3 (4.5)	0 (0.0)	6 (3.6)
Headache	3 (6.7)	2 (2.9)	2 (1.8)	4 (6.1)	3 (2.9)	4 (2.4)
Abdominal Pain	1 (2.2)	1 (1.4)	4 (3.6)	3 (4.5)	2 (2.0)	4 (2.4)
Thinking Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.5)	3 (2.9)	3 (1.8)
Dyspepsia	3 (6.7)	1 (1.4)	2 (1.8)	1 (1.5)	1 (1.0)	2 (1.2)
Flu syndrome	2 (4.4)	0 (0.0)	1 (0.9)	0 (0.0)	2 (2.0)	2 (1.2)
pruritus	0 (0.0)	3 (4.3)	1 (0.9)	1 (1.5)	0 (0.0)	2 (1.2)
Anorexia	2 (4.4)	2 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Arthralgia	2 (4.4)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.6)
Amnesia	2 (4.4)	0 (0.0)	0 (0.0)	1 (1.5)	2 (2.0)	1 (0.6)
Depression	4 (8.9)	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.0)	0 (0.0)
Malaise	2 (4.4)	0 (0.0)	1 (0.9)	1 (1.5)	0 (0.0)	0 (0.0)
Colitis	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a. Includes Placebo- or gabapentin-treated (Any Gabapentin) patients in any age group; sorted by gabapentin  $\geq 75$  years

Source: Table 15, P. 40, Vol. 3, 12-20-01

### Gender

The study population was well distributed across both genders with a nearly 50:50 representation. There were no clinically notable differences in the occurrence of AEs in men and women, although the treatment group differences were maintained in the gender subgroups. This was true for the entire neuropathy population as well as the PHN population.

Table 9.4 Adverse Events that Occurred in >5%<sup>a</sup> of Men or Women in the Original Five Completed Neuropathy Studies, Number (%) of Patients (ITT)

Adverse Event	Placebo		Any Gabapentin	
	Men N=268	Women N=269	Men N=413	Women N=407
Dizziness	17 (6.3)	18 (6.7)	78 (18.9)*	90 (22.1)*
Somnolence	12 (4.5)	14 (5.2)	67 (16.2)*	65 (16.0)*
Headache	13 (4.9)	19 (7.1)	19 (4.6)	27 (6.6)
Peripheral Edema	5 (1.9)	10 (3.7)	16 (3.9)	27 (6.6)
Asthenia	8 (3.0)	16 (5.9)	16 (3.9)	25 (6.1)
Nausea	10 (3.7)	18 (6.7)	20 (4.8)	23 (5.7)
Diarrhea	14 (5.2)	10 (3.7)	27 (6.5)	20 (4.9)
Infection	17 (6.3)	22 (8.2)	22 (5.3)	16 (3.9)
Pain	15 (5.6)	15 (5.6)	16 (3.9)	10 (2.5)

a Includes >5% of placebo- or gabapentin-treated (any gabapentin) men or women

\* Statistically significant compared with placebo (odds ratio confidence interval does not include 1 or p <0.05 from Fisher's exact test)

Source: Table 13, P. Vol. 1.52

#### Race

There were too few non-Caucasian patients for meaningful comparisons of AEs by race.

#### **SECTION 9.4 Pediatric Program**

The sponsor has requested a waiver for studies of gabapentin in PHN in pediatric patients ≤ 17 years of age. The sponsor reports that while PHN occurs with an annual incidence of 12 cases/100,000 population in adults, it is extremely uncommon in the pediatric population. The literature supplied by the sponsor supports this contention. According to one article cited, the incidence of PHN at one year after an acute eruption of herpes zoster was 4.2% in those less than 20 years old. Children comprised only 5-8% of cases of acute herpes zoster in this review<sup>1</sup>. The incidence of herpes zoster itself was less than 1.4/1,000 per year under the age of 20 in another review article<sup>2</sup>. A Mayo clinic study evaluating the epidemiology of herpes zoster in children and adolescents over a 21 year period<sup>3</sup>. There were 173 cases found resulting in an incidence of herpes zoster ranging from 20 cases per 100,000 person-years in area residents less than five years of age, to 63 cases per 100,000 person-years among ages 15-19. No PHN was diagnosed among this population.

Based on the available information concerning the occurrence of herpes zoster and PHN in pediatric patients, it would not be reasonably possible to conduct a study of the efficacy of gabapentin in PHN. The waiver for such studies should be granted.

<sup>1</sup> Portenoy RK, Duma C, Foley K. Acute Herpetic and Postherpetic Neuralgia: Clinical Review and Current Management. *Ann Neurol* 20:651-664, 1986.

<sup>2</sup> Hope-Simmons, RE. The Nature of Herpes Zoster: A Long-term Study and a New Hypothesis. *Proc. of the Royal Soc of Med* 58:9-20, 1965.

<sup>3</sup> Guess HA, Broughton MD, Melton LJ, Kurland LT. Epidemiology of Herpes Zoster in Children and Adolescents: A Population-Based Study. *Pediatrics* 76:512-516, 1985.

## APPENDICES

### Appendix A

#### Adverse events leading to Discontinuation

<b>Body System Preferred Term</b>	<b>Placebo N = 537</b>	<b>Any GBP N = 820</b>
Number of Patients Withdrawn Due to AEs	58 (10.8)	108 (13.2)
<b>Body as a Whole</b>	<b>16 (3.0)</b>	<b>22 (2.7)</b>
Asthenia	2 (0.4)	6 (0.7)
Accidental injury	2 (0.4)	4 (0.5)
Pain	2 (0.4)	5 (0.6)
Abdominal pain	2 (0.4)	1 (0.1)
Abscess	0 (0.0)	1 (0.1)
Body odor	0 (0.0)	1 (0.1)
Cyst	0 (0.0)	1 (0.1)
Flu syndrome	1 (0.2)	1 (0.1)
Headache	5 (0.9)	1 (0.1)
Hernia	0 (0.0)	1 (0.1)
Infection	1 (0.2)	1 (0.1)
Malaise	1 (0.2)	1 (0.1)
Back pain	1 (0.2)	0 (0.0)
Generalized edema	1 (0.2)	0 (0.0)
<b>Cardiovascular System</b>	<b>5 (0.9)</b>	<b>5 (0.6)</b>
Syncope	1 (0.2)	3 (0.4)
Congestive heart failure	0 (0.0)	1 (0.1)
Myocardial infarct	0 (0.0)	1 (0.1)
Angina pectoris	1 (0.2)	0 (0.0)
Cerebrovascular accident	1 (0.2)	0 (0.0)
Heart failure	1 (0.2)	0 (0.0)
Palpitation	1 (0.2)	1 (0.1)
<b>Digestive System</b>	<b>21 (3.9)</b>	<b>24 (2.9)</b>
Nausea	6 (1.1)	12 (1.3)
Diarrhea	5 (0.9)	6 (0.7)
Vomiting	1 (0.2)	6 (0.7)
Gastrointestinal disorder	2 (0.4)	3 (0.4)
Flatulence	3 (0.6)	2 (0.2)
Anorexia	1 (0.2)	1 (0.1)
Cholecystitis	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	1 (0.1)
Constipation	3 (0.6)	1 (0.1)
Dry mouth	1 (0.2)	1 (0.1)
Dyspepsia	5 (0.9)	1 (0.1)
Intestinal obstruction	0 (0.0)	1 (0.1)
Liver function tests abnormal	0 (0.0)	1 (0.1)
Rectal hemorrhage	0 (0.0)	1 (0.1)
Colitis	1 (0.2)	0 (0.0)
Malabsorption syndrome	1 (0.2)	0 (0.0)
<b>Hemic and Lymphatic</b>	<b>0 (0.0)</b>	<b>1 (0.1)</b>
Lymphoma-like reaction	0 (0.0)	1 (0.1)

Appendix A continues

## Appendix A, continued

<b>Metabolic and Nutritional Disorders</b>	<b>3 (0.6)</b>	<b>4 (0.5)</b>
Hyperglycemia	0 (0.0)	3 (0.4)
Peripheral edema	3 (0.6)	2 (0.2)
Weight gain	0 (0.0)	2 (0.2)
<b>Musculoskeletal System</b>	<b>3 (0.6)</b>	<b>4 (0.5)</b>
Arthritis	0 (0.0)	2 (0.2)
Myasthenia	2 (0.4)	2 (0.2)
Arthralgia	1 (0.2)	0 (0.0)
<b>Nervous System</b>	<b>22 (4.1)</b>	<b>72 (8.8)</b>
Dizziness	7 (1.3)	36 (4.4)
Somnolence	6 (1.1)	26 (3.2)
Thinking abnormal	0 (0.0)	5 (0.6)
Abnormal gait	0 (0.0)	3 (0.4)
Ataxia	0 (0.0)	3 (0.4)
Confusion	1 (0.2)	3 (0.4)
Hypesthesia	1 (0.2)	3 (0.4)
Twitching	0 (0.0)	3 (0.4)
Depersonalization	0 (0.0)	2 (0.2)
Depression	4 (0.7)	3 (0.4)
Incoordination	0 (0.0)	2 (0.2)
Stupor	0 (0.0)	2 (0.2)
Tremor	2 (0.4)	2 (0.2)
Vertigo	0 (0.0)	2 (0.2)
Extrapyramidal syndrome	0 (0.0)	1 (0.1)
Libido decreased	0 (0.0)	1 (0.1)
Myoclonus	0 (0.0)	1 (0.1)
Neuralgia	0 (0.0)	1 (0.1)
Nystagmus	0 (0.0)	1 (0.1)
Paresthesia	1 (0.2)	1 (0.1)
Speech disorder	1 (0.2)	1 (0.1)
Abnormal dreams	1 (0.2)	0 (0.0)
Anxiety	1 (0.2)	0 (0.0)
Insomnia	1 (0.2)	0 (0.0)
<b>Respiratory System</b>	<b>0 (0.0)</b>	<b>2 (0.2)</b>
Dyspnea	0 (0.0)	1 (0.1)
Hemoptysis	0 (0.0)	1 (0.1)
<b>Skin and Appendages</b>	<b>3 (0.6)</b>	<b>3 (0.4)</b>
Herpes zoster	0 (0.0)	1 (0.1)
Maculopapular rash	0 (0.0)	1 (0.1)
Pruritus	0 (0.0)	1 (0.1)
Alopecia	1 (0.2)	0 (0.0)
Rash	1 (0.2)	0 (0.0)
Sweating	1 (0.2)	0 (0.0)
Urticaria	1 (0.2)	0 (0.0)
<b>Special Senses</b>	<b>2 (0.4)</b>	<b>5 (0.6)</b>
Amblyopia	1 (0.2)	4 (0.5)
Diplopia	0 (0.0)	1 (0.1)
Eye pain	1 (0.2)	0 (0.0)

Appendix A continues

Appendix A, continued

<b>Urogenital System</b>	<b>1 (0.2)</b>	<b>1 (0.1)</b>
Genital edema	0 (0.0)	1 (0.1)
Scrotal edema	0 (0.0)	1 (0.1)
Breast neoplasm	1 (0.2)	0 (0.0)

Includes withdrawals due to non-TESS and TESS adverse events; 3 placebo-treated patients (constipation, dyspepsia, flatulence; dyspepsia; diarrhea), and 4 gabapentin-treated patients (twitching, accidental injury, depression, and hyperglycemia) withdrew due to non-TESS adverse events.

Source: Table 21, P. 56, Vol. 1.52, Original ISS 08-06-01 Dataset AELISTP, 11-30-01

**APPEARS THIS WAY  
ON ORIGINAL**

## Appendix B

### All Treatment Emergent Adverse Events in Original Five Completed Neuropathy Studies

	600 mg/d N=82		1200 N=82		1800 N=115		2400 N=344		3600 N=197		all GPN N=820		all PHN GPN N=336		placebo N=537	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Dizziness	7	8.5	4	4.9	33	28.7	77	22.4	47	23.9	168	20.5	95	28.3	35	6.5
Somnolence	4	4.9	3	3.7	20	17.4	54	15.7	51	25.9	132	16.1	72	21.4	26	4.8
Diarrhea	2	2.4	3	3.7	8	7.0	19	5.5	15	7.6	47	5.7	19	5.7	26	4.8
Headache	7	8.5	2	2.4	2	2.4	20	5.8	15	7.6	46	5.6	11	3.3	32	6.0
Infection	2	2.4	4	4.9	4	3.5	21	6.1	15	7.6	46	5.6	17	5.1	45	8.4
Nausea	2	2.4	1	1.2	1	0.9	29	8.4	13	6.6	46	5.6	13	3.9	30	5.6
Peripheral edema	4	4.9	1	1.2	5	4.3	18	5.2	15	7.6	43	5.2	28	8.3	15	2.8
Asthenia	5	6.1	4	4.9	6	5.2	15	4.4	11	5.6	41	5.0	19	5.7	24	4.5
Acc. injury	3	3.7	2	2.4	1	0.9	18	5.2	4	2.0	28	3.4	11	3.3	17	3.2
Dry mouth	1	1.2	1	1.2	7	6.1	9	2.6	9	4.6	27	3.3	16	4.8	5	0.9
Pain	2	2.4	4	4.9	6	5.2	11	3.2	3	1.5	26	3.2	9	2.7	30	5.6
Abdominal pain	2	2.4	0	0.0	3	2.6	14	4.1	4	2.0	23	2.8	9	2.7	18	3.4
Constipation	4	4.9	0	0.0	4	3.5	6	1.7	6	3.0	20	2.4	13	3.9	9	1.7
Flu syndrome	1	1.2	2	2.4	0	0.0	16	4.7	4	2.0	23	2.8	4	1.2	16	3.0
Back pain	0	0.0	2	2.4	1	0.9	8	2.3	7	3.6	18	2.2	4	1.2	8	1.5
Ataxia	1	1.2	1	1.2	1	0.9	4	1.2	12	6.1	19	2.3	11	3.3	0	0.0
Pharyngitis	1	1.2	1	1.2	3	2.6	5	1.5	8	4.1	18	2.2	4	1.2	10	1.9
Vomiting	0	0.0	0	0.0	4	3.5	8	2.3	5	2.5	17	2.1	11	3.3	14	2.6
Dyspepsia	3	3.7	0	0.0	1	0.9	9	2.6	4	2.0	17	2.1	4	1.2	12	2.2
Flatulence	2	2.4	0	0.0	1	0.9	3	0.9	9	4.6	15	1.8	7	2.1	7	1.3
Amblyopia	0	0.0	0	0.0	3	2.6	8	2.3	4	2.0	15	1.8	9	2.7	2	0.4
Weight gain	3	3.7	1	1.2	4	3.5	6	1.7	1	0.5	15	1.8	6	1.8	0	0.0
Amnesia	1	1.2	0	0.0	1	0.9	11	3.2	1	0.5	14	1.7	4	1.2	3	0.6
Confusion	0	0.0	1	1.2	1	0.9	4	1.2	8	4.1	14	1.7	3	0.9	4	0.7
Thinking abnormal	0	0.0	0	0.0	4	3.5	4	1.2	6	3.0	14	1.7	9	2.7	0	0.0
Rash	2	2.4	1	1.2	1	0.9	9	2.6	1	0.5	14	1.7	4	1.2	4	0.7
Hypesthesia	0	0.0	0	0.0	1	0.9	5	1.5	5	2.5	11	1.3	4	1.2	4	0.7
Depression	0	0.0	1	1.2	0	0.0	7	2.0	3	1.5	11	1.3	2	0.6	12	2.2
Abnormal gait	0	0.0	0	0.0	2	1.7	8	2.3	1	0.5	11	1.3	5	1.5	0	0.0
Hyperglycemia	1	1.2	1	1.2	0	0.0	3	0.9	4	2.0	9	1.1	4	1.2	2	0.4
Vertigo	1	1.2	2	2.4	0	0.0	3	0.9	3	1.5	9	1.1	1	0.3	2	0.4
Dyspnea	1	1.2	0	0.0	2	1.7	4	1.2	2	1.0	9	1.1	4	1.2	3	0.6
Tremor	0	0.0	0	0.0	2	1.7	6	1.7	1	0.5	9	1.1	6	1.8	6	1.1
Hypertension	4	4.9	3	3.7	0	0.0	2	0.6	0	0.0	9	1.1	0	0.0	6	1.1
Otitis media	0	0.0	1	1.2	2	1.7	1	0.3	4	2.0	8	1.0	4	1.2	4	0.7
Chest pain	1	1.2	1	1.2	1	0.9	2	0.6	3	1.5	8	1.0	2	0.6	4	0.7
Paresthesia	0	0.0	1	1.2	0	0.0	5	1.5	2	1.0	8	1.0	2	0.6	4	0.7
UTI	1	1.2	0	0.0	1	0.9	6	1.7	0	0.0	8	1.0	1	0.3	3	0.6
Rhinitis	0	0.0	0	0.0	1	0.9	1	0.3	5	2.5	7	0.9	2	0.6	4	0.7
Incoordination	0	0.0	0	0.0	2	1.7	1	0.3	4	2.0	7	0.9	5	1.5	0	0.0
Insomnia	1	1.2	1	1.2	0	0.0	1	0.3	4	2.0	7	0.9	3	0.9	11	2.0

Appendix B continues

Appendix B, continued

Nervousness	0	0.0	0	0.0	1	0.9	2	0.6	4	2.0	7	0.9	1	0.3	3	0.6
Conjunctivitis	0	0.0	1	1.2	1	0.9	3	0.9	2	1.0	7	0.9	4	1.2	0	0.0
Cough increased	0	0.0	0	0.0	0	0.0	5	1.5	2	1.0	7	0.9	3	0.9	6	1.1
Syncope	1	1.2	0	0.0	0	0.0	4	1.2	2	1.0	7	0.9	2	0.6	3	0.6
Neuralgia	0	0.0	1	1.2	0	0.0	1	0.3	4	2.0	6	0.7	5	1.5	4	0.7
Increased appetite	0	0.0	0	0.0	0	0.0	2	0.6	4	2.0	6	0.7	2	0.6	1	0.2
Myalgia	0	0.0	2	2.4	2	1.7	0	0.0	2	1.0	6	0.7	2	0.6	2	0.4
Bronchitis	0	0.0	2	2.4	0	0.0	2	0.6	2	1.0	6	0.7	1	0.3	3	0.6
Diplopia	0	0.0	0	0.0	0	0.0	5	1.5	1	0.5	6	0.7	4	1.2	1	0.2
Abnormal vision	0	0.0	0	0.0	1	0.9	4	1.2	1	0.5	6	0.7	3	0.9	1	0.2
Leg cramps	1	1.2	1	1.2	0	0.0	3	0.9	1	0.5	6	0.7	1	0.3	5	0.9
Neck pain	0	0.0	0	0.0	1	0.9	4	1.2	1	0.5	6	0.7	1	0.3	6	1.1
Libido decreased	0	0.0	0	0.0	1	0.9	5	1.5	0	0.0	6	0.7	1	0.3	0	0.0
Malaise	2	2.4	0	0.0	1	0.9	3	0.9	0	0.0	6	0.7	1	0.3	9	1.7
Pneumonia	1	1.2	0	0.0	0	0.0	1	0.3	3	1.5	5	0.6	3	0.9	0	0.0
Sinusitis	0	0.0	2	2.4	0	0.0	0	0.0	3	1.5	5	0.6	1	0.3	5	0.9
Twitching	0	0.0	0	0.0	0	0.0	3	0.9	2	1.0	5	0.6	3	0.9	1	0.2
GI disorder	0	0.0	0	0.0	0	0.0	3	0.9	2	1.0	5	0.6	2	0.6	3	0.6
Palpitation	2	2.4	1	1.2	0	0.0	0	0.0	2	1.0	5	0.6	0	0.0	3	0.6
Cellulitis	0	0.0	2	2.4	1	0.9	1	0.3	1	0.5	5	0.6	1	0.3	0	0.0
Oral moniliasis	1	1.2	1	1.2	0	0.0	2	0.6	1	0.5	5	0.6	1	0.3	0	0.0
Myasthenia	1	1.2	0	0.0	1	0.9	3	0.9	0	0.0	5	0.6	3	0.9	3	0.6
Speech disorder	0	0.0	0	0.0	1	0.9	1	0.3	2	1.0	4	0.5	3	0.9	1	0.2
Face edema	0	0.0	0	0.0	1	0.9	1	0.3	2	1.0	4	0.5	2	0.6	3	0.6
Depersonalization	1	1.2	0	0.0	0	0.0	1	0.3	2	1.0	4	0.5	1	0.3	1	0.2
Edema	0	0.0	0	0.0	0	0.0	3	0.9	1	0.5	4	0.5	3	0.9	1	0.2
Arthritis	1	1.2	0	0.0	1	0.9	1	0.3	1	0.5	4	0.5	2	0.6	3	0.6
Skin ulcer	0	0.0	3	3.7	0	0.0	0	0.0	1	0.5	4	0.5	1	0.3	0	0.0
Pruritus	0	0.0	1	1.2	0	0.0	3	0.9	0	0.0	4	0.5	3	0.9	8	1.5
Arthralgia	1	1.2	0	0.0	1	0.9	2	0.6	0	0.0	4	0.5	1	0.3	9	1.7
Arthrosis	1	1.2	0	0.0	1	0.9	2	0.6	0	0.0	4	0.5	1	0.3	1	0.2
Gastroenteritis	2	2.4	0	0.0	0	0.0	2	0.6	0	0.0	4	0.5	0	0.0	0	0.0
Nystagmus	0	0.0	0	0.0	0	0.0	0	0.0	3	1.5	3	0.4	3	0.9	0	0.0
Dysuria	0	0.0	0	0.0	0	0.0	0	0.0	3	1.5	3	0.4	1	0.3	0	0.0
Lung disorder	0	0.0	0	0.0	0	0.0	0	0.0	3	1.5	3	0.4	1	0.3	0	0.0
Asthma	0	0.0	0	0.0	0	0.0	1	0.3	2	1.0	3	0.4	2	0.6	2	0.4
Tooth disorder	1	1.2	0	0.0	0	0.0	0	0.0	2	1.0	3	0.4	2	0.6	1	0.2
Thirst	0	0.0	1	1.2	0	0.0	0	0.0	2	1.0	3	0.4	1	0.3	2	0.4
Hypertonia	0	0.0	1	1.2	0	0.0	0	0.0	2	1.0	3	0.4	0	0.0	2	0.4
Diabetes mellitus	0	0.0	0	0.0	0	0.0	2	0.6	1	0.5	3	0.4	1	0.3	0	0.0
Eye disorder	0	0.0	1	1.2	0	0.0	1	0.3	1	0.5	3	0.4	1	0.3	3	0.6
Impotence	0	0.0	0	0.0	1	0.9	1	0.3	1	0.5	3	0.4	1	0.3	0	0.0
Polyuria	1	1.2	0	0.0	1	0.9	0	0.0	1	0.5	3	0.4	1	0.3	0	0.0
Tongue disorder	0	0.0	0	0.0	0	0.0	2	0.6	1	0.5	3	0.4	1	0.3	0	0.0
Taste perversion	0	0.0	0	0.0	1	0.9	2	0.6	0	0.0	3	0.4	2	0.6	0	0.0

Appendix B continues

Appendix B, continued

Urinary incont.	0	0.0	0	0.0	0	0.0	3	0.9	0	0.0	3	0.4	2	0.6	0	0.0
Periodontal abscess	0	0.0	0	0.0	1	0.9	2	0.6	0	0.0	3	0.4	1	0.3	0	0.0
Weight loss	0	0.0	1	1.2	0	0.0	2	0.6	0	0.0	3	0.4	1	0.3	0	0.0
Abnormal dreams	0	0.0	1	1.2	0	0.0	2	0.6	0	0.0	3	0.4	0	0.0	4	0.7
Mucous membrane disorder	1	1.2	0	0.0	0	0.0	2	0.6	0	0.0	3	0.4	0	0.0	0	0.0
Stupor	1	1.2	0	0.0	0	0.0	2	0.6	0	0.0	3	0.4	0	0.0	0	0.0
Cardiovasc. dis.	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	2	0.6	2	0.4
Hypokinesia	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	2	0.6	0	0.0
Reflexes decreased	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	2	0.6	2	0.4
Urinary retention	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	2	0.6	0	0.0
Anxiety	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	1	0.3	3	0.6
Dry skin	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	1	0.3	0	0.0
Emotional lability	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	1	0.3	0	0.0
Euphoria	0	0.0	0	0.0	0	0.0	0	0.0	2	1.0	2	0.2	0	0.0	0	0.0
CHF	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	2	0.6	0	0.0
Allergic reaction	1	1.2	0	0.0	0	0.0	0	0.0	1	0.5	2	0.2	1	0.3	1	0.2
Anemia	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	1	0.3	0	0.0
CVA	1	1.2	0	0.0	0	0.0	0	0.0	1	0.5	2	0.2	1	0.3	1	0.2
Cholelithiasis	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	1	0.3	1	0.2
Ecchymosis	0	0.0	0	0.0	1	0.9	0	0.0	1	0.5	2	0.2	1	0.3	5	0.9
Gout	1	1.2	0	0.0	0	0.0	0	0.0	1	0.5	2	0.2	1	0.3	1	0.2
Herpes simplex	0	0.0	0	0.0	1	0.9	0	0.0	1	0.5	2	0.2	1	0.3	1	0.2
LFTs abnormal	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	1	0.3	0	0.0
Myocardial infarct	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	1	0.3	1	0.2
Abnormal stools	0	0.0	1	1.2	0	0.0	0	0.0	1	0.5	2	0.2	0	0.0	0	0.0
Hypoglycemia	0	0.0	0	0.0	0	0.0	1	0.3	1	0.5	2	0.2	0	0.0	2	0.4
Skin disorder	1	1.2	0	0.0	0	0.0	0	0.0	1	0.5	2	0.2	0	0.0	2	0.4
Anorexia	0	0.0	1	1.2	1	0.9	0	0.0	0	0.0	2	0.2	1	0.3	6	1.1
Breast pain	0	0.0	1	1.2	0	0.0	1	0.3	0	0.0	2	0.2	1	0.3	0	0.0
Ear pain	0	0.0	0	0.0	0	0.0	2	0.6	0	0.0	2	0.2	1	0.3	1	0.2
Fever	0	0.0	1	1.2	1	0.9	0	0.0	0	0.0	2	0.2	1	0.3	2	0.4
Herpes zoster	0	0.0	0	0.0	0	0.0	2	0.6	0	0.0	2	0.2	1	0.3	2	0.4
PVD	1	1.2	0	0.0	1	0.9	0	0.0	0	0.0	2	0.2	1	0.3	0	0.0
Vasodilatation	0	0.0	0	0.0	1	0.9	1	0.3	0	0.0	2	0.2	1	0.3	1	0.2
Vesiculobullous rash	1	1.2	0	0.0	0	0.0	1	0.3	0	0.0	2	0.2	1	0.3	3	0.6
Chills	1	1.2	1	1.2	0	0.0	0	0.0	0	0.0	2	0.2	0	0.0	1	0.2
Circumoral paresthesia	0	0.0	0	0.0	0	0.0	2	0.6	0	0.0	2	0.2	0	0.0	0	0.0
Deafness	0	0.0	0	0.0	0	0.0	2	0.6	0	0.0	2	0.2	0	0.0	3	0.6
Fungal dermatitis	0	0.0	1	1.2	0	0.0	1	0.3	0	0.0	2	0.2	0	0.0	0	0.0
Furunculosis	0	0.0	1	1.2	0	0.0	1	0.3	0	0.0	2	0.2	0	0.0	1	0.2
Gastritis	0	0.0	1	1.2	0	0.0	1	0.3	0	0.0	2	0.2	0	0.0	0	0.0
Hyperesthesia	0	0.0	1	1.2	0	0.0	1	0.3	0	0.0	2	0.2	0	0.0	1	0.2
Sweating	1	1.2	0	0.0	0	0.0	1	0.3	0	0.0	2	0.2	0	0.0	5	0.9

Appendix B continues

## Appendix B, continued

Abscess	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Alk. Phos incr.	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Cholecystitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Fecal incontinence	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
GGT increased	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Genital edema	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Hernia	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Intestinal obstruction	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Intestinal ulcer	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Lab test abnormal	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
LDH increased	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Melena	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Myoclonus	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Reaction uneval.	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	1	0.2
Rectal hemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Scrotal edema	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Sepsis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	1	0.2
Skin carcinoma	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	0	0.0
Urinary frequency	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	1	0.3	5	0.9
Body odor	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Gingivitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Increased capillary fragility	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Lymphadenopathy	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Neuropathy	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	1	0.2
Nocturia	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	1	0.2
Psoriasis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	1	0.2
Retinal disorder	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	1	0.2
Retinal hem.	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Retinal vasc. dis.	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Skin discoloration	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	1	0.2
Vestibular disorder	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	1	0.1	0	0.0	0	0.0
Cyst	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	1	0.3	1	0.2
Dysarthria	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	1	0.3	0	0.0
Extrapyramidal syn.	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	1	0.3	0	0.0
Hemoptysis	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	1	0.2
Movement disorder	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Phlebitis	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
PT decreased	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Retinal vein thromb.	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Stomatitis	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Taste loss	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Urinary urgency	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	1	0.3	0	0.0
Voice alteration	0	0.0	0	0.0	1	0.9	0	0.0	0	0.0	1	0.1	1	0.3	0	0.0
Acne	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	2	0.4

Appendix B continues

## Appendix B, continued

Agitation	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Akinesia	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Chills and fever	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
CLL	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Colitis	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	3	0.6
Duodenal ulcer	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Epistaxis	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Eye hemorrhage	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	3	0.6
Eye pain	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	3	0.6
Gynecomastia	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Hair disorder	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Heart failure	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.2
Hypotension	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Joint disorder	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	1	0.2
Libido increased	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Lymphoma like reaction	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Maculopapular rash	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Menstrual disorder	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Migraine	1	1.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	6	1.1
Mouth ulceration	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	2	0.4
Nausea, vomiting	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Neoplasm	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Orchitis	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Pelvic pain	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Pyelonephritis	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Rectal disorder	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Tendon disorder	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Thrombophlebitis	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Urine abnormality	0	0.0	0	0.0	0	0.0	1	0.3	0	0.0	1	0.1	0	0.0	0	0.0
Vaginal moniliasis	0	0.0	1	1.2	0	0.0	0	0.0	0	0.0	1	0.1	0	0.0	0	0.0
Alopecia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Angina pectoris	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Apathy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Arrhythmia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
BUN increased	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Bone pain	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Breast neoplasm	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Carcinoma of lung	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Cataract specified	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Congenital anomaly	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Ear disorder	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Eczema	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Generalized edema	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Hemorrhage	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Hiccup	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2

Appendix B continues

Appendix B, continued

Hypercholesteremia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Hypothyroidism	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Ileitis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Kidney calculus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Lacrimation dis.	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Malabsorption syn.	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Myocardial ischemia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
N, v, diarrhea	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Pancreatitis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Rheumatoid arthritis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
SGOT increased	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
SGPT increased	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Stomach atony	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Tachycardia	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Tendinous contracture	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Thrombosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Tinnitus	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	0.4
Urticaria	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2
Uterine fibroids enlarged	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2

Source: Database: aelistp.xpt, 11-30-01

**APPEARS THIS WAY  
ON ORIGINAL**

**Appendix C****TESS AEs in >1 Patient, Clinical Pharmacology Studies**

Adverse Event	Study 945-190	Study 1035-015
Dizziness	24	2
Somnolence	13	8
Dry mouth	11	
Asthenia	9	
Depersonalization	9	
Incoordination	8	
Pain	7	1
Thinking abnormal	6	
Amnesia	5	
Flatulence	5	1
Muscle spasms/stiffness	5	
Abdominal pain, Euphoria, Incoordination, Rhinitis	4 each	
Hyperkinesia	4	1
Amblyopia, Ataxia, , Hypertonia, Paresthesia, Peripheral edema, Pharyngitis, Pruritus	3 each	
Abnormal vision, Agitation, Back pain, Confusion, Eye disorder, Hypomenorrhea, Lacrimation disorder, Nausea, , Rash, Vasodilatation, Vertigo	2 each	
Nervousness	2	1
Headache	1	3

Source: Appendix C.3, P. 465 and C.7, P. 476, Vol. 1.53

**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/  
-----

Sharon Hertz  
5/24/02 04:02:04 PM  
MEDICAL OFFICER

Bob Rappaport  
5/24/02 04:08:32 PM  
MEDICAL OFFICER

I concur with Dr. Hertz's conclusions and recommendation that  
these applications are approvable.

**APPEARS THIS WAY  
ON ORIGINAL**



**FDA CENTER FOR DRUG EVALUATION AND RESEARCH**  
**DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS**  
**HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857**  
**Tel:(301) 827-7410**

---

**DIVISION DIRECTOR REVIEW AND BASIS FOR APPROVAL ACTION**

---

**DATE:** May 22, 2002

**DRUG:** Neurontin® (gabapentin)

**NDAs:** 21-397, Capsules 100, 300, 400 mg  
21-423, Tablets 600 and 800mg  
21-424, Oral Solution 250 mg/5ml

**NDA Code** Type 6 S NDA

**SPONSOR:** Parke-Davis Pharmaceutical Research  
A Division of Warner Lambert Company  
Pfizer

**INDICATION:** Postherpetic Neuralgia

---

***Summary***

Neurontin® (gabapentin) is a neuropharmacologic drug product approved in 1993 as adjunctive treatment medication for the treatment of partial complex epilepsy. Since approval, it has gained a reputation through off-label use for the treatment of neuropathic pain. The sponsor now submits a Type 6 NDA (New Drug Application) in support of a new indication—for the treatment of postherpetic neuralgia. There are two pivotal trials submitted as evidence of effectiveness for this indication, as well as a safety database of 563 patients with postherpetic neuralgia and additional 794 patients with other forms of neuropathic pain. The pharmacokinetics of gabapentin in this population was evaluated by a population pharmacokinetic approach, analyzing the exposure-response relationship from five clinical neuropathic pain studies, as well as from the two pivotal postherpetic neuralgia studies.

The sponsor has successfully demonstrated the safety and effectiveness of Neurontin® in the treatment of postherpetic neuralgia. Product labeling will include this new indication.

### *Efficacy*

The sponsor has submitted two adequate and well-controlled studies in patients with postherpetic neuralgia, which independently substantiated the effect of Neurontin® in reducing the final weekly mean pain score compared to baseline pain for the doses of Neurontin tested (1800 mg, and 2400 mg in one study and 3600 mg in the second) compared with placebo in the intent-to-treat analyses. These were the primary prospective efficacy analyses. This was further confirmed by responder analyses, which defined a response as a 50% reduction in pain between baseline and end of treatment. The effects on both the primary outcome analyses and the secondary analyses for both studies were statistically significant as described in the reviews of Dr. Sharon Hertz and Dr. Stella Grosser. The descriptive statistics and statistical outcomes are detailed in these reviews.

It has been pointed out that the development plan did not design for dose replication. The clinical and statistical review team made an effort to ascertain whether efficacy was evident during the early titration phases of both trials for the first several weeks, and therefore, whether dose replication could be established in the trial, which studied the higher dose. This was not a successful approach, however, as it was found that the amount of time spent on the lower doses of 1800 mg and 2400 mg in high dose study 945-295, were insufficient to achieve steady state.

Two additional methods using a pharmacokinetic/pharmacodynamic approach were undertaken to try and bridge the results of the two studies. In the first instance the results from the two postherpetic neuralgia studies, study 211 (testing 3600 mg of gabapentin against placebo) and study 430 (testing 1800 and 2400 mg of gabapentin against placebo) were compared and demonstrated comparable effect sizes. This was interesting but not compelling.

A pharmacokinetic approach using a modeling and simulation analysis was then applied to the data sets, taking into account baseline pain, demographics, dose, and placebo effects in the modeling. It was found that the results of study 211 and separately 430 could be predicted reliably based upon information from the comparative pivotal trial. This suggests that the results of the two pivotal studies would be the same in pain relief outcomes if the doses were the same. Details of these simulation and modeling analyses can be found in the pharmacokinetics reviews by Drs. Roy and Sun.

The efficacy of Neurontin® was clearly established in two separate placebo-controlled trials, and the effective dosing strategy was bridged through an elegant pharmacokinetic and pharmacodynamic model, which provided confirmation of the dose across studies.

This approach was felt to be acceptable because of the high predictability of the model and close similarity of the exposure response curves between the two studies, as well as the strong and consistent effect in all dose groups in both studies.

***Safety***

The safety of Neurontin® was established in a safety database of 1357 patients, over 500 of which were patients suffering from postherpetic neuralgia. The doses ranged from 0 to 3600 mg and duration of exposure at the highest dose did not exceed 6 weeks, and in lower doses up to 24 weeks. Combined with the finding of safety in the epilepsy development program, which included exposure and safety data of several years' duration, there was adequate safety exposure to support the finding of safety in postherpetic neuralgia, which could be characterized as largely self-limited. There were no unexpected adverse events, not previously described in the studies in epilepsy. The postherpetic neuralgia patients, on the whole, were significantly older than the epilepsy population. Therefore, there was an opportunity to better understand the safety profile of this product in the elderly population. There were, overall, more adverse events reported in patients over 75 years of age, with dizziness and peripheral edema most commonly reported.

In summary, there has been adequate demonstration of safety and effectiveness of Neurontin® in the treatment of postherpetic neuralgia to support approval.

***Action:*** Approval

---

Cynthia G. McCormick, MD,

Director

Division of Anesthetic, Critical Care and Addiction Drug Products  
Office of Drug Evaluation II, CDER, FDA

**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/

-----  
Cynthia McCormick  
5/22/02 12:27:18 PM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

N 21-397/ 21-423/ 21-424 Neurontin Capsules, Tablets and Oral Solution

For Clinical Safety Update Review see the main Clinical Review of these NDAs by Dr. Sharon Hertz.

**APPEARS THIS WAY  
ON ORIGINAL**