The frequency of these edema adverse events among pregabalin-treated patients was slightly higher than the frequency of peripheral edema alone for all indications with the exception of GAD. No additional edema adverse events in the GAD controlled trials were coded as either edema or generalized edema in either the placebo or pregabalin treatment groups. For all indications, the relative risk associated with pregabalin for the development of the broader array of edema-related adverse events was similar to the relative risk associated with pregabalin for the development of peripheral edema specifically. These data are presented in Appendix ALL. 202 (Summary of Safety, p. 7491) and table 83 above. Most of Pfizer's discussion of edema in controlled trials focuses on peripheral edema specifically. In their discussion of weight gain and edema, however, they discuss the relationship between weight gain and the broader array of edema-related adverse events.

Pfizer assessed age, gender, and BMI as risk factors for the development of peripheral edema, comparing the frequencies of peripheral edema across indications in different age groups (18-64, 65-74, and =75), genders, and baseline BMI categories (<28 and =28). They concluded that patients older than 64 were more likely to experience peripheral edema in neuropathic pain trials and that patients with baseline BMI =28 were more likely to experience peripheral edema in GAD trials. I conducted an analysis in each study grouping of relative risk for peripheral edema that was associated with pregabalin by gender, age group, and baseline BMI. I have included a table summarizing these data in the appendix. Neither age, baseline BMI, nor gender appeared to have an effect on the risk for developing peripheral edema that was strong or consistent across indications. Age and gender did appear to slightly modify the risk for the development of peripheral edema in the neuropathic pain trials. In these trials, increasing age was associated with decreased risk for peripheral edema in diabetic neuropathy studies and an increasing risk for peripheral edema in the postherpetic neuralgia studies. In diabetic neuropathy studies, the relative risk for the development of peripheral edema was greater for females than males. In postherpetic neuralgia studies, in contrast, the relative risk for the development of peripheral edema was greater for males than females. Since there were relatively few patients older than 64 in the epilepsy and GAD trials, effect modification by age was difficult to assess for these indications. Baseline BMI appeared to slightly modify risk for peripheral edema in the GAD and epilepsy trials. In epilepsy studies, the pregabalin-associated relative risk for peripheral edema was lower among patients with baseline BMI =28 than among patients with baseline BMI <28. In the GAD studies, in contrast, baseline BMI =28 was associated with a higher relative risk for the development of peripheral edema.

Peripheral Edema and Clinical Events, Vital Signs, and Laboratory Parameters

Pfizer examined the potential association between peripheral edema and selected cardiorespiratory events, vitals signs, and laboratory values in controlled studies. They presented the same laboratory and vital sign analyses for the patients who experienced the adverse event of peripheral edema as they had for the entire controlled trial population. They concluded that there were no clinically significant differences in

changes in blood pressure, heart rate, or respiratory rate observed in patients with peripheral edema compared with the overall controlled study population.

They also presented the frequency of selected cardiorespiratory adverse events in those patients with and without the adverse event of peripheral edema, concluding that pregabalin-treated patients who developed peripheral edema were more likely to experience hypertension and dyspnea compared to the overall population of pregabalin-treated patients. The following table summarizes data regarding cardiorespiratory events of interest in patients with and without peripheral edema:

FDA Table 84. Relative Risks for Selected Cardiorespiratory Adverse Events in Patients With and Without Peripheral Edema; Controlled Trials in NDA Integrated Safety Database (All Indications)

Adverse Event	% (no.) of patients with peripheral edema experiencing event		RR_{PE}	% (no.) of patients without peripheral edema experiencing event		RR_{NPE}
	Placebo N=42	Pregabalin N=336		Placebo N=2342	Pregabalin N=5172	
Arrhythmia	0.0% (0)	0.6% (2)	*	0.1% (3)	0.1% (3)	1.0
Atrial fibrillation	0.0% (0)	0.3% (1)	*	0% (0)	0.1% (3)	*
Cardiovascular disorder	0.0% (0)	0.9% (3)	*	0.1% (2)	0.1% (3)	1.0
Congestive heart failure	0.0% (0)	0.3% (1)	*	0.1% (3)	0.1% (5)	1.0
Hypertension	0.0% (0)	2.4% (8)	*	1.2% (27)	0.6% (31)	0.5
Hypotension	2.4% (1)	0.9% (3)	0.4	0.1% (2)	0.2% (10)	2.0
Palpitation	0.0% (0)	0.9% (3)	*	0.6% (15)	0.5% (24)	0.8
Tachycardia	2.4% (1)	0.3% (1)	0.1	0.4% (10)	0.3% (13)	0.7
Dyspnea	0.0% (0)	3.3% (11)	*	0.8% (19)	0.8% (43)	1.0

From Pfizer Appendices ALL.225-ALL.226 (Summary of Safety, pp. 7561-7562).

* Relative risk associated with pregabalin could not be calculated for these events given that there were no events in the placebo group.

The most striking differences observed between pregabalin-treated patients with peripheral edema and pregabalin-treated patients without peripheral edema were for hypertension and dyspnea, as observed by Pfizer. Other differences observed were slight. Despite the increased incidence of hypertension and dyspnea adverse events among pregabalin-treated patients with peripheral edema, there were no large or consistent differences in clinically important changes in blood pressure parameters, heart rate, or respiratory rate between pregabalin-treated patients with peripheral edema and the overall population of pregabalin-treated patients. Moreover, pregabalin-treated patients with peripheral edema did not demonstrate an increase in mean blood pressure parameters from baseline to termination compared to the overall population. The following table

summarizes changes in mean blood pressure parameters in those patients with peripheral edema and the overall population:

FDA Table 85.Changes from Baseline to Termination in Mean Systolic and Diastolic Supine and Sitting Blood Pressure for Overall Population and Patients With Peripheral Edema by Treatment Group; Controlled Trials in NDA Integrated Safety Database (All Indications)

Blood pressure Parameter		Mean Blood Pressure [mm Hg] (SD) in Overall population				Mean Blood Pressure [mm Hg] (SD) in Patients With Peripheral edema			
		Placebo		Pregabalin; all doses and regimens		Placebo		Pregabalin; all doses and regimens	
	No. of patients	*2384*		*5508*		*42*		*336*	
	No. of patients with baseline and termination BP measurements	*1153*	*1175*	*2641*	*2748*	*26*	*15*	*234*	*98*
		supine	sitting	supine	sitting	supine	sitting	supine	sitting
Systolic	Change from baseline	-2.9 (15.68)	-0.2 (12.62)	-4.3 (16.56)	-1.8 (12.60)	-6.5 (14.92)	1.9 (16.93)	-4.7 (19.92)	-3.6 (15.25)
Diastolic	Change from baseline	-1.2 (9.63)	0.1 (9.01)	-2.4 (9.85)	-1.0 (8.98)	-1.3 (10.85)	-0.3 (7.42)	-4.3 (12.90)	-0.7 (8.30)

From Pfizer Appendices Appendices ALL.113-ALL.114 (Summary of Safety, pp. 7169-7176) and ALL.219-ALL.220 (Summary of Safety, pp. 7513-7520).

Pfizer's analysis of vital sign changes potentially associated with peripheral edema demonstrated notable differences in weight change among patients with peripheral edema compared with the overall population. 11.1% (36/325) of pregabalin-treated patients with peripheral edema sustained a weight increase of at least 7% from baseline compared with 0% [0/41] of placebo-treated patients with peripheral edema. In the overall population, 7.7% (401/5181) pregabalin-treated patients experienced a weight increase of at least 7% compared to 1.7% (38/2233) of placebo-treated patients. The potential relationship between weight gain and peripheral edema is discussed in greater detail later in this section.

Pregabalin-treated patients with peripheral edema demonstrated no large or consistent differences in laboratory values compared with the overall population of pregabalin-treated patients. There did not appear to be laboratory evidence of deterioration in renal or hepatic function in the patients with peripheral edema. There were no striking differences observed in urine laboratory values measured.

I did observe small differences in BUN changes between pregabalin-treated patients with peripheral edema and the overall population of pregabalin-treated patients, although I did not observe corresponding differences in creatinine changes. There was a mean increase in BUN from baseline to termination of 1.05 mg/dL in pregabalin-treated patients with peripheral edema (compared with 0.48 mg/dL among placebo-treated patients with peripheral edema) and 0.54 mg/dL in the overall population of pregabalin-treated patients (compared with 0.14 mg/dl in the overall placebo-treated population). Among pregabalin-treated patients with peripheral edema, there were also slightly higher percentages of patients with BUN increases considered clinically important (4.9%) and BUN values changing to high at termination (9.2%) than were observed in the overall population of pregabalin-treated patients (in which 2.4% had values considered clinically important and 4.7% had values changing to high).

Pregabalin-treated patients with peripheral edema also had a slightly higher percentage of patients with clinically important decreases in hemo globin, hematocrit, total protein, and sodium. They also had a slightly higher percentage of percentage of patients with hemoglobin, hematocrit, and total protein changing to low at endpoint, but did not have a higher proportion of patients with sodium changing to low at endpoint. The following table summarizes these observed differences:

FDA Table 86. Changes in Selected Laboratory Values by Treatment Group and Presence of Peripheral Edema; Controlled Studies Trials in NDA Integrated Safety Database (All Indications)

Type of assessment	Laboratory value	Patients with peripheral edema		Overall group of patients	
		Placebo	Pregabalin	Placebo	Pregabalin
Clinically important decreases					
	Hemoglobin	0% (0/39)	1.2% (4/329)	0.6% (13/2226)	0.6% (32/5158)
	Hematocrit	0% (0/39)	2.4% (8/328)	1.1% (25/2226)	1.3% (68/5151)
	Total protein	0% (0/41)	0.6% (2/329)	0.3% (7/2249)	0.3% (18/5200)
	Serum sodium	0% (0/41)	2.1% (7/329)	0.9% (21/2249)	1.2% (64/5202)
Laboratory values changing to low at endpoint					
	Hemo globin	0% (0/36)	12.6% (35/278)	5.4% (109/2007)	6.7% (306/4596)
	Hematocrit	0% (0/37)	10.1% (30/296)	4.7% (98/2090)	4.7% (226/4782)

	Total protein	0% (0/40)	3.2% (10/315)	2.0% (43/2181)	2.2% (109/5060)
	Serum sodium	0% (0/40)	0.9% (3/318)	1.2% (27/2210)	1.4% (71/5101)

From Pfizer Appendices ALL.090-ALL.091 (Summary of Safety, pp. 4992-5009) and ALL.221 and ALL.223 (Summary of Safety, pp. 7521-7524 and 7541-7552).

Combined Controlled and Uncontrolled Studies

In the combined controlled and uncontrolled studies, 9.9% of pregabalin-treated patients had an adverse event of peripheral edema. The following table summarizes the proportion of pregabalin-treated patients that experienced peripheral edema by indication:

Pfizer Table 37. Percentage (No.) of Pregabalin-treated Patients With Peripheral Edema by Indication; Combined Controlled and Uncontrolled Studies in NDA Integrated Safety Database (All Indications)

Indication (Number of Patients)	Any Pregabalin [n (%)]
All Combined Controlled and Uncontrolled Studies (N=8666)	860 (9.9)
Combined Controlled and Uncontrolled NeP (N=2524)	436 (17.3)
Combined Controlled and Uncontrolled DPN (N=1413)	237 (16.8)
Combined Controlled and Uncontrolled PHN (N=1111)	199 (17.9)
Combined Controlled and Uncontrolled Epilepsy (N=1613)	152 (9.4)
Combined Controlled and Uncontrolled GAD (N=1962)	49 (2.5)

Pfizer Table 37 (Summary of Safety, p.90).

The overall incidence of peripheral edema was higher in the controlled and uncontrolled studies combined than in the controlled trials alone. In each indication with the exception of GAD, the incidence of peripheral edema was substantially higher than had been observed in the controlled trials for that indication. In the combined controlled and uncontrolled trials for GAD, the incidence of peripheral edema was very similar to the incidence observed in the GAD controlled trials alone. As was the case for the controlled trials, the incidence of peripheral edema was substantially higher in the neuropathic pain trials compared with the other indications. The incidence of peripheral edema was comparable in the postherpetic neuralgia and diabetic neuropathy trials.

As they did for the controlled trials, Pfizer compared the frequency of selected cardiorespiratory adverse events in patients with and without peripheral edema. The following table summarizes the data presented by the sponsor:

FDA Table 87. Relative Risks for Selected Cardiorespiratory Adverse Events in Patients With and Without Peripheral Edema; Combined Controlled and Uncontrolled Trials in NDA Integrated Safety Database (All Indications)

Adverse Event	% (no.) of patients with peripheral edema experiencing event; n=860	% (no.) of patients without peripheral edema experiencing event; n=7806
Arrhythmia	0.7% (6)	0.2% (14)
Atrial fibrillation	1.0% (9)	0.2% (18)
Cardiovascular disorder	1.7% (15)	0.3% (26)
Congestive heart failure	1.3% (11)	0.3% (27)
Hypertension	3.8% (33)	1.7% (134)
Hypotension	0.8% (7)	0.3% (27)
Palpitation	1.4% (12)	0.9% (68)
Tachycardia	1.0% (9)	0.6% (47)
Dyspnea	7.7% (66)	1.8% (140)

From Pfizer Appendices ALL.229-ALL.230 (Summary of Safety, pp. 7565-7566).

Relative to patients who did not develop peripheral edema, patients who experienced the adverse event of peripheral edema had higher frequencies of all cardiorespiratory events delineated in the table above. The largest risk differences observed between patients with and without peripheral edema were for the adverse events of dyspnea and hypertension. Interpretation of the data is difficult since the temporal sequence of the adverse events experienced is unknown, many other factors and possible confounding variables exist, and there is no placebo group to serve as a comparator.

Weight Gain and Edema

Pfizer performed two analyses to investigate the potential association between weight gain and edema in the controlled studies. In their first analysis, they examined the incidence of edema (adverse events coded to the preferred terms peripheral edema, edema, and generalized edema) among patients who had sustained a weight increase of =7% in the controlled studies. They concluded that few of the pregabalin-treated patients and none of the placebo-treated patients with weight gain of at least 7% had concurrent edema. The following table summarizes their findings:

FDA Table 88. Incidence of and Relative Risks for Edema in Patients With Weight Gain =7% and in Overall Population by Indication; Controlled Trials in NDA Integrated Safety Database

Indication	Patients with weight gain =7%			Overall population		
	Placebo	Pregabalin	Relative Risk	Placebo	Pregabalin	Relative risk
All controlled studies	0% (0/38)	12.7% (51/401)	*	2.1% (51/2384)	7.8% (430/5508)	3.7
Neuropathic pain studies	0% (0/13)	28.6% (30/105)	*	3.5% (30/857)	13.2% (241/1831)	3.8
Diabetic neuropathy	0% (0/6)	30.6% (15/49)	*	2.4% (11/459)	12.3% (120/979)	5.1
Postherpetic	0%	26.8%	*	4.8%	14.2%	3.0

neuralgia	(0/7)	(15/56)		(19/398)	(121/852)	
Epilepsy	0% (0/6)	8.3% (11/133)	*	2.0% (6/294)	5.0% (38/758)	2.5
GAD	0% (0/6)	0% (0/42)	*	0.4% (2/484)	2.3% (27/1149)	5.7

From Pfizer Appendix ALL.202 and ALL.240 (Summary of Safety, pp. 7491 and 7577).
*Relative risk could not be calculated in these cases because there were no events in the placebo group.

Based on the above data, it appears that weight gain was not limited to patients with adverse events of edema. In each indication, the majority of patients with weight gain of at least 7% did not have adverse events coded to edema preferred terms. In all indications except for GAD, however, the proportion of patients experiencing edema was higher among patients with weight gain of at least 7% than it was among the controlled trial population as a whole, suggesting that although edema does not entirely account for pregabalin-associated weight gain, there is an association between the two events. The neuropathic pain studies had the highest proportion of patients with weight gain of at least 7% who also developed peripheral edema during the controlled trials. None of the GAD patients with weight gain of at least 7% had adverse events coded to edema preferred terms.

In their second analysis, Pfizer compared the observed frequency of co-occurrence of edema and weight gain of =7%—1.0% (51/5181) in pregabalin-treated patients and 0% (0/2233) in placebo-treated patients—with the expected frequency of co-occurrence assuming complete independence of the two adverse events. They calculated the expected frequency in each treatment group by multiplying the observed frequency of weight gain of at least 7% by the observed frequency of edema, obtaining .04% for placebo-treated patients and 0.6% for pregabalin-treated patients.[38] They concluded on the basis of this analysis that although the observed rate of co-occurrence of the two events in pregabalin-treated patients was higher than expected assuming complete independence of the two events, edema alone does not account for weight gain among pregabalin-treated patients.

4.7.10 Human Malignancies

Pfizer noted that 57 subjects from phase II/III trials were diagnosed with malignant tumors during or after exposure to pregabalin (Summary of Safety, p.105). Duration of pregabalin exposure at the time the malignancy ranged from 1 to 1859 days. Skin (17 cases) and breast (8 cases) were the two most commonly reported cancers. Pfizer concluded that the data do not suggest a causal or correlative relationship between pregabalin and tumor development. A list of the reported malignancies is included as an appendix to this memo.

[38] 1.7% (38/2233) of placebo-treated patients had weight gain of =7% and 2.1% (51/2384) had an adverse event of edema, yielding a calculated expected frequency of co-occurrence of .04% (.017x.021). 7.7% (401/5181) of pregabalin-treated patients had weight gain of =7% and 7.8% (430/5508) of pregabalin-treated patients had an adverse event of edema, yielding a calculated expected frequency of co-occurrence of .6% (.077x.078).

4.8 Overdose

Pfizer summarized overdose data from the pregabalin program. The maximum reported pregabalin overdose was 15,000mg, although there was disagreement between the narrative and dosing records about whether this was correct. No subject who took a pregabalin overdose died or required a lengthy hospitalization. Reported symptoms for pregabalin overdose subjects included somnolence, ataxia, hypotension, agitation, paresthesia, LFTs abnormal, myasthenia, asthenia, amblyopia, euphoria, nausea, dizziness, hallucination, headache, and edema.

Pfizer identified pregabalin overdoses using data from two sources, the dosing records for subjects who took pregabalin doses >600mg/day in phase II/III trials, and SAEs of overdose or suicide attempt (Summary of Safety, p.72).

Pfizer reported that the dosing records included ninety-one subjects who took pregabalin dosages >600mg/day (dose range 625mg/day-2400mg/day, duration range 1-464 days). Seventy-one of these subjects with overdoses did not exceed 900mg/day and Pfizer reported that the AEs reported for these subjects were mild and without medically significant effects (Summary of Safety, p.72).

For the twenty subjects who took pregabalin dosages exceeding 900mg/day, two were hospitalized (SAEs: suicide attempt, overdose). Those events are summarized below.

009 008019 This 36 year old male with a history of seizure disorder, depression, and previous suicide attempts was admitted to hospitals on open label study days 443, 448, and 453 for suicidal ideation and suicide attempt. On day 443, he attempted suicide with an overdose of lorazepam. On day 448 he attempted suicide by taking a four day supply of his seizure medications (phenytoin 350mg/day, lamotrigine 700mg/day, carbamazepine 2000mg/day, and pregabalin 600mg/day). He reportedly banged his head and thrashed about, vomited twice, and was described as somnolent, non-communicative, and agitated. His pregabalin concentration was 8.02mg/ml six hours post ingestion. He AST was 210U/LWBC was $16.6x10^9$, and myoglobin was 5523ng/mL. He recovered from these events.

087 069008 This 41 year old male with GAD, social phobia, and panic disorder took an intentional overdose in a suicide attempt on open label study day 353. The narrative reported that the subject took 150 tablets of pregabalin 100mg (total dose 15000mg) along with 20mg of alprazolam, and an unknown quantity of diazepam. The narrative reported that the subject suffered from slight sedation. The narrative also reported that the subject recovered by 24 hours after the ingestion. The suicide attempt was attributed to numerous interpersonal and economic conflicts. *This was reported in the dosing record as a 1700mg ingestion and pregabalin blood levels were not measured.

Eighteen subjects ingested pregabalin dosages >900mg/day but did not have associated SAEs. Pfizer noted that the AEs reported within one week of the overdose included somnolence, agitation, paresthesia, LFTs abnormal, myasthenia, asthenia, ataxia, amblyopia, euphoria, nausea, dizziness, hallucination, headache, and edema. Pfizer noted that the subject with LFTs abnormal had the abnormal lab result the day following a motor vehicle accident.

Six additional subjects were identified with SAEs that involved overdoses but that were not captured in the dosing record. Five of these were intentional overdoses and one was unintentional. I summarize those events below.

011 016012 This 55 year old female with seizure disorder was hospitalized with ataxia and nystagmus one day after taking double her assigned dose of pregabalin 450mg/day. The ataxia and nystagmus resolved within 1 day.
012 055106 This 41 year old female with a history of seizure disorder, anxiety, vascular headaches, and s/p right occipital cavernous resection was hospitalized following a suicide attempt. Total exposure to pregabalin prior to this event was 221 days. She overdosed by taking approximately 40 pregabalin tablets. She was found unconscious and was treated with gastric lavage and activated charcoal. The narrative mentioned no other signs or symptoms. She was discharged to a psychiatric center the following day.
012 084117 This 55 year old female with seizure disorder took fifteen 100mg pregabalin capsules following a marital dispute. She reported that she felt OK at the time and her speech was reportedly clear. She was seen by her general practitioner. The narrative did not note any treatment for the overdose and the outcome was reported as recovered.
081 127007 This 19 year old male with social phobia was hospitalized following a suicide attempt 29 days after starting pregabalin. During the study he was found to be depressed and he stated that he felt the study medication was not helping him and that life was not worth living. He was discontinued from the study and started on fluoxetine and zolpidem. He stated that he would return his remaining trial medication at a follow up visit. He returned home and took twenty-five pregabalin 100mg capsules at one time. He was hospitalized and listed as recovered three days later. The narrative did not mention any symptoms or signs associated with the overdose and did not report any treatment.
081 129002 This 28 year old male with a history of social phobia overdosed on pregabalin on day two of treatment. He took seventeen pregabalin 100mg capsules and drank wine after a family conflict. He had no symptoms of depression prior to this event. He reported sedation as his only reaction. He required no treatment and the outcome was reported as recovered.
087 015011 This 35 year old female with GAD was hospitalized after 112 days of pregabalin (51 days in RCT and 61 days in open label study). She ingested eighty 100mg pregabalin capsules. The reason for the overdose was not provided. She experienced drowsiness, slurred speech, hypotension, and ataxia. She recovered the next day and was discharged. The discharge diagnoses included impulsive overdose and known depression.

4.9 Withdrawal and Rebound

Pfizer provided analyses of data, predominately from psychiatry studies, to support their conclusion that pregabalin was associated with discontinuation symptoms seen with anti-depressants and not like symptoms seen with discontinuation of benzodiazepines.

Pfizer noted that pregabalin discontinuation following chronic administration in rats did not suggest physical dependence. They also noted that there were no clear effects of pregabalin on suppression of benzodiazepine withdrawal in diazepam dependent monkeys (Summary of Safety, p.74).

Pfizer reported on Discontinuation Emergent Signs and Symptoms (DESS) during short term controlled psychiatry trials. Discontinuation adverse events were defined as events that started during the taper or withdrawal phase or events that worsened during the taper or withdrawal phase. Pfizer explained that most pregabalin doses in these studies were tapered over 3-6 days (Memo 720-30173, p.42). Pfizer reported that 15.7% (n=290) of pregabalin subjects and 11.1% (n=91) of placebo subjects experienced at least one DESS.

DESS that were reported for at least 1% of pregabalin subjects and at least twice as frequently compared to placebo were insomnia (pregabalin 2.4%, 44/1851; placebo 0.7%, 6/817), and infection (pregabalin 1.7%, 31/1851; placebo 0.7%, 6/817).

Pfizer provided a separate analysis of DESS for pooled data from a GAD (088) and a SAD (082) study that used a relapse prevention design. In these two studies, 21% (n=52) of pregabalin subjects and 17.3% (n=42) of placebo subjects had at least one DESS. The following table lists DESS that were reported for at least 1% of pregabalin subjects and at least twice as frequently compared to placebo.

FDA Table 89. Summary of DESS in Psychiatric Studies 082 and 088

[Number of Patients (%)]

Preferred Term	Placebo N = 243		Pregabalin 450 mg/d N = 249	
Any DESS	**42**	**(17.3)**	**52**	**(20.9)**
Insomnia	2	(0.8)	13	(5.2)
Nausea	2	(0.8)	10	(4.0)
Diarrhea	2	(0.8)	7	(2.8)
Chills	0	(0.0)	5	(2.0)
Anorexia	1	(0.4)	4	(1.6)
Infection	2	(0.8)	4	(1.6)
Nervousness	0	(0.0)	4	(1.6)
Depression	0	(0.0)	3	(1.2)
Dyspepsia	2	(0.8)	3	(1.2)
Gastrointestinal disorder	0	(0.0)	3	(1.2)
Paresthesia	0	(0.0)	3	(1.2)
Vasodilatation	0	(0.0)	3	(1.2)

From Pfizer Table 28, p.76 Summary of Safety

Pfizer reported that in a DPN study, the pregabalin treated subjects had a lower DESS risk (10.5%, 9/86) than did placebo (16%, 13/81) or amitriptyline (13.8%, 12/87) subjects. In a study of 30 healthy volunteers, DESS included anxiety (n=2), nervousness/personality disorder/thinking abnormal (n=1), sinusitis (n=2) and arthralgia (n=1) (Summary of Safety p.76).

Pfizer interpreted results from a physician withdrawal checklist (PWC) as not suggestive of benzodiazepine like withdrawal. During the pregabalin controlled psychiatry studies, Pfizer used the PWC to look for symptoms related to benzodiazepine like withdrawal. Pfizer noted that following abrupt withdrawal of benzodiazepines, PWC total score mean change has been in the range of 12 to 25 points. In the short term controlled psychiatry studies, Pfizer found PWC changes that were numerically greater and in some cases statistically significantly greater than placebo (Summary of Safety, pp.76-77). In one study, at the first follow up visit the pregabalin 600mg/day group had a PWC mean change of 4.81 and after the second follow up visit (after 8 days off treatment) had a mean change of 9.41. Pfizer attributed the increase at the second follow up visit to a return of anxiety following termination of treatment (Summary of Safety, p.77). Following long term studies, Pfizer noted PWC mean changes (0.6 to 2.05) that were

statistically significantly greater than placebo at both follow up visits, but lower than the results of 12 to 25 reported for benzodiazepines (Summary of Safety, p.77).

Pfizer assessed subjects in a short-term (083) and long-term (088) study post hoc for rebound anxiety. Pfizer reasoned that because of the short half-life of pregabalin, rebound anxiety would be observed at the first follow-up visit as elevated HAM-A score, but the HAM-A scores would return to closer to termination values by the second follow-up visit. Pfizer concluded that there was no evidence of rebound anxiety in patients receiving long-term treatment in study 088 and that the results from study 083 were more consistent with relapse of anxiety rather than rebound anxiety (Summary of Safety, p.78).

4.10 Drug Abuse

Pfizer concluded that pregabalin "does not appear to produce physiological dependence beyond what might be associated with any unscheduled anxiolytic or antidepressant compound" (Clinical Overview, p.134). Pfizer also stated that "pregabalin was characterized by a novel profile of subjective effects, suggesting that pregabalin will be acceptable to patients and unlikely to be abused (Clinical Overview, p. 126). They noted that pregabalin is in the same pharmaceutical class as gabapentin, which lacks dependence or abuse signals in its post-marketing database.

The Controlled Substance Staff (HFD-009) reviewed the pregabalin drug abuse potential data and concluded that pregabalin has similar abuse potential to diazepam. The Controlled Substance Staff, in a 3/25/04 letter to Pfizer, conveyed that would recommend that pregabalin be placed into Schedule IV of the CSA. In the letter, the Controlled Substance Staff cited evidence supporting their conclusion about the abuse potential of pregabalin including the high rate of euphoria among pregabalin subjects relative to placebo in controlled trials. They also noted that in the clinical abuse potential study in sedative/alcohol abusing subjects, the subjective responses to "good drug effect", "high", "liking", and "liking (end of session)" for pregabalin doses of 200mg and 450mg were similar or greater than the responses for diazepam doses of 15mg and 30mg. The Controlled Substance Staff also noted that pregabalin was associated with self-administration in rhesus monkeys at 3.2 and 10mg/kg infusion doses during initial access to the drug.

Pfizer has responded the Controlled Substance Staff letter and discussions are ongoing.

4.11 Human Pregnancy and Lactation

There have been 17 confirmed pregnancies in patients exposed to pregabalin through the Safety Update (see page 71, Summary of Clinical Safety; pages 443 and 1179, Safety Update). Pfizer reported that these pregnancies resulted in seven live births (including one set of twins) of eight babies, four therapeutic abortions, three spontaneous abortions, and three unknown outcomes.[39] Pfizer reported six confirmed pregnancies among

[39] In addition, a pregnancy was reported in a patient participating in study 167, an ongoing study not in the integrated safety database. Patient 164_158004 reported a pregnancy based on a urine pregnancy test. This

placebo-treated patients. These pregnancies resulted in one live birth, three therapeutic abortions, one spontaneous abortion, and one unknown outcome.

Pfizer reported that when pregnancies were detected, pregabalin was discontinued and the patients were withdrawn from the studies in which they were participating.[40] They reported that exposure to pregabalin in the patients who became pregnant ranged from two to 1199 days at dosages ranging from 150 mg to 600 mg/day. I used the estimated dates of conception and dates of pregabalin discontinuation provided in the narratives to estimate the dates of fetal exposure to pregabalin relative to conception in the pregnancies that resulted in live births. I determined that in five cases, the women who became pregnant were receiving pregabalin on the estimated date of conception and that the subsequent fetal exposure time ranged from 13 to 75 days. In two cases, pregabalin was started after the estimated date of conception. In these cases, the fetuses were exposed from days 14 to 16 and 24 to 64.

Pfizer reported that the seven live births produced eight healthy children. The only anomaly reported was a "nickel sized scalp hemangioma" in the child of patient 009_007107. This baby was otherwise healthy at birth and follow-ups conducted at six months and one year. Follow-up information at one year was reported for five babies with in utero pregabalin exposure; all five children were reported to be healthy at one year. Health at birth is the only information available for three babies.

One patient who had become pregnant while receiving pregabalin was placed on pregabalin again 40 days after giving birth. This patient did not breast-feed. Pfizer stated that pregabalin has not been studied in lactating women. They report that pregabalin is present in the milk of rats but that it is unknown whether it is excreted in human breast milk.

4.12 Drug-Drug Interaction

Pfizer's presentation of drug-drug interactions was based on data from clinical pharmacology drug interaction studies and population pharmacokinetic analyses. Pfizer did not examine the effect of concomitant use of classes of medications or specific medications on AEs or lab parameters within the Phase II/III safety database.

In their Summary of Clinical Pharmacology Studies, Pfizer reported that valproic acid, carbamazepine, and lamotrigine had no effect on pregabalin pharmacokinetics and that pregabalin did not effect the pharmacokinetics of valproic acid, carbamazepine (and its metabolite), lamotrigine or phenytoin. Pfizer stated that gabapentin pharmacokinetics were unaltered by pregabalin and that the rate but not extent of pregabalin absorption was reduced by 26% (single dose) and 18% (multiple dose) with pregabalin coadministration

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pregnancy was not confirmed by a serum pregnancy test and Pfizer reports that the outcome of this pregnancy is unknown. No additional information about this pregnancy is presented in the Safety Update.

[40] The narratives demonstrated one exception to this rule; patient 011_059027 had a positive pregnancy test on study day 1199. Pregabalin was continued and the patient had a miscarriage on study day 1218. Pregabalin treatment continued unchanged. See narrative on page 2487 of the Safety Update.

Pfizer noted that multiple doses of pregabalin did not significantly affect lorazepam, oxycodone, or ethanol single-dose pharmacokinetics. Pfizer also reported that single doses lorazepam, oxycodone, or ethanol had no effect on the steady-state pharmacokinetics of pregabalin. In addition, Pfizer reported that multiple oral doses of pregabalin administered with lorazepam, oxycodone, or ethanol did not result in clinical important effects on respiration. Pfizer felt that pregabalin appears to potentiate or be additive in the impairment of cognitive and gross motor function caused by oxycodone, ethanol, and lorazepam. Pfizer reported that pregabalin had no effect on the pharmacokinetics of norethindrone and ethinyl estradiol (Ortho-Novum). Pfizer also reported that population pharmacokinetic analyses in patients with pain disorders demonstrated that oral hypoglycemics, diuretics, and insulins had no effect on the clearance of pregabalin.

5. Review of Systems

5.1 Cardiovascular

Cardiovascular causes of death were commonly identified for pregabalin subjects who died. Of the 55 deaths that occurred in pregabalin subjects in the NDA, twenty eight were cardiovascular or potentially cardiovascular in nature. The cardiovascular causes of death in the pregabalin NDA included cardiomyopathy, myocardial infarction, congestive heart failure, and pulmonary embolism. In addition there were deaths attributed to heart arrest and sudden death in the Body as a Whole organ system group, which may also represent cardiovascular causes of death. The majority of pregabalin subjects who died from cardiovascular causes were from the neuropathic pain indication studies where these types of events are expected, given the age and underlying disease in these subjects and the prevalence of cardiovascular disease in such a population. The cardiovascular deaths reported in the safety update were similar in nature to those reported in the NDA.

In the controlled trials through the safety update, cardiovascular SAEs occurred in 0.5% (13/2449) of placebo subjects compared to 0.7% (40/5781) of pregabalin subjects. No single type of cardiovascular SAE was reported for more than 0.1% of pregabalin subjects in the controlled trials. The most common cardiovascular SAEs among pregabalin subjects in the controlled trials were angina pectoris (pregabalin 0.1%, n=5; placebo 0.1%, n=1), congestive heart failure (pregabalin 0.1%, n=4; placebo 0.1%, n=1), and myocardial infarct (pregabalin 0.1%, n=4; placebo 0.1%, n=1). For the combined controlled and uncontrolled trials database through the safety update, the cardiovascular SAEs reported for more than 0.1% of subjects were myocardial infarct (0.4%, 36/9278), congestive heart failure (0.3%, 30/9278), angina pectoris (0.3%, 25/9278), cerebrovascular accident (0.2%, 22/9278) coronary artery disorder (0.2%, 21/9278), syncope (0.2%, 21/9278) and atrial fibrillation (0.2%, 14/9278).

In the controlled trials through the safety update, cardiovascular AEs led to discontinuation of 0.7% (17/2449) of placebo subjects compared to 0.6% (37/5781) of pregabalin subjects. No single type of cardiovascular AE led to discontinuation of more

than 0.1% of pregabalin subjects in the controlled trials or the combined controlled and uncontrolled trials through the safety update.

In the controlled trials through the safety update, cardiovascular AEs were reported by 5.8% (141/2449) of placebo subjects compared to 5.6% (324/5781) of pregabalin subjects. No single type of cardiovascular AE was reported for more than 1% of pregabalin subjects in the controlled trials. For the combined controlled and uncontrolled trials through the safety update, the cardiovascular AEs reported by more than 1% of pregabalin subjects were hypertension (2.1%, 191/9278), and vasodilatation (1.3%, 120/9278).

Analysis of the NDA ECG data did not reveal evidence of pregabalin associated QT prolongation, but Pfizer did find evidence of PR interval prolongation. Pfizer noted that pregabalin increased the PR interval at doses =300mg/day, with mean lengthening of the PR interval of 3-6msec compared to placebo. Pfizer's outlier analyses for PR prolongation appeared to demonstrate slight increases in risk for PR increase =25% from baseline and for on-treatment PR >200msec. Pfizer found no meaningful differences between pregabalin and placebo subjects for adverse events coded to terms related to AV block, based on a small number of such events.

Pregabalin treated subjects in controlled trials appeared to have slightly greater mean decreases in blood pressure and slightly greater outlier risks for low blood pressure compared to the placebo subjects. A review of the AEs potentially related to hypotension in the controlled trials found similar risks by treatment for syncope (pregabalin 0.3%, 20/5781; placebo 0.2%, 5/2449), hypotension (pregabalin 0.2%, 13/5781; placebo 0.1%, 3/2449), and postural hypotension (pregabalin 0.2%, 11/5781; placebo 0.1%, 3/2449) based on a small number of events. There was a clearly elevated risk for dizziness AEs among pregabalin subjects (pregabalin 28.9%, 1673/5781; placebo 8.6%, 211/2449) although the relationship between this event and low blood pressure is not known

5.2 Digestive System

The digestive system related causes of death reported for pregabalin subjects in the NDA included adenocarcinoma of the liver, liver metastasis from unknown primary, colon cancer, intestinal obstruction, and necrotizing pancreatitis.

In the NDA controlled trials through the safety update, digestive system SAEs occurred in 0.3% (7/2449) of placebo subjects compared to 0.3% (16/5781) of pregabalin subjects. No single type of digestive system SAE was reported for more than 0.1% of pregabalin subjects in the controlled trials. For the NDA combined controlled and uncontrolled trials database the digestive system SAE reported for more than 0.1% of subjects was gastrointestinal disorder (0.2%, 15/9278 included the following verbatim terms: appendicitis, n=8; GERD, n=3; diverticulosis and biliary dyskinesia, n=1 each). Among the digestive system SAEs from the combined controlled and uncontrolled trials, there were three cases of pancreatitis and one case of necrotizing pancreatitis. One pancreatitis SAE case occurred in the setting of alcohol use, two cases were associated with biliary

stones (cholelithiasis, vesicular lithiasis), and one case had no identified confounding factors identified. There were no cases of acute hepatic failure or hepatic necrosis SAEs.

In the NDA controlled trials through the safety update, digestive system AEs led to discontinuation of 1.6% (39/2449) of placebo subjects compared to 2.4% (140/5781) of pregabalin subjects. Nausea (pregabalin 1%, 57/5781; placebo 0.7%, 18/2449), dry mouth (pregabalin 0.4%, 24/5781; placebo 0.1%, 3/2449), vomiting (pregabalin 0.3%, 16/5781; placebo 0.3%, 8/2449), diarrhea (pregabalin 0.3%, 15/5781; placebo 0.2%, 6/2449), and constipation (pregabalin 0.2%, 11/5781; placebo 0.1%, 2/2449), were the digestive system AEs leading to discontinuation of more than 0.1% of pregabalin subjects in controlled trials. In the combined controlled and uncontrolled trials through the safety update, the following AEs led to discontinuation in more than 0.1% of pregabalin subjects: nausea (1%, 96/9278), diarrhea (0.4%, 34/9278), dry mouth (0.3%, 31/9278), vomiting (0.3%, 28/9278), constipation (0.3%, 27/9278), anorexia (0.2%, 14/9278), and dyspepsia (0.2%, 14/9278).

In the controlled trials through the safety update, digestive system AEs were reported by 22.3% (546/2449) of placebo subjects compared to 26.6% (1540/5781) of pregabalin subjects. The following digestive system AEs were reported by more than 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo: dry mouth (pregabalin 8.8%, 511/5781; placebo 3.5%, 85/2449), constipation (pregabalin 4.7%, 270/5781; placebo 2.3%, 57/2449), and increased appetite (pregabalin 2.3%, 132/5781; placebo 0.8%, 20/2449). In the controlled trials the risk for pancreatitis among pregabalin subjects (<0.01%, 2/581) was similar to the risk among placebo subjects (<0.1%, 1/2449) based on a small number of events. For the combined controlled and uncontrolled trials through the safety update, the digestive system AEs reported by more than 1% of pregabalin subjects were nausea (9.7%, 903/9278), dry mouth (9.1%, 840/9278), constipation (6.3%, 582/9274), diarrhea (6.2%, 576/9278), dyspepsia (3.7%, 345/9278), vomiting (3.5%, 322/8274), flatulence (3.1%, 291/9278), increased appetite (3.1% 287/9278), anorexia (1.9%, 172/9278), and gastrointestinal disorder (1.2%, 109/9278) and gastroenteritis (1.1%, 98/9278). In addition, there were a total of ten cases of pancreatitis and one case of necrotizing pancreatitis in the combined controlled and uncontrolled trials database. One additional pancreatitis case was reported from an ongoing study not yet entered into the database. One pancreatitis case occurred prior to pregabalin exposure and many of the remaining cases were associated with confounding factors (ex. cholelithiasis, alcohol use).

There did not appear to be notable differences by treatment for transaminase mean changes from baseline or outliers in the controlled trials. The NDA database included six pregabalin subjects who had transaminase values >3xULN along with total bilirubin >2mg/dL. Two of the cases were likely related to cholelithiasis, one case occurred in a subject with a history of alcohol abuse and hospitalizations for pancreatitis; one subject was rechallenged following the event without recurrence; one event was noted eight days after a subject had discontinued from a trial following a GI bleed (on day 6); and the last event occurred in a subject who had slightly elevated AST and total bilirubin at baseline (case summarized on page 115).

5.3 Nervous System

The nervous system related causes of death reported for pregabalin subjects in the NDA included convulsion, cerebrovascular accident, cerebral hemorrhage, intracranial hemorrhage, and brain metastasis.

In the NDA controlled trials through the safety update, nervous system SAEs occurred in 0.4% (11/2449) of placebo subjects compared to 0.3% (18/5781) of pregabalin subjects. No single type of nervous system SAE was reported for more than 0.1% of pregabalin subjects in the controlled trials. For the NDA combined controlled and uncontrolled trials database, depression (0.2%, 17/9278) was the only nervous system SAE reported for more than 0.1% of subjects.

In the NDA controlled trials through the safety update, nervous system AEs led to discontinuation of 2.7% (66/2449) of placebo subjects compared to 9.5% (552/5781) of pregabalin subjects. Dizziness (pregabalin 4.1%, 236/5781; placebo 0.6%, 15/2449), somnolence (pregabalin 4.1%, 236/5781; placebo 0.3%, 7/2449), ataxia (pregabalin 1%, 56/5781; placebo <0.1%, 1/2449), and confusion (pregabalin 1%, 55/5781; placebo 0.2%, 4/2449) were the nervous system AEs leading to discontinuation of at least 1% of pregabalin subjects and twice as frequently compared to placebo in controlled trials. In the combined controlled and uncontrolled trials, the following AEs led to discontinuation of more than 1% of pregabalin subjects: dizziness (3.8%, 357/9278), somnolence (3.5%, 323/9278), and thinking abnormal (1.2%, 110/9278).

In the NDA controlled trials through the safety update, nervous system AEs were reported by 27.6% (676/2449) of placebo subjects compared to 55.6% (3216/5781) of pregabalin subjects. The following nervous system AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo: dizziness (pregabalin 28.9%, 1673/55781; placebo 8.6%, 211/2449), somnolence (pregabalin 21.7%, 1257/5781; placebo 7.5%, 183/2449), thinking abnormal (pregabalin 5.3%, 305/5781; placebo 1.6%, 38/2449), ataxia (pregabalin 4.6%, 265/5781; placebo 1%, 25/2449), incoordination (pregabalin 3.9%, 223/5781; placebo 0.7%, 17/2449), euphoria (pregabalin 3.6%, 206/5781; placebo 0.4%, 11/2449), amnesia (pregabalin 2.8%, 163/5781; placebo 1%, 24/2449), confusion (pregabalin 2.7%, 156/5781; placebo 0.6%, 14/2449), vertigo (pregabalin 1.7%, 100/5781; placebo 0.4%, 11/2449), speech disorder (pregabalin 1.7%, 96/5781; placebo 0.1%, 2/2449), abnormal gait (pregabalin 1.5%, 87/5781; placebo 0.1%, 3/2449), depersonalization (pregabalin 1.4%, 82/5781; placebo 0.4%, 9/2449), libido decreased (pregabalin 1.4%, 80/5781; placebo 0.3%, 7/2449), twitching (pregabalin 1.2%, 69/5781, placebo 0.5%, 12/2449), hypesthesia (pregabalin 1%, 60/5781, placebo 0.4%, 11/2449), and stupor (pregabalin 1%, 59/5781, placebo 0.1%, 2/2449). For the combined controlled and uncontrolled trials, the nervous system AEs reported by more than 1% of pregabalin subjects were:

Dizziness (33.1%, n=3070)	Somnolence (26.3%, n=2438)
Thinking abnormal (8%, n=741)	Ataxia (6.5%, n=602)

Insomnia (5.9%, n=545)
Amnesia (5%, n=467)
Depression (4.6%, n=428)
Confusion (3.9%, n=364)
Anxiety (2.8%, n=264)
Hypesthesia (2.3%, n=212)
Vertigo (2.2%, n=200)
Libido decreased (2%, n=188)
Depersonalization (1.8%, n=163)
Neuropathy (1.6%, n=146)
Stupor (1.2%, n=109)
Incoordination (5.4%, n=497)
Euphoria (4.6%, n=429)
Nervousness (4.5%, n=418)
Tremor (3.9%, n=363)
Parasthesia (2.8%, n=260)
Abnormal gait (2.2%, n=201)
Speech disorder (2.1%, n=196)
Twitching (2%, n=184)
Hypertonia (1.6%, n=148)
Emotional lability (1.5%, n=139)
Nystagmus (1.1%, n=103)

5.4 Respiratory System

The respiratory system related causes of death reported for pregabalin subjects in the NDA included apnea, pneumonia, COPD exacerbation, airway obstruction, and aspiration.

In the controlled trials through the safety update, respiratory system SAEs occurred in 0.1% (3/2449) of placebo subjects compared to 0.3% (18/5781) of pregabalin subjects. No single type of respiratory system SAE was reported for more than 0.1% of pregabalin subjects in the controlled trials. For the NDA combined controlled and uncontrolled trials database pneumonia (0.5%, 47/9278) and lung disorder (0.2%, 14/9278) were the respiratory system SAEs reported for more than 0.1% of subjects.

In the controlled trials through the safety update, respiratory system AEs led to discontinuation of 0.3% (7/2449) of placebo subjects compared to 0.4% (22/5781) of pregabalin subjects. No single type of respiratory AE led to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials or the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, respiratory system AEs were reported by 7.1% (174/2449) of placebo subjects compared to 8.3% (480/5781) of pregabalin subjects. No respiratory system AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo. In the combined controlled and uncontrolled trials, the respiratory system AEs reported by more than 1% of pregabalin subjects were pharyngitis (4.1%, 383/9278), sinusitis (3.9%, 364/9278), rhinitis (3.3%, 305/9278), bronchitis (2.6%, 241/9278), dyspnea (2.4%, 222/9278), cough increased (1.5%, 129/8666), pneumonia (1.4%, 121/8666), and lung disorder (1.6%, 151/9278), and pneumonia (1.4%, 133/9278). In addition, there were four cases of lung fibrosis and two cases of pulmonary hypertension in the combined controlled and uncontrolled trials database (narratives for the 3 lung fibrosis and 1 pulmonary hypertension SAEs are included in Appendix 2).

5.5 Musculoskeletal System

* Although Pfizer included the AE CK increased under the Metabolic Endocrine body system, we include it here.

No pregabalin NDA deaths were attributed to musculoskeletal related causes.

In the NDA controlled trials, musculoskeletal system SAEs occurred in no placebo subjects compared to 0.1% (4/5781) of pregabalin subjects. Two pregabalin subjects (<0.1% 2/5781) and no placebo subjects in the controlled trials had SAEs of myopathy. One pregabalin subject (<0.1% 1/5781) and no placebo subjects in the controlled trials had SAEs of CK increased. No single type of musculoskeletal system SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials. The combined controlled and uncontrolled trials included two SAEs of myopathy and three SAEs of CK increased.

In the controlled trials through the safety update, musculoskeletal system AEs led to discontinuation of 0.1% (3/2449) of placebo subjects compared to 0.3% (16/5781) of pregabalin subjects. No single type of musculoskeletal AE led to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials or the combined controlled and uncontrolled trials. In the controlled trials, two pregabalin (<0.1%, 2/5781) and no placebo subjects discontinued for myopathy. In the controlled trials, five pregabalin (0.1%, 5/5781) and no placebo subjects discontinued for CK increased. In the combined controlled and uncontrolled trials, two pregabalin subjects (<0.1%, 2/9278) discontinued for myopathy and 11 (0.1%, 11/9278) discontinued for CK increased.

In the NDA controlled trials, musculoskeletal system AEs were reported by 3.7% (88/2384) of placebo subjects compared to 4.3% (237/5508) of pregabalin subjects. No musculoskeletal system AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo. Two pregabalin (<0.1%, 2/5508) and no placebo subjects had AEs of myopathy. CK increased AEs were reported for 0.7% (39/5508) of pregabalin subjects and 0.3% (7/2384) of placebo subjects. In the combined controlled and uncontrolled trials, the musculoskeletal system AEs reported by more than 1% of pregabalin subjects were arthralgia (2.6%, 238/9278), myalgia (1.8%, 164/9278), arthritis (1.5%, 135/9278), leg cramps (1.4%, 134/9278), and myasthenia (1.3%, 121/9278). Less than 0.1% (4/9278) of pregabalin subjects had an AE of myopathy and 1.2% (112/9278) had an AE of CK increased.

The pregabalin controlled trial lab data demonstrated greater mean increases in creatine kinase among pregabalin subjects compared to placebo subjects. Pregabalin subjects also had slightly greater high outlier risks for creatine kinase.

5.6 Urogenital System

Renal cell cancer was the only urogenital system related cause of death reported in the NDA database.

In the controlled trials through the safety update, urogenital system SAEs occurred in 0.1% (2/2449) of placebo subjects compared to 0.1% (8/5781) of pregabalin subjects. No single type of urogenital system SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials. The combined controlled and uncontrolled trials included five SAEs of kidney calculus.

In the controlled trials through the safety update, urogenital system AEs led to discontinuation of 0.2% (4/2449) of placebo subjects compared to 0.6% (32/5781) of pregabalin subjects. Impotence (pregabalin 0.3%, 17/5781; placebo 0/2449) was the only urogenital AE that led to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials. The urogenital system AEs that led to discontinuation of more than 0.1% of subjects in the combined controlled and uncontrolled trials were impotence (0.4%, 33/9278) and anorgasmia (0.2%, 14/9278).

In the controlled trials through the safety update, urogenital system AEs were reported by 5.3% (131/2449) of placebo subjects compared to 7.5% (432/5781) of pregabalin subjects. Impotence (pregabalin 1.3%, 78/5781; placebo 0.4%, 9/2449) was the only urogenital system AE reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo. Kidney calculus was reported as an AE for 0.1% (2/2449) of placebo subjects and 0.1% (6/5781) of pregabalin subjects in the NDA controlled trials database. No placebo subjects and one pregabalin subject had an AE of acute kidney failure. In the combined controlled and uncontrolled trials, the urogenital system AEs reported by more than 1% of pregabalin subjects were urinary tract infection (3.7%, 340/9278), impotence (2.2%, 205/9278), and anorgasmia (1.1%, 100/9278). Kidney calculus was reported for 0.3% (n=27) and acute kidney failure for 0.1% (n=9) of pregabalin subjects in the combined controlled and uncontrolled trials database.

Lab data did not suggest meaningful differences between pregabalin and placebo subjects in creatinine mean changes from baseline or creatinine outlier risks.

5.7 Skin and Appendages

No pregabalin NDA deaths were attributed to skin/appendages related causes.

In the controlled trials through the safety update, skin and appendage system SAEs were reported for no placebo subjects and 4 pregabalin subjects. No single type of skin and appendages system SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials. The combined controlled and uncontrolled trials included one SAE of Stevens Johnson Syndrome.

In the controlled trials through the safety update, skin and appendage system AEs led to discontinuation of 0.4% (10/2449) of placebo subjects compared to 0.4% (22/5781) of pregabalin subjects. Rash (pregabalin 0.2%, 12/5781; placebo 0.2% 5/2449) was the only skin and appendage AE that led to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials. The only skin and appendage system AE that led to

discontinuation of more than 0.1% of subjects in the combined controlled and uncontrolled trials was rash (0.3%, 31//9278).

In the controlled trials through the safety update, skin and appendage system AEs were reported by 6.4% (156/2449) of placebo subjects compared to 5.3% (308/5781) of pregabalin subjects. No skin and appendage system AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo. In the combined controlled and uncontrolled trials, the skin and appendage system AEs reported by more than 1% of pregabalin subjects were rash (4.8%, 445/9278), pruritis (1.5%, 140/9278), and sweating (1.3%, 123/9278). Stevens Johnson Syndrome was reported for one subject in the combined controlled and uncontrolled trials database.

Preclinical studies documented a finding of tail skin ulcers in rats and monkeys but not mice. There did not appear to be evidence of differences in risk between pregabalin and placebo subjects for skin and appendage AE terms suggestive of skin ulcers.

5.8 Hemic and Lymphatic System

No pregabalin NDA deaths were attributed to hemic and lymphatic system related causes.

In the controlled trials through the safety update, hemic and lymphatic system SAEs were reported for no placebo subjects compared to 0.1% (7/5781) of pregabalin subjects. No single type of hemic and lymphatic system SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials. The combined controlled and uncontrolled trials included one pancytopenia SAE and one thrombocytopenia SAE.

In the controlled trials through the safety update, hemic and lymphatic system AEs led to discontinuation of 0.1% (2/2449) of placebo subjects compared to 0.1% (7/5781) of pregabalin subjects. No hemic and lymphatic AE led to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials or the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, hemic and lymphatic system AEs were reported by 1.2% (29/2449) of placebo subjects compared to 1.6% (90/5781) of pregabalin subjects. No hemic and lymphatic system AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo. In the combined controlled and uncontrolled trials, the only hemic and lymphatic system AE reported by more than 1% of pregabalin subjects was ecchymosis (1.9%, 172/9278). Thrombocytopenia was reported for 0.4% (38/9278) of pregabalin subjects and pancytopenia by one pregabalin subject in the combined controlled and uncontrolled trials database.

The pregabalin controlled trial lab data demonstrated greater mean decreases in platelet counts among pregabalin subjects compared to placebo subjects. Pregabalin subjects also had slightly greater outlier risks for low platelet counts.

Preclinical lab data found platelet increases in mice and platelet decreases in rats. A study in monkeys demonstrated no increases in platelet count, no platelet morphological abnormalities and no evidence of drug-related platelet aggregation (Nonclinical Overview, p.34; Memo RR 745-03746).

5.9 Metabolic and Nutritional

No pregabalin NDA deaths were attributed to metabolic and nutritional related causes.

In the controlled trials through the safety update, metabolic and nutritional SAEs were reported for 0.1% (3/2449) of placebo subjects compared to 0.2% (9/5781) of pregabalin subjects. No single type of metabolic and nutritional SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, metabolic and nutritional AEs led to discontinuation of 0.3% (7/2449) of placebo subjects compared to 0.9% (51/5781) of pregabalin subjects. Peripheral edema (pregabalin 0.6%, 32/5781; placebo 0.2%, 4/2449) and weight gain (pregabalin 0.2%, 10/5781; placebo <0.1%, 1/2449) were the only metabolic and nutritional AE leading to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials. Weight gain (1.1%, 99/9278), peripheral edema (1.1%, 99/9278) and edema (0.2%, 14/9278) were the metabolic and nutritional AEs leading to discontinuation of more than 0.1% of subjects from the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, metabolic and nutritional AEs were reported by 4.9% (121/2449) of placebo subjects compared to 14.7% (852/5781) of pregabalin subjects. The metabolic and nutritional AEs reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo were peripheral edema (pregabalin 6.4%, 372/5781; placebo 1.9%, 46/2449), weight gain (pregabalin 6%, 347/5781; placebo 0.9%, 21/2449) and edema (1.1%, 64/5781; placebo 0.3%, 8/2449) . In the combined controlled and uncontrolled trials, the metabolic and nutritional AEs reported by more than 1% of pregabalin subjects were weight gain (12.4%, 1154/9278), peripheral edema (10.1%, 935/9278), edema (1.6%, 147/9278), and hyperglycemia (1.1%, 100/9278), .

The weight data collected during the controlled trials demonstrated that pregabalin subjects experienced a greater mean increase in weight and a higher risk of weight gain of at least 7% of baseline body weight when compared to placebo subjects.

5.10 Endocrine

No pregabalin NDA deaths were attributed to endocrine related causes.

In the controlled trials through the safety update, no endocrine SAEs were reported for more than 0.1% of pregabalin subjects. In the combined controlled and uncontrolled trials no endocrine SAEs were reported for more than 0.1% of subjects.

In the controlled trials through the safety update, no placebo subjects and three pregabalin subjects discontinued for endocrine AEs. No endocrine AEs led to discontinuation of more than 0.1% of subjects from the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, endocrine AEs were reported by 0.2% (4/2449) of placebo subjects compared to 0.3% (15/5781) of pregabalin subjects. Diabetes mellitus (pregabalin 0.2%, 9/5781; placebo 0.2%, 4/2449) was the only endocrine AE reported for more than 0.1% of pregabalin subjects. In the combined controlled and uncontrolled trials, diabetes mellitus (0.4%, 41/9278) and hypothyroidism (0.3%, 27/9278) were the only endocrine AEs was reported by more than 0.1% of pregabalin subjects.

5.11 Special senses

No pregabalin NDA deaths were attributed to special senses related causes.

In the controlled trials through the safety update, special senses SAEs were reported for 0.1% (2/2449) of placebo subjects compared to 0.1% (5/5781) of pregabalin subjects. No single type of special senses SAE was reported for more than 0.1% of pregabalin subjects in the controlled or the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, special senses AEs led to discontinuation of 0.3% (7/2449) of placebo subjects compared to 1.5% (88/5781) of pregabalin subjects. Amblyopia (pregabalin 0.8%, 44/5781; placebo 0.1%, 2/2449), diplopia (pregabalin 0.3%, 20/5781; placebo 0.1%, 2/2449), and abnormal vision (pregabalin 0.2%, 14/5781; placebo 0/2449), were the special senses AEs leading to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials. Amblyopia (0.8%, 74/9278), diplopia (0.3%, 27/9278), visual field defect (0.3%, 24/9278), and abnormal vision (0.2%, 18/9278), were the AEs leading to discontinuation of more than 0.1% of subjects from the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, special senses AEs were reported by 7.7% (189/2449) of placebo subjects compared to 14% (812/5781) of pregabalin subjects. The special senses AEs reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo were amblyopia (pregabalin 6.2%, 357/5781; placebo 2%, 49/2449), diplopia (pregabalin 2%, 115/5781; placebo 0.4%, 11/2449) and abnormal vision (pregabalin 1.9%, 108/5781; placebo 0.4%, 11/2449). In the combined controlled and uncontrolled trials, the special senses AEs reported by more than 1% of pregabalin subjects were amblyopia (8.7%, 808/9278), diplopia (3.4%, 313/9278), abnormal vision (2.9%, 269/9278), visual field defect (2.2%,

202/9278), eye disorder (1.5%, 141/9278), conjunctivitis (1.5%, 138/9278), otitis media (1.4%, 131/9278), and retinal disorder (1.1%, 98/9278).

5.12 Body as a Whole

The Body as a Whole organ system generally included pregabalin deaths due to cancer and sudden death.

In the controlled trials through the safety update, 0.3% (8/2384) of placebo subjects and 0.7% (43/5508) of pregabalin subjects had a SAE classified in the Body as a Whole category. Accidental injury (pregabalin 0.3%, 16/5781; placebo 0.0%, 1/2449) and chest pain (pregabalin 0.2%, 9/5781; placebo 0.1%, 3/2449) were the Body as a Whole SAEs that occurred in more than 0.1% of pregabalin subjects in the controlled trials database. In the combined controlled and uncontrolled trials database, accidental injury (1%, 89/9278), chest pain (0.3%, 32/9278), infection (0.3%, 27/9278), and cellulitis (0.2%, 25/9278) were the Body as a Whole SAEs reported for more than 0.1% of study subjects.

In the NDA controlled trials through the safety update, Body as a Whole AEs led to discontinuation of 2.1% (51/2449) of placebo subjects compared to 3.1% (177/5781) of pregabalin subjects. Asthenia (pregabalin 0.9%, 54/5781; placebo 0.4%, 9/2449), headache (pregabalin 0.9%, 52/5781; placebo 0.7%, 17/2449), accidental injury (pregabalin 0.3%, 18/5781; placebo 0.1%, 3/2449), pain (pregabalin 0.2%, 11/5781; placebo 0.1%, 2/2449), and face edema (pregabalin 0.2%, 10/5781; placebo 0.1%, 3/2449) were the Body as a Whole AEs leading to discontinuation of more than 0.1% of pregabalin subjects in the controlled trials. Asthenia (1%, 92/9278), headache (1%, 90/9278), accidental injury (0.4%, 37/9278), abdominal pain (0.3%, 25/9278), pain (0.2%, 20/9278), and face edema (0.2%, 15/9278) were the Body as a Whole AEs leading to discontinuation of more than 0.1% of subjects from the combined controlled and uncontrolled trials.

In the controlled trials through the safety update, Body as a Whole AEs were reported by 34.3% (839/2449) of placebo subjects compared to 35.8% (2067/5781) of pregabalin subjects. No Body as a Whole AEs were reported by at least 1% of pregabalin subjects in the controlled trials and at least twice as frequently compared to placebo subjects. In the combined controlled and uncontrolled trials, the Body as a Whole AEs reported by more than 1% of pregabalin subjects were infection (16.1%, 1496/9278), headache (15.7%, 1457/9278), accidental injury (11.6%, 1080/9278), asthenia (11.2%, 1073/9278), pain (9.5%, 884/9278), flu syndrome (7%, 645/9278), back pain (5.1%, 471/9278), abdominal pain (4.1%, 379/9278), chest pain (3.2%, 296/9278), fever (1.3%, 121/9278), allergic reaction (1.3%, 117/9278), face edema (1.3%, 116/9278), and generalized edema (1.1%, 102/9278).

6. Discussion

Pfizer's approach to capturing safety data in the pregabalin trials appeared adequate and should have allowed characterization of common pregabalin-associated adverse events. Pfizer's description of the safety data in the pregabalin NDA and Safety Update also

appeared adequate. The coding of adverse events generally appeared acceptable, although there were instances of splitting similar adverse events to different terms, lumping dissimilar adverse events to single terms and rare instances of incorrect coding. The results of the coding process should have allowed a sufficient assessment of pregabalin's adverse event profile.

The number of subjects exposed to pregabalin exceeded the ICH guidelines for exposure and Pfizer exposed a considerable number of subjects to the proposed maximum intended pregabalin dose (600mg/day). As with most NDA safety databases, based on the number of subjects exposed in the development program, there was limited power to identify and or describe differences in risk for infrequent drug related adverse events.

Due to the diversity of the populations treated for the studied indications, the pregabalin safety database included distinct groups of predominately adult subjects. The overall, PHN, epilepsy, and GAD subjects treated with pregabalin had a slight female predominance while the DPN subjects treated with pregabalin had a slight male predominance. The neuropathic pain subjects treated with pregabalin group had the highest mean age (DPN mean age 60 years, PHN mean age 71.4 years) followed by the GAD (mean age 39 years) and the epilepsy (mean age 38 years) pregabalin treated subjects.

The overall AE risks were slightly higher in the epilepsy controlled trials (pregabalin 84%, placebo 70.1%) compared to the GAD trials (pregabalin 82%, placebo 71%) and the neuropathic pain trials (pregabalin 69%, placebo 55%). The AEs identified as occurring commonly among pregabalin subjects and more frequently compared to placebo subjects were generally similar across the different patient populations.

In the integrated controlled trials safety database, pregabalin was not associated with increased mortality risk compared to placebo, based on a small number of deaths. Pfizer calculated an SMR that did not suggest an increased mortality risk for open label pregabalin trials compared to a standard (U.S.) population. While this comparison does not identify a mortality signal with pregabalin, our confidence in this comparison is limited due to our lack of information about the similarities and differences between the studied population and the standard population The mortality risk for pregabalin treated subjects was not uniform across indications, with the highest mortality risk observed among pregabalin subjects in the post-herpetic neuralgia and diabetic neuropathy study populations. The NDA GAD database included a single death that occurred more than one month after last pregabalin dose. The epilepsy deaths in the NDA database were due to causes typically seen in epilepsy drug development programs and did not include clusters of deaths due to unusual causes. The deaths reported from the neuropathic pain studies were generally the types of deaths expected in an older population with comorbidities (cardiovascular, malignancy related) although there was a death in this population due to necrotizing pancreatitis. The contribution of pregabalin in this event was not clear. The narrative attributed the event to vesicular lithiasis. None of the following causes of death occurred in the pregabalin safety database: acute hepatic failure, serious skin reactions, rhabdomyolysis, or aplastic anemia.

Pregabalin was associated with a slightly higher risk for treatment emergent SAEs compared to placebo (pregabalin 2.2%, placebo 1.8%, Safety Update) in the integrated controlled trials database. Accidental injury (pregabalin 0.3%, 16/5781, placebo 0/2449) and chest pain (pregabalin 0.2%, 9/5781, placebo 0.1% 3/2449) were the two treatment emergent SAEs that occurred in at least 5 pregabalin subjects and were more frequent among pregabalin subjects in the integrated controlled trials database through the Safety Update. For both the epilepsy controlled trials and the GAD controlled trials, SAEs were more common among placebo subjects compared to pregabalin subjects. In epilepsy controlled trials, accidental injury was the only SAE reported by at least 1% of pregabalin subjects (pregabalin 1.2%, 9/758, placebo 0.3%, 1/294). In the GAD controlled trials accidental injury was the only SAE reported for more than one pregabalin subject (n=2). The combined controlled and uncontrolled trials safety database through the Safety Update included infrequent but potentially important treatment emergent SAEs of acute kidney failure (0.1%, 9/9278), pancreatitis or necrotizing pancreatitis (<0.1%, 4/9278), lung fibrosis (<0.1%, 3/9278), myopathy (<0.1%, 2/9278), pancytopenia (<0.1%, 1/9278), thrombocytopenia (<0.1%, 1/9278), angioedema (<0.1%, 1/9278), pulmonary hypertension (<0.1%, 1/9278), and Stevens Johnson Syndrome (<0.1%, 1/9278). In some cases Pfizer provided reasonable explanations for events. In the other cases, the potential for a causal relationship between the event and pregabalin was not excluded. Some of these events are addressed in the following paragraphs.

Compared to placebo, pregabalin was associated with an approximately two fold increased risk of discontinuing due to AEs in controlled trials (pregabalin 13.7%, 794/5781; placebo 6.6%, 161/2449, Safety Update). The difference in discontinuation due to AEs risk was most pronounced for several CNS AEs, specifically dizziness (pregabalin 4.1%, 236/5781; placebo 0.6%, 15/2449), somnolence (pregabalin 3.4%, 197/5781; placebo 0.3%, 7/2449), ataxia (pregabalin 1%, 56/5781; placebo <0.1%, 1/2449), and confusion (pregabalin 1%, 55/5781; placebo 0.2%, 4/2449). In both the epilepsy and GAD controlled trials, pregabalin subjects also had a greater risk for discontinuation due to AEs compared to placebo. In epilepsy controlled trials the AEs leading to discontinuation of at least 1% of pregabalin subjects and twice as frequently compared to placebo were predominately CNS related and included dizziness, somnolence, ataxia, asthenia, amblyopia, diplopia, tremor, confusion, thinking abnormal and headache. In GAD controlled trials the AEs leading to discontinuation of at least 1% of pregabalin subjects and twice as frequently compared to placebo were dizziness, somnolence, thinking abnormal and incoordination. For the combined controlled and uncontrolled trials safety group through the Safety Update, the list of AEs leading to discontinuation of at least 1% of pregabalin subjects included mostly CNS related AEs (dizziness 3.8%, 357/9278; somnolence 3.5%, 323/9278; thinking abnormal 1.2%, 110/9278; peripheral edema 1.1%, 99/9278; weight gain 1.1%, 99/9278; nausea 1%, 96/9278; asthenia 1%, 92/9278; headache 1%, 90/9278).

With the exception of CK and platelets, there did not appear to be evidence of differences in lab analyte results for pregabalin and placebo treated subjects in the controlled trials. The lab data analyses demonstrated greater mean platelet count decreases, as well as

increased risk for low outliers for platelet count for pregabalin subjects. The lab analyses also demonstrated greater mean CK increases and greater high outlier risks for CK for pregabalin subjects. These findings are discussed further in following paragraphs.

Pfizer's analyses of vital sign data did not suggest meaningful treatment related differences in blood pressure, heart rate, or respiratory rate, but pregabalin was associated with weight gain. In the integrated controlled trials, pregabalin subjects experienced a mean weight increase of 1.6kg compared to 0.3kg among placebo subjects. Pregabalin subjects had a 4.5 fold increase risk of gaining at least 7% of baseline body weight compared to placebo subjects. In the combined controlled and uncontrolled trials database, 4.5% (353/8666) of pregabalin subjects gained at least 15% of their baseline body weight. In an analysis that included only subjects treated with pregabalin for more than one year, the mean weight gain at end of treatment was 4.5kg. While the weight gain effect was present in all indication groups, the epilepsy subjects had the greatest weight gain risk. In the controlled epilepsy studies, 18% (133/737) pregabalin subjects gained at least 7% of body weight compared to 2.1% (6/292) of placebo subjects. Epilepsy controlled trials were generally longer than the other controlled trials, and when weight gain data were limited to the first six weeks of the epilepsy controlled trials (similar duration as the controlled trials for the neuropathic pain and GAD indications), there did not appear to be differences among the different indications. Within the epilepsy controlled trials, weight gain differences for pregabalin and placebo subjects were not explained by imbalances in the use of concomitant valproate or topiramate (drugs associated with weight changes).Weight gain appeared to be dose related, and the risk did not appear to be affected by gender, BMI, or age. Pfizer did report finding a higher incidence of increased appetite AEs among subjects who gained at least 7% of baseline body weight compared to those who did not gain that much weight. Pfizer concluded that the observed weight gain was not associated with increased risk of cardiovascular AEs, although the data on which these analyses are based are not capable of addressing long term effects of weight gain. Pfizer concludes that weight gain was not associated with increases in blood pressure but the data were not capable of addressing long term effects on blood pressure. Pfizer uses data from a small number of subjects who were observed after discontinuing pregabalin to support a conclusion that pregabalin associated weight gain is reversible. The wording they suggest in proposed labeling appears somewhat of an overstatement given the small number of subjects and the fact that the weight gain was not completely reversed upon follow up.

The phase II/III ECG data included in the submission did not suggest an effect of pregabalin on the QT interval but pregabalin did appear to slightly prolong the PR interval. The NDA did not include preclinical evaluations of the effect of pregabalin on ion channels or clinical pharmacological studies examining the effects of pregabalin on ECG. The QT data in the pregabalin NDA come from ECGs performed during phase II/III trials. Analyses of pooled ECG data did not support that pregabalin causes prolongation of the QT interval, although the use of a single baseline and a single end of study QT measurement is a recognized limitation of these data. Although the predictive value of such data are not known, similar data have detected QT prolongation in other drug development programs. Pregabalin was associated with slight prolongation of the

PR interval. This finding was not associated with an increased reporting of clinical events related to PR prolongation in the controlled trials in the safety database (e.g. first degree, second degree or complete heart block). The effect of pregabalin in patients with underlying PR prolongation or in patients concomitantly taking other drugs that prolong the PR interval has not been described.

The submission provides evidence of a possible association between pregabalin and myopathy/rhabdomyolysis. The evidence consists of cases of myopathy in pregabalin-treated subjects as well as differences in creatine kinase lab results when comparing pregabalin subjects to placebo subjects in the controlled trials NDA database.

In the controlled trials through the Safety Update, two pregabalin (<0.1%, 2/5781) and no placebo subjects (0/2449) had myopathy AEs. Both of these myopathy events were also SAEs. The narratives for both SAEs of myopathy included potential confounding factors. One of the myopathy SAEs occurred in a subject who also reported recent weight lifting workouts. The second myopathy SAE occurred in a subject who was hospitalized for acute renal failure (worsening renal function appeared to predate the myopathy diagnosis), and pneumonia. A non SAE of myopathy was also reported during in the NDA and this event occurred in a patient hospitalized for cellulitis, and the myopathy resolved with continued pregabalin treatment. For the combined controlled and uncontrolled trials database through the Safety Update, four pregabalin subjects had AEs of myopathy (4/9278), three of which were noted above. The fourth myopathy case (verbatim term of fascioscapulohumeral muscular dystrophy, 011 070015) was a non serious event and did not appear to represent an additional case of rhabdomyolysis. The NDA submissions included information about six pregabalin subjects with CK >5xULN that were temporally associated with muscle pain AEs (ex. myalgia, muscle cramps).

Pfizer measured creatine kinase for a subset of subjects in pregabalin trials included in the NDA and these data suggest that pregabalin subjects experienced greater mean increases in CK and increased risks of outlier elevations in CK when compared to placebo subjects. In the controlled trials, the mean CK change from baseline to end of study was 9.7 U/L for pregabalin subjects compared to a mean increase of 4.8 U/L for placebo subjects. When the mean change from baseline to end of studies were looked at for each indication separately, pregabalin subjects in epilepsy, DPN and PHN controlled studies had mean CK increases at end study (range 7.8 to 62.7 U/L) that were higher than the changes observed for placebo subjects (range -3.1 to 2.1U/L). In GAD controlled studies, pregabalin subjects had mean increases in CK that were similar to pregabalin subjects in other controlled studies (10.3 U/L) but the placebo group experienced a greater mean increase (16 U/L). The mean change from baseline to maximum on-treatment CK value was 60.1 U/L for the pregabalin group compared to 27.9 U/L for the placebo group. For each indication, the mean change from baseline to maximum CK was higher for the pregabalin group compared to the placebo group. In most of the outlier analyses, pregabalin subjects experienced a greater risk of CK elevation to predetermined cutoff values when compared to placebo.

Neither the myopathy cases alone nor the lab data alone confirm an increased risk of drug related myopathy, but taken together the data suggest that pregabalin may be associated with increased risk of myopathy over background. As mentioned above, both of the SAE myopathy cases are confounded, and the contribution of pregabalin to these events is difficult to assess. The lab data demonstrate that for the studied population, increases in CK occur in the background. Pfizer identified placebo subjects with CK increases >1,000 U/L. Some of the pregabalin subjects had increases in CK >1,000U/L at baseline and some experienced elevations of CK with pregabalin that resolved with continued treatment, supporting that pregabalin was not responsible for all of these observed elevations in CK. Despite the background elevations in CK, pregabalin subjects did experience unexplained mean change increases and increased outlier risks that were greater than observed in placebo subjects, suggesting an effect beyond what was observed in the background. Within the available data set, the risk difference (risk in pregabalin subjects minus risk in placebo subjects) is small for the outliers as well as for myopathy cases. We do not know if these estimates derived from NDA will be reliable when pregabalin is administered to a more heterogeneous population that is followed less closely.

In the NDA, Pfizer concluded that "pregabalin appears to elevate creatine kinase levels in some patients. Review of individual patient cases does not suggest a clinically important risk of renal dysfunction associated with the elevations in creatine kinase." While there may not have been renal dysfunction in the cases reviewed by Pfizer, this does not seem particularly reassuring given the observed myopathy cases. Pfizer's proposed labeling that mentions the CK mean change differences and outlier differences appears inadequate since it does not mention myopathy or warn the prescriber and patient to be alert for myopathy associated symptoms.

Pfizer's analyses suggested an effect of pregabalin on platelet counts. The low platelet counts did not appear to be associated with decreases in WBC counts or hemoglobin. For the pooled controlled trials data, pregabalin subjects experienced a mean decrease in platelet count from baseline to end of study of -9.542 $x10^3/\mu L$ compared to -0.333 $x10^3/\mu L$ for placebo subjects. Pregabalin subjects also had higher risks for low platelet outliers when compared to placebo subjects. There did not appear to be differences in risk between pregabalin and placebo treated subjects for adverse events potentially related to bleeding. A review of the AEs in patients with decreases in platelet counts did not suggest increases in risk for bleeding related events. A review of subjects with low platelet counts demonstrated that in many cases these subjects had low platelet counts at baseline, that the on-treatment low platelet results were transient, and that in most cases these low platelet results were not associated with bleeding AEs. There were some individuals who had their lowest platelet count as their last available lab result. Pfizer did not identify or propose a mechanism of the observed low platelet counts. Pfizer did not propose labeling language that describes the platelet count changes. Despite the lack of increased risk for bleeding related AEs in the NDA, I feel that the pregabalin label should describe the platelet count findings. We do not know the impact of the platelet count changes in a larger, more heterogeneous, and less closely followed cohort of users who may have a higher burden of underlying illness and may be taking more medications.

Pfizer reported that through the safety update, eleven pregabalin subjects in the safety database had AEs of pancreatitis (preferred terms pancreatitis, necrotizing pancreatitis). One additional pregabalin subject from an ongoing study that had not yet been included in the safety database also had an AE of pancreatitis (166 074022). One of the safety database pancreatitis cases (088 516021) was definitely not related to pregabalin since it occurred prior to the subject taking pregabalin. Of the remaining ten cases in the safety database, five were SAEs and five were not considered SAEs. For the five cases that were SAEs, one case (040 047001) was not considered treatment emergent presumably since it was attributed to biliary lithiasis. For the remaining four SAE pancreatitis cases, one was attributed to vesicular lithiasis (necrotizing pancreatitis, 045 053002), one was associated with alcohol intake (034 036006), one was associated with cholelithiasis (029 036002), and one had no identified confounding factors identified (030 131005). For the five pancreatitis non-SAE cases, four (014 021008, 029 009011, 030 106008, 149 387005) were diagnosed clinically in the absence of laboratory changes and for three individuals the events resolved without changes in pregabalin dosing. In the fourth case, the event was described as chronic pancreatitis and the subject had been receiving treatment with pancrealipase prior to starting pregabalin. The fifth non-SAE pancreatitis case was a subject (029 035002) who experienced increases in amylase (highest value 367 U/L, baseline value 125U/L, ULN 115 U/L) that were not associated with symptoms and that resolved with continued pregabalin (6/22/04 Submission). For the pancreatitis case from the ongoing study that had not been entered into the safety database, the event occurred after over 500 days of pregabalin treatment, and there were no confounding factors identified in the narrative. The investigator held this subject's pregabalin for nine days and then re-started it without recurrence of the pancreatitis.

Although there are a number of pancreatitis cases in the safety data presentations, the relationship to pregabalin is not clear. In the controlled trials, the risk for pancreatitis AEs was similar for pregabalin (<0.1%, 2/5781, neither event an SAE) and placebo (<0.1%, 1/2449) based on a small number of cases. Many of the SAE cases had documented confounding factors that are known causes of pancreatitis (alcohol, cholelithiasis). The one case with pregabalin re-challenge did not result in recurrence of pancreatitis. Given the confounding of the cases, I believe it would be reasonable to follow closely post marketing pancreatitis reports.

Pregabalin is associated with an increased risk of hemangiosarcoma in animals and this finding has had notable impact on the development and regulatory history of pregabalin including imposition of clinical holds and reassessment of ongoing trials. Although Pfizer expended a great deal of effort describing a possible mechanism for hemangiosarcoma in animals, they spent very little effort assessing human malignancies in the NDA database. Their assessment of human malignancies was essentially a list of these diagnoses in the development program and the statement that the cases did not suggest a relationship between pregabalin and cancer. During our review, we requested a more quantitative assessment of malignancies in the pregabalin development program that compares NDA malignancy risks to background risks. While a positive finding from such an assessment may be useful, we recognize that a negative finding may be of limited value, given that

these data will not address longer exposures and will be based on a relatively small number of subjects (<10,000). Pfizer had not submitted their quantitative assessment of human malignancies at the time of completion of this review.

Pregabalin subjects had increased risk of edema related adverse events. Analysis of lab data did not support that edema was related to hepatic or renal dysfunction. While Pfizer concludes that edema is not related to hemodilution, changes in total protein, sodium, hemoglobin, and hematocrit all support evidence of some degree of hemodilution in patients with peripheral edema.

The data suggest the possibility that pregabalin-associated peripheral edema is associated with an increased risk for clinical events such as dyspnea and hypertension. Pfizer contends that peripheral edema was not associated with cardiorespiratory adverse events. Although differences observed for most cardiorespiratory events were very small, pregabalin-treated patients with peripheral edema in both the controlled studies and the combined controlled and uncontrolled studies had higher frequencies of all cardiorespiratory adverse events selected for presentation than did pregabalin-treated patients without peripheral edema. The largest differences observed in frequencies of selected cardiorespiratory adverse events between pregabalin-treated patients with and without peripheral edema were for dyspnea and hypertension. The difference in the frequency of dyspnea between pregabalin-treated patients with and without peripheral edema was particularly striking in the controlled and uncontrolled studies combined, although this finding is difficult to interpret given the lack of a placebo group and the unknown nature of the temporal relationship between the two events. Despite these limitations, the large difference in dyspnea incidence between patients with and without peripheral edema in these studies is concerning and cannot be easily dismissed.

Pfizer analyzed the relationship between edema and weight gain in their NDA but did not address this issue in their labeling proposal. Pfizer's adequate exploration of the relationship between edema and weight gain in their NDA suggests that while edema does not solely account for the weight gain that is associated with pregabalin, there does appear to be an association between the two events. In all indications except for GAD, the proportion of patients experiencing edema was higher among patients with weight gain of at least 7% than it was among the controlled trial population as a whole. A weakness of this analysis is that we cannot be certain of the extent of edema ascertainment. Edema as an adverse event is likely to be underreported. It may well be that the association between edema and weight gain is stronger than it currently appears in Pfizer's analyses, since underreporting of edema would have the effect of making the association between weight gain and peripheral edema appear weaker than it actually is. While this is speculative, it is my opinion that a statement based on the available data regarding the association between peripheral edema and weight gain should be made in labeling.

The pregabalin ophthalmologic data were reviewed by an internal FDA consultant, Dr. Wiley Chambers, who concluded that visual acuity and visual field changes were more commonly seen among pregabalin subjects. Dr. Chambers made specific labeling

recommendations to describe these findings, and HFD-170 has been in negotiation with Pfizer about these points. In addition, Dr. Chambers suggested additional studies to further assess the effect of pregabalin on vision, to be completed as Phase IV commitments. We will follow these negotiations and pursue the recommendations of Dr. Chambers.

The available data on the effect of pregabalin on sperm was reviewed by consultants from HFD-580, and they recommended labeling language to describe available data and gave input for a Phase IV study design to further assess the findings. HFD-580 felt that the human study performed by Pfizer to assess the effect of pregabalin on human sperm was not capable of providing reasonable assurance of no effect on human sperm, primarily citing inadequate power to detect clinically meaningful changes. HFD-170 has been discussing the HFD-580 recommendations with Pfizer.

Pregabalin animal studies documented a finding of tail dermatopathy but the human adverse event data did not support differences in risk between pregabalin and placebo subjects for skin related AEs in the controlled clinical trials. Pfizer described the animal findings as ranging from erythema to necrosis, and commented that the lesions occurred within the first two weeks of exposure and tended to resolve with continued exposure. While Pfizer did not implement specific surveillance or questionnaires to look for these findings in humans, it seems reasonable to expect that if there was a similar drug related effect in humans, it would have been captured with AEs in the controlled trials.

Pregabalin had its most frequent adverse effects on the central nervous system. Pfizer regrouped the CNS AEs to provide a more clinically meaningful assessment of these events. Their analyses support that pregabalin affects motor function by causing ataxia, gait changes, and coordination problems. While the absolute risks for these events varied for pregabalin subjects across indications, the relative risks compared to placebo were similar, due to variability in the background risks across indications. Pfizer reported that pregabalin was also associated with an increased risk of accidental injuries. Their analysis of the relationship between a grouping of CNS and accidental injuries did not provide clear results but perhaps an analysis focusing on coordination abnormalities would have been more informative. Pfizer also demonstrated increased risk for CNS AEs that describe mental status and concentration. The differences for the neuropsychiatric AEs between pregabalin and placebo subjects appeared less remarkable. While no direct comparative data are provided, the description of these events seems similar to CNS events observed in other anti-epileptic drug development programs.

The pregabalin NDA database does not provide strong evidence of an increased risk of suicide, although suicidality was not prospectively studied in a systematic fashion. Two suicides were reported by Pfizer, one by a subject whose treatment assignment remains blinded, and the second by a subject more than 30 days after stopping pregabalin (treatment duration two days). The depression and suicidality SAE and AE data did not provide strong evidence of differences in risk by treatment during pregabalin controlled trials.

Unresolved Issues:

We will request additional analyses of available ECG PR interval data to evaluate the impact of pregabalin on subjects with baseline PR interval prolongation and to examine the impact of pregabalin on the PR interval in subjects who are taking other medications that prolong the PR interval

We will follow up on the request for quantitative analyses of the human cancer rates in the development program.

We will request additional analyses to clarify the relationship between peripheral edema, dyspnea, and hypertension

We will request an analysis of blood pressure change from baseline in controlled trials that stratifies patients by whether they experienced dizziness.

7. Appendices

Appendix 1

Table 135. Ongoing Studies Not in the Integrated Phase 2/3 Integrated Safety Database

Patient Population Study Number	Indication	Description	Estimated Number of Patients Exposed[a] Pregabalin	PBO	Comparator
Controlled Pain					
108	Pain	IBS	11	11	--
125	NeP	Spinal Cord Injury	26	26	--
155	NeP	Dose Titration in DPN/PHN	DPN: 201 PHN: 72	65	--
Total Controlled Pain			***310***	***102***	--
Uncontrolled Pain					
166	NeP	DPN/PHN	50	--	--
202	NeP	Spinal Cord	12	--	--
Total Uncontrolled Pain			***62***	--	--
Controlled Epilepsy					
112	Epilepsy	Lamotrigine Comparison	32	32	32
157	Epilepsy	Titration	182	91	--
167	Epilepsy	Sleep EEG	2 --	--	
Total Controlled Epilepsy			***216***	***123***	***32***
Uncontrolled Epilepsy					
114	Epilepsy	112 Extension	26	--	--
164	Epilepsy	157 Extension	49	--	--
Total Uncontrolled Epilepsy			***75***	--	--
Controlled Psychiatry					
090/152	Psych	GAD Elderly	100	50	--
091	Psych	Panic Disorder	117	59	59
093/192	Psych	Panic Relapse Prevention	190	--	--
Total Controlled Psychiatry			***407***	***109***	***59***
Estimated Number of Patients Exposed in Ongoing Studies			***1070***	***334***	***91***

IBS = Irritable bowel syndrome.

[a] For the blinded, controlled studies, patient exposures were estimated based on the randomization scheme. For uncontrolled studies, new pregabalin exposures are estimated based on the randomization scheme of the controlled study and the proportion of patients expected to continue in the open-label extension study.

Appendix 2
Selected Pregabalin SAEs
NDA

Kidney function abnormal (5)

040 017017 This 41 year old female with a history of pancreatitis, hypertension, hyperprolactinemia, TIAs, peripheral edema, hyperuricemia, diabetes mellitus, diabetic nephropathy and neuropathy developed terminal renal insufficiency during treatment with pregabalin. She enrolled in an RCT and her baseline creatinine was 2.1mg/dL. She received amitriptyline in that trial and her end of the study her creatinine was 2.3mg/dL. She enrolled in the open label trial and her creatinine was 2.4mg/dL on visit day 8. By visit day 36 of the open label trial her creatinine increased to 2.8mg/dL. On study day 64, her creatinine was 2.6mg/dL. Her creatinine remained relatively stable until study day 253 when it was 4mg/dL. She was subsequently hospitalized and started dialysis. Her worsening renal function was attributed to progression of her diabetic nephropathy. Her concomitant medications were valsartan, carvediolol, furosemide, digitoxin, insulin, and phenprocoumon.

040 062006 This 59 year old female with a history of diabetes mellitus and neuropathy developed worsening renal function during open label pregabalin treatment. She had a baseline creatinine of 1.4mg/dL prior to entering the RCT. Following the RCT where this subject received placebo, she developed heart failure. The narrative also described a vasculitic rash on both shins. When the heart failure resolved, she entered the open label trial and started pregabalin treatment. On study day 8 she was noted to have worsening renal function (creatinine 2.4mg/dL) and anemia (Hgb 8.7 g/dL). Pregabalin was stopped on study day 19, and on study 21 she was diagnosed with crescentic glomerulonepritis. On study day 24 she had a positive ANA and ANCA. The narrative mentioned that she received steroids and cyclophosphamide. One and a half years after stopping pregabalin, she continued to have renal insufficiency (creatinine 3.4mg/dL) and anemia (Hgb 11.7 g/dL). The investigator felt that this event began prior to initiation of pregabalin.

149 356024 This 71 year old male with diabetes mellitus, neuropathy, chronic renal failure, and hypothyroidism developed worsening renal function. His baseline creatinine was 3.5mg/dL with a BUN of 77.9mg/dL. On study 9, his creatinine was 2.9mg/dL and his BUN was 68.9mg/dL. By study day 30, his creatinine was 3.5mg/dL and his BUN was 83.8mg/dL. On study 36 he was hospitalized for an ankle ulcer and his hospital course was complicated by worsening renal function (not specified) and severe epistaxis. Study drug was stopped on day 50 and the narrative reported that he had recovered by study day 58. Follow up labs on day 85 included a creatinine of 3.6mg/dL and a BUN of 72.8mg/dL. Concomitant medications at the time of the event were levothyroxine, gliclazide, aspirin, paracetamol, vitamins and minerals.

045 053005 This 85 year old male with post herpetic neuralgia was admitted to a hospital with neck pain and pulmonary edema and was subsequently diagnosed with a myocardial infarction. His hospital course was complicated by worsening renal function (creatinine increased from 1.6mg/dL to 4.9mg/dL) cardiogenic shock and death. Concomitant medications were tramadol and piroxicam.

045 054008 This 69 year old male with a history of prostatectomy and post herpetic neuralgia was hospitalized on study day 705 for pneumonia, acute respiratory insufficiency, and acute renal insufficiency. He presented with dyspnea, fever, cough, and malaise and a chest x-ray documented bilateral pneumonia. He was treated with ceftriaxone, clarithromycin and a bolus dose of amiodarone (cardiac rhythm abnormality not noted). His condition worsened and he required mechanical ventilation. He subsequently developed severe hypotension, atrial fibrillation, tachycardia, metabolic acidosis, hypoxemia, and anuria. He died the reported causes of death were pneumonia, acute respiratory insufficiency and acute renal insufficiency.

Acute kidney failure (4)

014 017006 This 71 year old male with diabetes mellitus, neuropathy, renal insufficiency, left renal artery stenosis, atrophic right kidney, and gout developed acute renal failure. The subject was hospitalized on study day 8 (open label pregabalin) following a fall (possible syncope), inability to rise due to weakness, and shoulder pain. His creatinine was 4.2mg/dL, BUN was 78mg/dL and potassium was 5.1. During a preceding RCT where he received placebo, his creatinine was 1.6 mg/dL and during a preceding open label pregabalin trial his creatinine ranged from 1.6-2.1mg/dL. He was considered recovered by study day 12. He continued in this open label trial and his creatinine ranged from 1.9-2.2mg/dL.

029 043036 This 62 year old female with diabetes mellitus, neuropathy, thyroid carcinoma, hypertension, and congestive heart failure was hospitalized for acute renal failure on open label study day 301. The narrative noted that she visited her cardiologist on open label study day 287 with worsening symptoms of congestive heart failure and that changes to her medication regimen were made. She visited her doctor on study day 297 and changes were made to her diuretic and potassium medications (not specified). On study day 302, she collapsed and her BUN was 205 , creatinine 5.4, sodium 124 and potassium 7.9 (no units provided in the narrative). She was treated with kayexalate, calcium gluconate, bicarbonate, saline, a diuretic, an ace inhibitor and her insulin was switched to pioglitazone. On open label study day 306, her BUN was 25, creatinine 1.3, and potassium 4.2. Renal ultrasound was reportedly unremarkable. The subject recovered and continued in the study.
149 430001 (See below, myopathy)
030 115009 This 79 year old female with a history of post herpetic neuralgia, congestive heart failure, and atrial fibrillation, experienced rectal bleeding due to exudative colitis resulting in hospitalization on open label study day 78 and acute renal failure resulting in hospitalization on open label study day 99. The subject experienced blood in her stools and a colonoscopy revealed exudative colitis with mucosal edema, focal acute congestion, and mild chronic inflammation. Pregabalin was stopped and warfarin was held. On study day 99, twenty days after stopping pregabalin she was hospitalized for acute renal failure. The narrative reported that BUN, creatinine and potassium were elevated but did not provide these results. She was treated with kayexalate and intravenous fluids and her diuretics (furosemide and aldactone) and her captopril were held. Her lab results returned to baseline and the event was attributed to volume depletion.

Kidney failure (1)

040 073003 This 43 year old female with a history of diabetes mellitus and neuropathy was hospitalized on open label study day 427 for gastroenteritis that was associated with prerenal failure and metabolic acidosis. She recovered from all of these events and continued in the study.

Creatinine increased (1)

030 108005 This 79 year old female with a history of post herpetic neuralgia and bladder surgery experienced increased creatinine on open label study day 474. Her concomitant medications included donepezil, citalopram, aspirin, calcium, tocopherol, pyridoxine, senna, magnesium, acetaminophen/diphenhydramine, and hydrocodone. In a preceding RCT where she received pregabalin, her creatinine ranged from 1.1-1.3mg/dL. During this open label study, her creatinine ranged from 1.2-1.6mg/dL and on her last lab value prior to this event (study day 455), she had a creatinine of 1.2mg/dL. On study day 476 she had a creatinine of 1.9mg/dL. Her primary care physician rechecked her labs and her creatinine was 2.1mg/dL. A renal ultrasound demonstrated her right kidney was 8.4cm and her left kidney was 8.2cm with both renal cortices appearing thin. A nephrologist felt that she had longstanding kidney disease. She continued in the study and her creatinine results ranged from 1.2-1.3mg/dL. She entered another open label pregabalin trial and her creatinine results ranged from 1.1-1.3mg/dL in that trial.

Nephrosis (1)

040 067004 This 35 year old male with a history of diabetes mellitus and neuropathy was hospitalized for poor control of blood sugar and nephrotic syndrome on open label study day 27. Concomitant medications were metoclopramide, ranitidine, mebeverine, and insulin. The subject presented on study day 20 with non-ketotic uncontrolled hyperglycemia, edema of the face, ankles and hands, and feeling unwell. He was treated with sliding scale insulin. A 24-hour urine protein was collected but the results were not reported. He had urinalyses during the study and his UA was negative for protein on study day 8. He was reportedly started on captopril and lisinopril. His hospital course was complicated by chest pain. His blood sugars improved, and his edema decreased and he was considered recovered. He continued in the study and on study days 42 and 70 he had UA protein results of 30 but on study day 140 and 183 the UA was negative for protein.

Nephritis (1)

088 516045 This 34-year-old white woman with generalized anxiety disorder was diagnosed with a bladder infection (cystitis) and kidney infection (nephritis) on Day 134 (3 days posttreatment with open-

label pregabalin) and was hospitalized on Day 138. Concomitant medications included norethisterone acetate/ethinylestradiol, citalopram hydrobromide and gabapentin. The patient was treated with intravenous antibiotics and released on Day 140 however the symptoms did not resolve and she was rehospitalized on Day 141 for observation. The patient was released considered recovered on Day 142.

Glomerulitis (1)

040 062006 Event summarized above.

Pancreatitis (4)

029 036022 This 44 year old male with diabetes and neuropathy was hospitalized on day 161 of pregabalin treatment for pancreatitis, acute cholecystitis and cholelithiasis. ERCP and sphincterotomy were performed and the subject was also treated with antibiotics. He subsequently underwent a laparoscopic cholecystectomy that was converted to an open cholecystectomy due to adhesions. The subject recovered.
030 131005 This 80 year old female with post herpetic neuralgia was hospitalized for pancreatitis on study day 147 of open label pregabalin treatment. Total duration of pregabalin was 184 days. Concomitant medications included paroxetine, lorazepam, doxepin, dextropropoxyphene and paracetamol/hydrochloride. On study day 92, her amylase was 77 U/L. While hospitalized, her lipase and amylase were increased (not specified). The narrative reported no gall bladder inflammation and that abdominal CT and MRI were negative. She recovered without sequelae.
034 036006 This 41 year old male with a history of alcohol abuse was admitted to a hospital for pancreatitis on study day 173. He presented with nausea and vomiting. An abdominal ultrasound demonstrated fatty liver. Labs included lipase 400IU/L, amylase 96 U/L, total bilirubin 3.5mg/dL, ALP 252 U/L, AST 455 U/L, and blood alcohol 243mg/dL. He was treated with IV fluids, recovered, and continued in the study. Concomitant medications at the time of the event were doxazosin, potassium, omeprazole, fluoxetine, allopurinol, and diclofenac. He had a second admission for pancreatitis on study day 324. This event occurred after several days of alcohol use. He was discontinued from the study at that time.
040 047001 This 71 year old female with diabetes and neuropathy was hospitalized with pancreatitis on open label study day 154 (total duration of pregabalin use 216 days at the time of this event). She was taking no concomitant medications at the time of this event. She was diagnosed with pancreatitis secondary to biliary lithiasis. She recovered from this event and pregabalin was restarted. On open label study day 190, she was hospitalized for an abdominal abscess. She underwent a laparotomy and abscess evacuation. She was also treated with antibiotics and parenteral nutrition. The narrative reported that she recovered.

Necrotizing pancreatitis (1)

045 052013 This 66 year old female with post herpetic neuralgia and a history of cholecystectomy was hospitalized on open label study day 733 for necrotizing pancreatitis. Earlier in the study (study day 236) she was hospitalized for hepatic abscess which was resolved by study day 405. The narrative noted that she was diagnosed with vesicular lithiasis of the pancreas. The narrative reported that "she was operated on that same day and underwent an endoscopic retrograde cholangiopancreatography (ERCP) with local anesthesia and sedation." Her post procedure course was complicated by DIC and progression to hemorrhagic necrotic acute pancreatitis. Her death was attributed to multiple organ failure. The only reported concomitant medication was omeprazole.

Cardiomyopathy (3)

014 015009 This 46 year old female with a history of diabetes mellitus and neuropathy, morbid obesity, atrial flutter, edema, and hypertension died and the cause of death was cardiomyopathy. This subject had two hospitalizations during the open label trial for treatment of cellulitis and recovered. She was hospitalized on study day 431 for SVT and atrial flutter. Pregabalin was stopped on study day 445. The narrative stated "An echocardiogram did not reveal any clots or holes but one fast chamber." A chest x-ray revealed an increased heart size but not failure. The subject signed out of the hospital against medical advice, while still in atrial flutter, and died on day 455. An autopsy reported that dilated cardiomyopathy was the cause of death.
035 022105 This 55 year old male with a history partial seizures, "heart attack" x 2, and intermittent chest pain, was found dead by his mother. An autopsy was not performed and cause of death was attributed to

respiratory failure secondary to congestive heart failure and cardiomyopathy. He had received a total of 499 days of pregabalin treatment. Concomitant medications included phenytoin, paroxetine, metoprolol, trazodone, and cerivastatin.
025 004031 This 39 year old male with generalized anxiety disorder was hospitalized for cardiomyopathy after 9 days of pregabalin treatment and pregabalin was stopped. He underwent an angioplasty and was treated with Zestril, digoxin, and furosemide.

Cholestatic jaundice (2)

009-011006 This 64 year old male with intractable epilepsy, was hospitalized on study day 13 for increasing confusion. He was taking pregabalin 600mg/d BID at the time of the event. On study days 1-4 he developed ataxia and tremors and on study day 5 he developed headache. He was instructed to hold the evening doses of the study medication. The symptoms abated and he was told to resume his previous study medication dose. Subsequently, his symptoms recurred and on study day 12 he had moments of myoclonus, confusion, diplopia, and visual hallucinations. He was instructed to taper the study medication and withdraw from the study but investigators determined he was unable to follow instructions due to confusion and therefore he was admitted to a hospital on study day 13. On study day 14 he was withdrawn from the study. Last pre-study labs (study day -4) included an ALT of 26U/L, an AST of 27U/L and a total bilirubin of 0.4mg/dL. He was diagnosed with cholestatic jaundice and had the following lab results AST 47U/L, ALT 87U/L, ALP 2356 U/L, GGT 616U/L, and bilirubin 1.3mg/dL (3/19/04 submission). He was discharged from the hospital on study day 21. Concomitant medications included carbamazepine, valproic acid, folic acid, glipizide, propranolol, furosemide, amitriptyline, lansoprazole, and prednisone
149 369001 This 69 year old male with diabetes mellitus and neuropathy was diagnosed with cholestasis on study day 333 and carcinoma of the head of the pancreas on study day 346.

Jaundice (1)

149 415019 This 66 year old female with diabetes, neuropathy, hypertension, recent myocardial infarction, angina, cholelithiasis, hypercholesterolemia, and cataracts developed a GI bleed, jaundice, myocardial infarction, and died. Study medication was stopped on day six, after the subject experienced bleeding from the alimentary tract and black tarry stools. She received a transfusion and endoscopy documented two esophageal erosions, fresh clots in the stomach, and a duodenal ulcer. On day 14 she developed jaundice and an ultrasound documented cholelithiasis. On day 18 she experienced an MI and died. Concomitant medications at the time of the event were atenolol, cilazapril, potassium, amlodipine, lovastatin, hydrochlorothiazide, insulin, and gliclazide.

Abnormal LFT (3)

009-033005 This 44 year old male with partial seizures had elevated liver function tests. His baseline LFTs included AST 55U/L, ALT 92U/L, a total bilirubin of 0.3mg/dL and ALP 303U/L. On study day 14 his labs included AST 61U/L, ALT 121U/L, total bilirubin 0.3mg/dL and ALP 304U/L. His liver function tests results were similar on study day 28. On study day 56 his AST was 585U/L, ALT 840 U/L, total bilirubin 0.5mg/dL and ALP was 440U/L. A RUQ ultrasound showed a dilated common bile duct and intrahepatic ducts. Hepatitis A,B,C, and CMV serologies were negative and EBV serology showed evidence of a potential infection. Concomitant medications included phenytoin, topiramate, ibuprofen, folic acid, alendronate, hydroxyzine, famotidine, detrol, and paracetamol/oxycodone. The subject was withdrawn from the study on study day 59. Termination labs on day 112 included AST 30U/L, ALT 52U/L, total bilirubin 0.3mg/dL and ALP 172U/L. He later entered the open label extension. On study day 28 of the OL phase, his ALT was 71U/L, AST 39U/L, ALP 293U/L, and total bilirubin was 0.4mg/dL.
On study day 38, his ALT was 466U/L, AST 148U/L, ALP 291U/L and total bilirubin was 0.3mg/dL. On study day 48, his ALT was 143 U/L, AST 44U/L, ALP 275U/L and total bilirubin was 0.3mg/dL. Between study days 57 and 245, ALT fluctuated between 98 and 120U/L, AST between 41 and 64U/L, ALP 272 and 342U/L, and total bilirubin 0.2 and 0.3mg/dL. On study days 36-243 his pregabalin dose was 600mg/day, TID. At the last visit, ALT was 57U/L, AST 28U/L, ALP 292U/L and total bilirubin 0.4mg/dL.
011-070011 This 60 year old male with a history of complex partial and secondary general seizures, alcohol and tobacco abuse and recent weight loss was taking pregabalin 600mg/d at the time of the event and had been taking pregabalin for 211. He died and his AEs included metastatic carcinoma, abdominal ascites, dyspnea, painful left shoulder, confusion, and abnormal liver function. The coded cause of death

was carcinoma. This subject was diagnosed with metastatic adenocarcinoma on study day 128. The narrative noted that at baseline the ALT, AST and ALP were elevated and that on study day 113, the AST was slightly elevated (29 U/L) and the ALP was elevated (900U/L). A CT on study day 128 demonstrated that the liver had extensive metastatic disease and that there were bilateral lung metastases. He withdrew from the open label study on day 170 and died 21 days later.

014 021004 This 44 year old female with diabetes mellitus, and neuropathy developed elevated liver function test results. The narrative reported that this subject was diagnosed with hyperthyroidism and started on propylthiouracil. Approximately two weeks later she entered a pregabalin trial and was randomized to placebo. Baseline LFTs for this study included ALT 20 U/L, AST 21 U/L, ALP 201 U/L, and total bilirubin 0.9mg/dL. On study day 15, while receiving placebo, she had the following results: ALT 81 U/L, AST 55 U/L, ALP 222 U/L, and total bilirubin 1.1mg/dL. On study day 28, the transaminases and ALP decreased slightly while the total bilirubin increased to 1.5mg/dL. At the termination visit for this study, she had the following results: ALT 42 U/L, AST 43 U/L, ALP 230 U/L, and total bilirubin 1.1mg/dL. She then enrolled in the open label study and began pregabalin treatment. The narrative reported negative results for Hepatitis A, B, and C, and a positive test for CMV. On study day 71 her ALT was 1234U/L, her AST was 824U/L and her total bilirubin was 3.7mg/dL with an ALP of 824U/L. Pregabalin was held on day 71, and propylthiouracil was stopped on day 77. She was treated with radioactive iodine on day 85. Lab tests on day 127 included an ALT of 19 U/L, AST U/L, and a total bilirubin of 1 mg/dL. Pregabalin was re-started on day 136and LFTs remained normal on pregabalin.

Allergic reaction (2)

029 033007 This 60 year old female with diabetes mellitus, and neuropathy was hospitalized with atrial fibrillation and had ruled out for an MI and while hospitalized developed a rash on both thighs. The rash was attributed to amoxicillin, which was started ten days earlier for a sore throat.

034 021006 This 34 year old female with a history of seizures, headaches, allergies, hypertension, panic attacks, anxiety, depression, left atrial enlargement, and mild ventricular hypertrophy was hospitalized for an allergic reaction. This subject was initially hospitalized on study day 171 for bilateral ear pain that was treated with non specified intravenous antibiotic therapy and amoxicillin, trimethoprim/sulfamethoxazole, cephalexin, colistin sulfate/neomycin sulfate/thonium bromide/hydrocortisone acetate otic suspension, oxycodone/acetaminophen, and amoxicillin clavulanate. On study day 174 she was re hospitalized for the allergic reaction. Pfizer characterized the reaction only as a rash (3/19/04 submission). While hospitalized for the allergic reaction she was treated with paracetamol/dextropropoxyphene, diphenhydramine, fluconazole, methylprednisolone, potassium chloride, and glyceryl trinitrate. She continued in the study.

Anaphylactoid reaction (2)

014 015029 This 48 year old male with a history of diabetes, neuropathy, and hypersensitivity to cephalexin developed anaphylactic shock one day after he was administered cephalexin for a puncture wound.

196 011008 This 67 year old female with a history of post herpetic neuralgia, coronary artery disease, pacemaker insertion, duodenal ulcer, hypertension and osteoporosis experienced anaphylaxis on study day 10 of double blind pregabalin treatment. Concomitant medications included naproxen, paracetamol, aspirin, sotalol, ranitidine, ascorbic acid, multivitamins, and salmon calcitonin. Study medication was stopped on study day 11. On study day 12, the subject complained of facial edema, lower left leg edema, burning pain of the left shank, and warmth of the skin. She was hospitalized and noted to have facial and periorbital edema, erythema of the right side of the face, left leg edema with pain, erythema of the left leg, high blood pressure, tachycardia, and dyspnea. The events were reported as recovered on study day 12.

Rash (2)

092 622013 This 45 year old female with panic disorder was hospitalized for rash associated with a black widow spider bite.

040 062006 Event summarized above.

Stevens Johnson syndrome (1)

035-055113 This 27 year old male with multiple medical problems including Chiari type I malformation, polymicrogyria, and schizencephaly was hospitalized for Stevens Johnson Syndrome. He received 308 days of pregabalin, and it was stopped for lack of effect. Concomitant medications included lamotrigine (started study day 288), valproate, allopurinol, ibuprofen, phenoxymethylpenicillin, topiramate, sulfacetamide, paracetamol, and doxazosin. On day 316 (eight days after stopping pregabalin) he was hospitalized with pruritic rash, cough, sore throat, fever, mild dyspnea and sore eyes. He was treated with diphenhydrinate, prednisone, xylocaine, pentothal, succinylcholine, dopamine, potassium, cefataxime, phenylephrine, fentanyl, propofol, midazolam, hydrocortisone and ciprofloxacin. He recovered and the event was felt due to lamotrigine. (Start date of lamotrigine confirmed by Pfizer as day 288, 3/19/04 Submission).

CPK increased (3)

009-008016 This 31 year old male had a history of refractory seizures and Sturge Weber syndrome. On study day 84, while taking pregabalin 600mg/day TID, he had an elevated CPK of 4722U/L (isoenzymes 100% MM) during routine clinical lab work. This lab result was not associated with an AE of myalgia. Two days later his CPK was 1031U/L. Other study CPKs were: Day 14=150U/L, Day 28=187U/L, Day 56= 193U/L. On day 91 the subject's CPK was 244U/L. The lab abnormality was attributed to doing yard work in hot weather. Concurrent medications were lamotrigine and verapamil. He continued into the open label extension where he was exposed for 707 days and experienced no additional elevated CPK results
009-008015 This 26 year old male with refractory seizures experienced elevated CPK of 7,893 U/L (100% MM) on day 142 of pregabalin treatment (86 days of double blind, 56 days of open label treatment). At the same time his AST was 111 U/L, potassium 3.9mEq/L and creatinine was 1.0mg/dL. He was taking pregabalin 450mg/day at the time of the event. Follow up CPK four days later was 1,805U/L and seven days after that it was 203U/L. During the preceding double blind study, his CPKs ranged from 137 to 239 U/L. This subject had no recorded AEs of myalgia. Concomitant medications were carbamazepine and valproate. The abnormality was attributed to a strenuous soccer game on study day 55.
009-034006 This 48 year old female experienced an increase in CPK to 5,262U/L (100% MM) after 310 days of pregabalin (92 days in a controlled trial and 218 days in the open label extension). At the same time her AST was 165U/L, potassium was 4.2mEq/L and Creatinine was 1.1mg/dL. Fourteen days later, a repeat CPK was 292U/L. She continued in the trial with no additional elevated CPK results. Concomitant medications were topiramate and lamotrigine. The event was attributed to strenuous exercise. This subject had no recorded AEs of myalgia.

Myopathy (2)

080 112001 This 30 year old male with a history of social phobia, mitral valve prolapse, experienced rhabdomyolysis. This subject had a screening CPK of 94U/L, AST of 24U/L and ALT of 22 U/L. After 16 days of pregabalin, he had his labs drawn and his CPK was 30,700 U/L, his AST was 507 U/L and ALT was 142 U/L and the potassium at that time was reportedly normal. His labs were rechecked the next day and his CPK was 44,700 U/L, his AST was 787 U/L and ALT was 170 U/L and his potassium was now 8.4mEq/L. The subject did experience myalgias, which he attributed to work outs. His only concomitant medication was propranolol. He was admitted to a hospital and treated with IV hydration and urine alkalinization. He was discharged two days later without sequelae. By study day 32, all labs had returned to normal.
149 430001 This 31 year old female with a history of diabetes mellitus, neuropathy, nephrotic syndrome, gastroparesis, retinopathy, recurrent UTIs, and hypertension developed acute renal failure, rhabdomyolysis, and pneumonia. The study drug was stopped on study day 59 for the adverse events of pneumonia, rhabdomyolysis, acute renal failure, and fever. The narrative reported that this subject was admitted to a hospital on study day 60 with acute renal failure, fever, lethargy, shortness of breath, cough, dehydration, and painful swelling and weakness in her legs. The patient profile submitted by Pfizer included lab values from study day 59 and at that time her CPK was 79 U/L and her creatinine was 2.7mg/dL (baseline creatinine 1.4 mg/dL). While hospitalized she was diagnosed with pneumonia and myopathy. On study day 60, her CPK rose to 4504 U/L, and her creatinine was 5.6mg/dL. She was treated with antibiotics, insulin, heparin, and intravenous fluids. Her creatinine improved to 2 mg/dL and creatinine kinase to 124 U/L. and she was discharged on study day 72.

Acidosis (1)

040 073003 Event summarized above

Face edema (1)

196 206001 This 81 year old female with a history of post herpetic neuralgia, osteoporosis, depression, insomnia, hysterectomy, toe surgery, and renal insufficiency was found on the floor by her general practitioner, on the sixteenth day of pregabalin treatment. She had edema of her feet, facial edema, dizziness, drowsiness, and muscle weakness. Study medication was stopped and the dizziness, drowsiness, face and bilateral foot edema were considered resolved two days later. On the third hospital day, she fell out of bed and fractured her fibula. Concomitant medications at the time of hospitalization were amitriptyline, trazodone, paracetamol, calcium, flurazepam, altizide (thiazide diuretic), spironolactone, and nimesulide (NSAID).

Leukopenia (1)

196 410016 This 76 year old female with a history of post herpetic neuralgia, arthrosis, and increased CPK, had leucopenia (neutropenia with atypical lymphocytes) reported as an SAE on day 93, the termination visit for an RCT where she received pregabalin treatment. Concomitant medications included piroxicam, omeprazole, and lorazepam. The following table summarizes her hematological test results from her patient profile.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-7	6.8	2.49	14.2	266
29	6.8	2.74	12.3	282
93	6.8	1.78	13.7	249

The event was reported due to the low neutrophil differential result (26.2%) and the reported finding of atypical lymphocytes. She was enrolled into the subsequent open label trial where her WBC ranged from 8.4-9.8x10E9, and her ANC ranged from 3.22-4.2x10E9. She had no additional hematological AEs reported during the open label trial.

Pancytopenia (1)

029 015001 This 72 year old female with diabetes and neuropathy was diagnosed with pancytopenia and myelodysplasia (leukemoid reaction). Concomitant medications included glimepiride, alendronate, cisapride, magnesium, paracetamol/dextropropoxyphene and gabapentin. In 8/98 she enrolled in an RCT and was randomized to pregabalin. She had no reported AEs in the RCT and her WBC ranged from 6.2-9 x10E9, her Hgb ranged from 11.2-12.3g/dL and her platelet count ranged from 155-184 x10E9. She completed the RCT and in enrolled in the open label extension and her first reported labs in the open label extension included a WBC count of 6.3x10E9, an ANC of 5.21 x10E9, a Hgb of 11.3g/dL and a platelet count of 134 x10E9. On , she had pancytopenia recorded as an AE. On her labs from she had a WBC of 5x10E9, an ANC of 3.79x10E9, a Hgb of 10.6g/dL, and a platelet count of 100x10E9. On her next set of lab results from 6/99, there was little difference in Hgb and platelet count but her WBC count declined to 3.4x10E9 with an ANC of 2.32x10E9. She developed intermittent epistaxis starting in . On , she was hospitalized for cognitive changes from which she recovered. She was re-hospitalized in with diarrhea, malaise, and cholecystitis. A laparoscopic cholecystectomy was performed. The platelet count at the time was 87 x10E9. She had no bleeding complications. Around the same time she had a WBC 4.1x10E9, Hgb 11.4g/dL and was admitted to the hospital for further evaluation. A bone marrow biopsy performed on revealed cellular changes with final diagnosis of myelodysplastic syndrome and pregabalin was stopped. She required platelet and red blood cell transfusion support on a regular ongoing basis. She was readmitted to a hospital 518 days after completing the open label trial for somnolence secondary to a hip fracture after a fall. She was still pancytopenic and markedly thrombocytopenic with her myelodysplasia. She appeared profoundly anemic, with her underlying anemia complicated with possible bleed into the femur and thigh. She was thought to have possible sepsis. Comfort measures only were applied with no transfusions or antibiotics. The patient expired the following day (519 days post therapy). The investigator considered the events unlikely to be related to study medication. The sponsor considered the unlabeled events unrelated to study medication.

Lung fibrosis (3)

014 013006 This 71 year old male with diabetes, neuropathy, Raynaud's, and gastroesophageal reflux was diagnosed with pulmonary fibrosis. He discontinued pregabalin for this AE and his total duration of exposure was 184 days. The patient profile noted that he was treated for pulmonary fibrosis with cyclophosphamide and prednisone. Concomitant medications at the time of the event were glipizide, metformin, nizatidine, nifedipine, aspirin, ascorbic acid, multivitamins, and omeprazole.
045 066002 This 62 year old male with post herpetic neuralgia discontinued pregabalin on study day 44 for severe dizziness which resolved two days after stopping pregabalin. Approximately forty days after stopping pregabalin, he was hospitalized for heart failure and possible pulmonary fibrosis. The narrative reported that the subject recovered from both events.
082 225008 This 65 year old male with a history of working with asbestos was diagnosed with asbestosis (lung fibrosis) by lung biopsy.

Pulmonary hypertension (1)

104 439008 This 63 year old female with a history of back pain, died on open label study day 93 from pulmonary hypertension and myocardial infarction. She participated in an RCT and received pregabalin and upon completion of the RCT enrolled in the open label extension. This subject was admitted to a hospital for dyspnea on open label day 11. She was diagnosed with pulmonary hypertension approximately 2 months later and the preceding admission for dyspnea was felt to be related to pulmonary hypertension. The CRF listed hypoxia, pulmonary insufficiency, right ventricular overload, lupus, pulmonary hypertension, congestive heart failure, angina, and acute myocardial infarction as treatment emergent AEs. Pfizer reported that the investigator only became aware of the subject's long standing history of lupus after reading the discharge summary following the subject's death (3/19/04 submission).

Safety Update

Acute kidney failure

029 043019 This 43 year old female with neuropathic pain, diabetes mellitus, baseline renal insufficiency (creatinine 2.2mg/dL) experienced a myocardial infarction and cardiopulmonary arrest on study day 45 and was noted to have a creatinine of 2.9mg/dL during the hospitalization. On study day 119, her nephrologist diagnosed chronic renal failure (creatinine 3.1-3.4mg/dL). She began peritoneal dialysis on study day 161. The renal failure was attributed to diabetes and poor compliance.
029 024003 This 55 year old male with neuropathic pain, diabetes mellitus and multiple other medical problems, had an SAE of renal failure on study day 348. The renal failure event was attributed to an unspecified antibiotic. The narrative did not mention the subject's creatinine level. The subject's pregabalin dose was reduced during the event and upon resolution the subject resumed his prior pregabalin dose. The narrative noted that the renal failure did not recur. Medications prior to the renal failure event included metformin, insulin, ibuprofen, amitriptyline, gabapentin, furosemide, clonazepam, venlafaxine, warfarin, and lisinopril.
040 079004 This 74 year old female with diabetic peripheral neuropathy and coronary artery disease was hospitalized with diarrhea, vomiting, dizziness, slow atrial fibrillation, elevated creatinine of 2.8mg/dL, and elevated potassium of 8.5mmol/L. The acute renal failure was attributed to dehydration. She was treated with atropine, IV hydration, insulin, and resonium (for elevated potassium) and all other medications were held. She required intubation for airway protection in light of delirium. She recovered from the delirium and renal failure and was restarted on pregabalin. She did not experience additional episodes of renal failure but pregabalin was eventually discontinued due to a stroke that followed surgery for appendicitis.
131 105011 This 77 year old male with neuropathic pain and a hospitalization for TIA (study days 307-309) was found to have renal insufficiency of unknown etiology on Study Day 370. Blood urea nitrogen was 77 mg/dL (normal range: 5-26 mg/dL); and creatinine levels were 5.9 mg/dL (normal range: 0.5-1.5 mg/dL). Baseline creatinine was 1.3mg/dL and study creatinine results ranged from 1.2-1.8mg/dL prior to this event. In response to this finding, treatment with pregabalin was temporarily discontinued on Study Day 382. On Study Day 396, a renal ultrasound was unremarkable and revealed kidneys of normal size with no obvious cyst, mass, stones, hydronephrosis, or abnormal echogenicity. On Study Day 397, the subject was hospitalized for renal failure. At that time, blood urea nitrogen was 68 mg/dL and creatinine was 13 mg/dL. On Study Day 400, the subject was found to be uremic. On that day, blood urea nitrogen was 79 mg/dL and creatinine was 9.0 mg/dL. The subject was started on dialysis the same day. On Study

Day 401, the subject felt significantly better and was discharged from the hospital to continue on dialysis. On Study Day 411, treatment with pregabalin was resumed. Illnesses present at the onset of the event and other relevant medical history included hypertension, gastroesophageal reflux, benign prostate hypertrophy, seasonal allergies, hyperlipidemia, diabetes mellitus, senile tremor, chronic back pain, back surgeries, meniscular repair right knee, multiple fibrotic teratosis, hypotonic bladder, bilateral hearing loss, purpural edema, intermittent dizziness, sleep apnea, erectile dysfunction, sacroiliitis, somatic dysfunction of lumbar spine, degenerative osteoarthritis, edema of the lower extremities, occasional falls and dizziness, stroke, prostate surgery, right and left knee surgery, and familial tremor in the right hand. Concomitant therapy taken within 2 weeks before the onset of the event included propranolol, terazosin, fexofenadine, famotidine, tocopherol, paracetamol, ginkgo biloba, dietary supplement MFM (methylsulfonylmethane), gemfibrozil, furosemide, glibenclamide, pioglitazone, cetirizine, and acetylsalicyclic acid.

149 354028 This 83 year old male with diabetic peripheral neuropathy had treatment with pregabalin recommenced on study day 172 following a mandatory drug holiday that was complicated by withdrawal related vomiting. The next day after restarting pregabalin, the subject experienced fever, cough, and severe lethargy and was admitted to the intensive care unit. On admission, a chest x-ray showed bronchopneumonia, an electrocardiogram (ECG) revealed an acute myocardial infarction, an elevated creatinine level indicated acute renal failure, and the subject had hyperglycemia. The subject was treated with an insulin infusion, nitroglycerin patch, furosemide, intravenous antibiotics, subcutaneous heparin, and oxygen was administered. The subject responded to the treatments and was transferred to a ward on Study Day 177. On Study Day 179, the subject recovered from the bronchopneumonia, acute myocardial infarction, and acute renal failure (discharge date not provided). This subject was readmitted on study day 238 after collapsing but not losing consciousness at home. He had a low blood sugar at the time. He was diagnosed with pneumonia, acute myocardial infarction and renal failure. The only creatinine provided was .11 (no units). He continued on pregabalin and had another hospitalization for pneumonia but no other renal failure events.

Petechial rash

155 138018 This 50 year old male with neuropathy and diabetes was hospitalized for a purpuric rash (Henoch-Schonlein rash) on his calves, increased sodium, increased BUN, and increased creatinine on study day 65. The rash appeared on study day 63 and lab tests revealed a creatinine of 2.2mg/dL (no baseline provided), and a BUN of 33mg/dL. Study medication was stopped and the subject was hospitalized two days later. On hospitalization, the subject had a serum sodium of 146mEq/L, a creatinine of 1.6mg/dL, and a BUN of 26mg/dL. The narrative stated that no treatment was given during the hospitalization and that the elevated sodium resolved on day 66, the elevated creatinine and BUN resolved on day 67 and that the rash had resolved on day 68. Concomitant medications included insulin, atorvastatin, levothyroxine, lisinopril, indapamide, fenofibrate, aspirin, metformin, and venlafaxine.

Liver damage

196 007009 This 64 year old female with post-herpetic neuralgia was hospitalized on study day 212 with very high transaminases and total bilirubin. Approximately seven days prior to hospitalization she began experiencing abdominal pain and four days after the start of the abdominal pain she was instructed to stop pregabalin. She subsequently developed headache and continued to experience abdominal pain. She was hospitalized, concomitant medications (fenofibrate and ranitidine) were stopped, and she had an AST of 1266U/L, total bilirubin of 2.9mg/dL, GGT of 642 IU/L, and an LDH of 1103 U/L. Hepatitis serologies included Hepatitis A IgM antibody negative, Hepatitis B core antibody negative, and hepatitis B surface antibody positive (consistent with past Hep B immunization), CMV IgG was positive and CMV IgM was negative, EBV IgG was positive and EBV IgM was negative. The narrative reported that there were no recent changes in concomitant medications and no acetaminophen use. Approximately one month after stopping pregabalin, lab results were as follows: AST 34U/L, ALT 63U/L, total bilirubin 0.8mg/dL, and LDH 333IU/L. The subject's abdominal pain resolved.

Myalgia

155 071005 This 41 year old male with neuropathy and diabetes mellitus developed myalgia on study day 201 (total pregabalin duration 299 days) and was hospitalized for this event on study day 215. The narrative provided the following lab results:

Parameter (Units)	Study Day			
	215	218	221	223
ALT (IU/L)	102	84	88	61
AST (IU/L)	60	49	30	29
BUN	15	24	35	--
Creatine kinase (IU/L)	352	235	74	87
Chloride (mEq/L)	111	--	--	--
Potassium (mEq/L)	4.94	--	--	--
ALP (IU/L)	--	--	93	--
Creatinine (mg/dL)	0.8	0.8	0.8	--

Study medication was stopped on day study 218 and myalgia subsided by day 220. The subject was discharged from the hospital on day 229. Concomitant medications included furosemide, potassium, cilazapril, bisoprolol, and insulin. The narrative noted that this subject also had transiently elevated hepatic transaminases during a previous trial where he received pregabalin.

Angioedema

155 124003 This 75 year old male with post herpetic neuralgia, type 2 diabetes mellitus, hypertension, coronary heart disease, atrial fibrillation, and chronic obstructive pulmonary disease was hospitalized on study day 31 for angioedema (Quincke edema). Concomitant medications at the time of the event included cefpodoxime, enalapril, metoprolol, phenprocoumon, furosemide, metolazone, adenoprostal (pollen extract), Symfona, glimepiride, glucophage forte, Tranispeg M, paracetamol, cetirizin, Laxiplant, and sosartan. Symptoms included swelling of his upper lip and swelling and pruritis of his hands. He also experienced a sensation of suffocation. He self-medicated with salbutamol and ipratropium with improvement of suffocation sensation. He was subsequently admitted to an ICU and treated with prednisone, and his enalapril, cefpodoxime, and pregabalin were stopped. He continued in the study and pregabalin was re-started without recurrence of the angioedema.

In addition to the SAEs noted above, Pfizer reported information about additional SAEs from ongoing studies (n=35 subjects, Listing ALL33.2) and SAEs from completed studies that had not yet been entered into the Oracle clinical trials database (n=54 subjects, Listing ALL.32). I reviewed the listings to look for SAEs of potential concern. Listing ALL.32 included subject 166 074022 with pancreatitis and subject 198 810003 with acute renal failure and listing ALL 33.2 included a subject 125 001006 with decreased platelet count. I summarize details for those events below.

Pancreatitis

166 074022 This 62-year-old male subject with no history of alcoholism received pregabalin for the treatment of painful diabetic peripheral neuropathy. The subject was initially enrolled in double-blind study and received pregabalin for a total of 83 days. The subject continued in the open label pregabalin study. The total daily dose closest to the onset of the event was 450 mg. Duration of treatment to the onset of event was 524 days. On Study Day 524, the subject was admitted to the hospital for nausea, vomiting and generalized abdominal pain. The symptoms were diagnosed as acute pancreatitis. On Study Day 525, the subject's serum amylase level was 568.6 U/L (reference range not provided). On Study Day 528, the serum amylase level was 21.3 U/L. In response to the event, pregabalin was held for nine days. The event did not reappear after the pregabalin was re-administered. During the hospitalization, the subject received parenteral hydration, isosorbide dinitrate, insulin, analgesics, and a relaxant. The event was considered resolved on Study Day 531. Illnesses present at the onset of the event and other relevant medical history included hypertension, diabetes mellitus type 2. Concomitant therapy taken within two weeks before the

onset of the event included enalapril and metformin. In the opinion of the investigator, this event was due to dietary indiscretion.

Acute Renal Failure

198 810003 This 85-year-old male subject received pregabalin for the treatment of post herpetic neuralgia. The subject was initially enrolled in an RCT and received pregabalin for a total of 92 days. The subject continued in an extension study. On Study Day 420, the subject was hospitalized for acute kidney failure caused by nephrolithiasis and had a Double-J catheter placed. The narrative included no lab data. Pregabalin was temporarily stopped from Study Days 420 to 423 while the subject was hospitalized and then restarted. The subject was discharged from the hospital and re-admitted on Study Day 434 for recurrent acute kidney failure and an infected abdomen. The subject was diagnosed with sepsis possibly secondary to the Double-J catheter. In response to the recurrence of the acute kidney failure and the sepsis, pregabalin was permanently discontinued when the subject was admitted to the hospital. The subject was considered recovered from the recurrent acute kidney failure. There were no known concomitant medications taken 2 weeks before the onset of the event.

Decreased Platelet Count

125 001006 This 41-year-old male subject received pregabalin for the treatment of neuropathic pain. On Study Day 29, the subject was found to have a weight gain of 11 kg since baseline, hemodilution (sodium: 132 mmol/L), and decreased platelet count (23 x 109/L) at week 4. Baseline platelet count was 117 x 109/L, and week 2 platelet count was 65 x 109/L. The declines in platelet count did not appear to be associated with meaningful decreases in WBC count or hemoglobin. A physical examination revealed increased girth of hip and calf measurements, and 3+ pitting edema. The subject was also noted to be extremely drowsy during his interview, and was subsequently referred to cardiology for further evaluation. In response to these findings, treatment with pregabalin was permanently discontinued, and the subject was restarted on his previous treatment and dose of gabapentin. On Post Therapy Day 1, a physician evaluated the subject and felt that the clinical signs and symptoms were suggestive of salt-and-water overload. The subject was also diagnosed with a concurrent urinary tract infection, and was treated with norfloxacin. One week following withdrawal from the study, the subject remained drowsy, had slurred speech, and responded slowly to his interview questions. On Post Therapy Day 8, the subject was admitted to a spinal cord injury rehabilitation center for observation and supportive care due to his slurred speech and decreased cognitive function. At that time, the subject's weight had decreased by 5 kg, and he was noted to have 2+ pitting edema, and a low platelet count (26 x 109/L). On Post Therapy Day 10, the subject was transferred to another hospital to exclude sepsis, and was found to have multi-resistant *P. aeruginosa* in the urine. The subject was treated with IV ceftriaxone for 3 days followed by oral cephalexin. His general condition and alertness improved. The subject's biochemistry and hematology values also improved. On Post Therapy Day 14, the subject was transferred back to the rehabilitation center. On Post Therapy Day 20, based on the subject's low platelet count, concomitant treatment with carbamazepine was discontinued. The same day, the subject's hemodilution resolved (sodium: 135 mmol/L), By Post Therapy Day 21, the subject had continued to improve, had resolution of the pitting edema, and body weight had returned to pre-study levels. The decreased platelet count resolved. Illnesses present at the time of the onset of the event and other relevant medical history included recurrent urinary tract infection, episodes of autonomic dysreflexia, heterotrophic ossification, seborrheic dermatitis, methicillin-resistant *Staphylococcus aureus*, reactive depression, constipation, and pressure sore of the left ischial tuberosity. Concomitant therapy taken within 2 weeks before the onset of the event included zinc sulfate, oxybutynin, baclofen, carbamazepine, ascorbic acid, vaccinium macrocarpon, bisacodyl, senna fruit, diazepam, Coloxyl with Senna® (sennoside A and B, docusate sodium), dantrolene, betamethasone valerate, prazosin, cefalexin monohydrate, and norfloxacin, and gabapentin.

Appendix 3
Discontinuation for AEs of potential concern

CPK Increased

014 017005 This 64 year old male with a history of diabetes mellitus, neuropathy, hyperlipidemia, atypical chest pain, CVA, and osteoarthritis discontinued pregabalin treatment for elevated creatine kinase. This subject received pregabalin for 43 days in an RCT (creatine kinase not measured during this study) and for 749 days in an open label study (CPK ranged from 157-275 U/L). Eleven months after completing the open label study this subject enrolled in a second open label study, and had a baseline creatine kinase of 228U/L. He received pregabalin for 98 days and then started on a mandatory drug holiday. On day 2 of the drug holiday, he was noted to have an elevated creatine kinase (424 U/L). The narrative noted that the elevated creatine kinase persisted (590U/L, highest reported) and the subject discontinued for this adverse event 12 days after resuming pregabalin following the drug holiday. Concurrent medications included lovastatin, ramipril, citalopram, metoclopramide, aspirin, esomeprazole, furosemide, insulin, rosiglitazone, hydrocodone, trazodone, baclofen, and acetaminophen. The creatine kinase elevation was reported as resolved 22 days after discontinuing pregabalin (the termination creatine kinase reported in the CRT was 389U/L).

131 104008 This 53 year old female with a history of diabetes mellitus, neuropathy, pernicious anemia, and hypercholesterolemia discontinued from pregabalin treatment for elevated creatine kinase and elevated ALT results. Her baseline creatine kinase was 216U/L, ALT was 128U/L and AST was 66 U/L. On study day 35, her creatine kinase was 423 U/L, ALT was 163 U/L and AST was 92U/L. Her labs were repeated on study day 40 and her creatine kinase was 492 U/L, ALT was 126 U/L and her AST was 75 U/L. She discontinued on study day 45 and her last off treatment labs (day 71) included a creatine kinase of 131 U/L, an ALT of 112 U/L and an AST of 51 U/L. Work up for these abnormal labs included hepatitis B and C serologies (negative), ESR (reported as negative), CK fractionation (result not reported) GGT (55) and aldolase (result not reported). Her highest recorded total bilirubin was 0.5mg/dL. Concomitant medications include metformin, irbesartan, acetaminophen, and Correctol.

009 005002 This 29 year old female with partial seizures s/p left frontal lobectomy, discontinued for elevated CPK and other AEs. Her baseline creatine kinase was elevated at 478U/L. On study day 13, while taking pregabalin 600mg/d TID, she had a creatine kinase of 835 U/L. Concomitant medications included valproate, lamotrigine, flavoxate, and oxybutynin. On study day 19 she developed edema and on study day 21 she developed intermittent ataxia, cognitive slowing, dizziness, and blurred vision. By study day 23, her creatine kinase was 378 U/L. The blurred vision resolved on study day 24 and her ataxia, cognitive slowing, and dizziness resolved on study day 25. She did not have an AE of myalgia during this study. She withdrew from the study on study day 27 for the events listed above. She entered the open label study and the edema resolved while elevated creatine kinase continued ranging from a low of 240U/L to a high of 436U/L.

009 014012 This 40 year old male with partial seizures discontinued from pregabalin treatment for elevated creatine kinase results during an open label study. This subject participated in the preceding double blind study but creatine kinase was not tested either at baseline or during placebo treatment. On open label study day 28, his creatine kinase (first available) was 611 U/L. His creatine kinase remained elevated throughout treatment and the highest recorded value was 1378 U/L on study day 507. He discontinued on day 566 and his follow up creatine kinase on day 614 was 370 U/L. Concomitant medications were topiramate and carbamazepine.

083 301019 This 33 year old female with generalized anxiety disorder discontinued from pregabalin treatment for elevated creatine kinase. This subject had a baseline creatine kinase of 198U/L. She completed 28 days of pregabalin treatment and entered the dose tapering phase. Her day 28 creatine kinase was 4925 U/L. Study medication was stopped on day 30. Subsequent creatine kinase results were 178 U/L (day 42), 339 U/L (day 49) 509 U/L (day 56), and 169 U/L (day 70). Concomitant medications were aspirin, ibuprofen, oxymetazoline, and medroxyprogesterone.

031 216010 This 74 year old male with chronic pain, osteoarthritis, gout, hypertension, obesity, and thrombocytopenia discontinued from pregabalin treatment for elevated creatine kinase. He was treated with pregabalin in an RCT which did not measure creatine kinase. No baseline creatine kinase result was reported for the open label study. On open label study day 29 his creatine kinase was 937U/L. Eight days later his creatine kinase was 996U/L and his creatine kinase peaked at 1019U/L on open label day 57. He

was withdrawn from the study on open label day 59 and on four days later his creatine kinase was 750U/L. He had two additional creatine kinase results in the CRT, 549 U/L on day 72 and 637 U/L on day 83. The narrative also mentioned that this subject had follow up creatine kinase tests on day 132 (317 U/L) and on day 530 (358 U/L). Concomitant medications included allopurinol, atenolol, indapamide, nambumetone, and multivitamins.

032 322019 This 39 year old female with chronic low back pain, gastroesophageal reflux, irritable bowel syndrome, asthma, ovarian cysts, obesity, and degenerative joint disease discontinued from pregabalin treatment for elevated creatine kinase. This subject did not have a baseline creatine kinase test. On study day 21, her creatine kinase was 1139 U/L. This was associated with an AE of myalgia but the subject did not have an associated increase in creatinine. She was discontinued from the trial on day 22. Her termination visit creatine kinase on day 29 was 108U/L. Concomitant medications included conjugated estrogens, medroxyprogesterone, salmeterol, albuterol, omeprazole, triamcinoline acetonide cream, acetaminophen/diphenhydramine, acetaminophen/aspirin/caffeine, ibuprofen, acetaminophen hydrocodone, diphenhydramine, and fluticasone.

082 214044 This 29 year old male with social phobia, discontinued from pregabalin treatment on study day 71 for elevated creatine kinase, elevated AST and elevated ALT. The following table presents this subject's lab results:

Study day	ALT	AST	Creatine kinase
-7	29 U/L	28U/L	165U/L
57	90U/L	139U/L	3583U/L*
59	93U/L	99U/L	1788U/L*
78	26U/L	28U/L	183U/L
106	68U/L	112U/L	3144U/L*
120	42U/L	36U/L	404U/L

*CK fraction 100% MM

This subject's baseline creatinine was 1.2mg/dL and his highest recorded creatinine was 1.3mg/dL. This subject's baseline total bilirubin was 0.6mg/dL and his highest recorded total bilirubin was 0.9mg/dL. This subject was taking no other medications during this study.

104 419028 This 42 year old male with chronic low back pain, seasonal allergies, hypertension, and alcoholism discontinued from pregabalin treatment for elevated creatine kinase. His baseline creatine kinase was 146U/L. On day 21 his creatine kinase was 1243U/L (100% MM). On day 27, his creatine kinase was 3749U/L (100% MM). He withdrew from the study on day 29, when he had a creatine kinase of 5735 (100% MM). This subject had a baseline creatinine of 1.1mg/dL and his highest on study creatinine was 1.2mg/dL. The narrative reported that the subject was lost to follow up. He was taking no other medications during the study.

105 519005 This 48 year old female with fibromyalgia/chronic pain and hypertension discontinued pregabalin treatment for elevated creatine kinase. This subject received pregabalin during an RCT and had an elevated creatine kinase that was reported as an AE. Her baseline (pre-treatment) creatine kinase results in that RCT were 1493U/L (100% MM) and 273U/L. Her on study creatine kinase results ranged from 312-645U/L. She completed that study and enrolled in the extension study. On open label study day 28 her creatine kinase was 490U/L (100% MM) and on open label study day 56 her creatine kinase was 424 U/L. Her open label study day 101 creatine kinase was 2845 (100% MM). She withdrew on open label day 101 and the narrative reported that a muscle biopsy from day 112 was normal. Concomitant medications included furosemide, spironolactone, and metoprolol. This subject had been taking atorvastatin (started about 3 months prior to this trial) and it was stopped 5 days prior to starting pregabalin.

105 535009 This 52 year old female with fibromyalgia/chronic pain, asthma, and osteoarthritis, discontinued from pregabalin treatment for elevated creatine kinase. After completing an RCT where she received placebo (creatine kinase results ranged from 236U/L to 267U/L), this subject enrolled in an open label trial. On open label study day 31, her creatine kinase was 316U/L (identified as an AE). Her creatine kinase results subsequently ranged from 274U/L to 440U/L and she discontinued from the trial on study day 135 (termination visit creatine kinase result on day 135 was 208U/L). Concomitant medications included unnamed nutritional supplements, salmeterol, and montelukast.

Myopathy/Rhabdomyolysis

080-112001 Summarized with SAEs

149-430001 Summarized with SAEs

ALT (SGPT) increased

131-104008 Summarized above (CPK increased).

085-408022 This 18 year old female with generalized anxiety disorder, s/p L nephrectomy, migraine headaches, and asthma, discontinued from pregabalin treatment for elevated ALT. She participated in an RCT where she received pregabalin and her baseline ALT was 16U/L, AST 18U/L and total bilirubin 0.3mg/dL. Her only other labs in the RCT were on day 42 (termination) and her ALT was 68U/L, AST was 36U/L and total bilirubin was 0.3mg/dL. She entered the open label study and was discontinued on open label day 9. Her labs at the time of termination included an ALT of 27U/L, and AST of 23U/L and a total bilirubin of 0.3mg/dL. Her only reported concomitant medication was paracetamol.

088-504004 This 29 year old male with generalized anxiety disorder, eczema, seasonal allergies, and food allergies discontinued from pregabalin treatment for elevated ALT. His baseline ALT was 52U/L, AST was 27U/L and total bilirubin was 0.5mg/dL. On day 35 (first on-treatment lab) his ALT was 145U/L his AST was 42U/L and his total bilirubin was 0.7mg/dL. He was discontinued at this time. Subsequent labs included ALT 109U/L, AST 39U/L and total bilirubin 0.5mg/dL on day 39, ALT 104U/L, AST 33U/L and total bilirubin 0.5mg/dL on day 42 and ALT 68U/L, AST 23U/L and total bilirubin 0.6mg/dL on day 49. This subject was not taking any other medications at the time of this event.

088-507025 This 27 year old female with generalized anxiety disorder, migraine headaches and urinary frequency, discontinued from pregabalin treatment for elevated ALT. Her baseline ALT was 27U/L AST was 25U/L and total bilirubin was 0.3mg/dL. On day 49 (first on-treatment labs) her ALT was 63U/L, AST was 50U/L and total bilirubin was 0.4mg/dL. On day 51 her ALT was 65U/L, AST was 52U/L and total bilirubin was 0.4mg/dL. She was discontinued from the study on day 55 and there were no follow up labs (subject reportedly lost to follow up). Concomitant medications included conjugated estrogens, and unspecified vitamins.

088-515016 This 21 year old male with generalized anxiety disorder, impotence, and elevated ALT and AST, discontinued from pregabalin treatment for elevated ALT and AST. This subject had baseline ALT of 86U/L, AST of 39U/L, and total bilirubin of 0.7mg/dL. On study day fourteen his ALT increased to 219U/L, AST increased to 118U/L, and his total bilirubin was 0.5mg/dL. He was discontinued from the study on day 19 and by day 33 both ALT and AST were below baseline values (68U/L and 30U/L, respectively). Concomitant medications included famotidine and naproxen.

032-326011 This 60 year old female with chronic back pain, uterine cancer, and hiatal hernia, discontinued from pregabalin treatment for elevated ALT and AST. Her baseline ALT was 68U/L, AST was 40U/L and total bilirubin was 0.2mg/dL. On day 21 her ALT increased to 262U/L, her AST to 123U/L, and her total bilirubin was 0.4mg/dL. On day 28 her ALT was 101U/L, her AST was 56U/L, and her total bilirubin was 0.3mg/dL. Study drug was stopped on day 35 and her ALT was 59U/L, her AST was 32U/L and her total bilirubin was 0.3mg/dL on that day. Concomitant medications included multivitamins and iron.

082-214044 Summarized above (CPK increased).

104-421029 This 39 year old female with a history of chronic back pain, and elevated ALT, discontinued pregabalin treatment for elevated ALT and AST. This subject received pregabalin in an RCT and her baseline labs included AST 28U/L, ALT 40U/L and total bilirubin 1.1mg/dL. In the RCT her AST ranged from 42-56U/L, her ALT ranged from 63-87U/L and her highest total bilirubin was 0.8mg/dL. She enrolled in the open label study and on open label day 7 had an ALT of 176U/L, an AST of 102U/L and a total bilirubin of 0.5mg/dL. She was discontinued from the study on open label day 11. On open label day 27 (off pregabalin) her ALT was 159 U/L, AST was 64 U/L and total bilirubin was 0.4mg/dL. Her final labs on day 41 included an ALT of 207U/L, an AST of 67U/L and a total bilirubin of 0.9mg/dL.Work up for elevated transaminases included a positive hepatitis C test. Concomitant medications included non-specified nutritional supplements.

160-226006 This 62 year old female with post herpetic neuralgia, eczema, and elevated cholesterol, discontinued pregabalin treatment for elevated ALT. At baseline, her ALT was 46U/L, AST was 30U/L and total bilirubin was 0.8mg/dL. On day 10, her ALT was 77U/L, AST was 40U/L and total bilirubin was 0.6mg/dL and study medication was stopped on day 12. On day 15 her ALT was 68U/L, AST was 33U/L and total bilirubin was 1.0 mg/dL and on day 29 her ALT was 26U/L, her AST was 21U/L and her total bilirubin was 0.7mg/dL. Concomitant medications included furosemide, multivitamins and Metamucil.

AST (SGOT) increased

088-515016 Summarized above (ALT increased).
032-326011 Summarized above (ALT increased).
082-214044 Summarized above (CPK increased).
104-421029 Summarized above (ALT increased).

Liver Function Tests abnormal

029-007010 This 53 year old female with diabetes mellitus, neuropathy, fatty liver, and hypothyroidism, discontinued from pregabalin treatment for abnormal LFTs. This subject first participated in an RCT where she received placebo and her ALT ranged from 63-75U/L, her AST ranged from 25-36U/L and her total bilirubin ranged from 0.4-0.5mg/dL. She completed the RCT and entered an open label study. On study days 28-93 her ALT ranged from 44-73U/L, AST ranged from 21-34U/L and total bilirubin from 0.3-0.4mg/dL. On study day 161, her ALT increased to 93 U/L, ALT to 39U/L and her total bilirubin was 0.4mg/dL. Her study medication was stopped on day 164. On day 177, her ALT was 96 U/L, ALT was 45U/L and her total bilirubin was 0.4mg/dL. A liver biopsy on day 267 revealed fatty liver. Follow up labs on day 314 included an ALT of 79 U/L, an ALT of 67U/L and a total bilirubin of 0.3mg/dL. Concomitant medications included levothyroxine, salbutamol, aspirin, ibuprofen, acetaminophen, triamcinolone, metformin, and glyburide.
009-033005 Summarized with the SAEs
085-410003 This 27 year old female with a history of generalized anxiety disorder, asthma, allergies, and PMS, discontinued pregabalin treatment for abnormal LFTs. This subject participated in an RCT where her baseline (pre treatment) ALT results were 99 and 41U/L, AST results were 35 and 21U/L and total bilirubin results were 0.2 and 0.4mg/dL. During the RCT where she received pregabalin, on day 42 (last day prior to study taper) her ALT was 111U/L, AST was 74U/L and total bilirubin was 0.4mg/dL. Her last day of study drug was day 48 and on day 50 her ALT was 84U/L, AST was 33U/L and her total bilirubin was 0.4mg/dL. Follow up labs on day 71 included ALT 185U/L, AST 130U/L and total bilirubin 0.3mg/dL. She entered the open label trial and received pregabalin for three days prior to discontinuing. On open label day 7 her ALT was 104U/L, AST was 38U/L and total bilirubin was 0.2mg/dL. Concomitant medications included salbutamol, fexofenadine, budesonide, cilest, and Vicks Formula 44M.
088-510092 This 20 year old male with a history of generalized anxiety disorder, back and neck pain, and insomnia, discontinued pregabalin treatment for abnormal LFTs. His baseline ALT was 43U/L, AST was 53U/L and total bilirubin was 0.8mg/dL. He also had a baseline creatine kinase of 1144U/L (100% MM) on that day. On day 50 (first on-treatment labs), his ALT was 158U/L, AST was 123U/L and total bilirubin was 0.6 mg/dL. He had a creatine kinase of 2513U/L (100% MM) on that day, He was discontinued on study day 57. His labs from day 57 included an ALT of 149U/L, an AST of 74U/L, a total bilirubin of 0.5mg/dL and a creatine kinase of 925U/L (100% MM). Follow up labs on day 71 included an ALT of 83U/L, an AST of 55U/L, a total bilirubin of 0.4mg/dL and a creatine kinase of 1278U/L (100% MM). Concomitant medications were naproxen and ibuprofen.
031-206005 This 43 year old male with chronic pain, osteoarthritis, borderline hypertension, and depression, discontinued pregabalin treatment for abnormal LFTs. The subject received pregabalin in an RCT. Baseline labs included ALT 46U/L, AST 35U/L and total bilirubin 0.5mg/dL. On study days 7 and 24, his transaminases and total bilirubin were little changed from baseline. On study day 42 his ALT was 62U/L, AST was 40U/L, and total bilirubin was 0.5mg/dL. On study day 64, his transaminases and bilirubin results were similar to the results from day 42. The last lab values from the RCT included an ALT of 76U/L, an AST of 48U/L, and a total bilirubin of 0.6mg/dL. He entered the open label study and on open label day 29 (first available labs) his ALT was 78U/L, AST was 51U/L and total bilirubin was 0.6U/L. On open label day 47 his ALT was 68U/L, AST was 43U/L and total bilirubin was 0.5U/L and on open label day 57 his ALT was 66U/L, AST was 43U/L and total bilirubin was 0.5U/L. He was discontinued on day 57 of the open label study. The narrative provided additional follow up LFTs and on open label day 102 his ALT was 58U/L, and AST was 45U/L. Concomitant medications included piroxicam.
031-216003 This 61 year old male with a history of chronic pain, osteoarthritis, borderline hypertension, elevated cholesterol, and overweight, discontinued pregabalin treatment for abnormal LFTs. This subject participated in an RCT and received pregabalin. Baseline LFTs included ALT 57U/L, AST 37U/L, and total bilirubin 1mg/dL. During the RCT his ALT ranged from 50-58U/L, AST ranged from 38-45U/L and

total bilirubin ranged from 0.6-0.9mg/dL. He enrolled in the open label trial and during the first year of treatment his LFTs varied little with ALT ranging from 46-69U/L, AST ranging from 39-58U/L and total bilirubin ranging from 0.7-1.2mg/dL. On open label day 451 his ALT was 91, AST was 56 and total bilirubin was 1mg/dL. Hepatitis A, B, and C serologies were negative. His pregabalin dose was decreased and repeat labs on day 483 included an ALT of 89U/L, and AST of 60U/L and a total bilirubin of 1.4mg/dL. Pregabalin was held three days and then restarted with tapering doses for the purpose of discontinuation. On study day 511, his ALT was 135U/L, AST was 66U/L and total bilirubin was 1.3mg/dL and the subject was instructed to stop all medications and was scheduled for a liver ultrasound (results not reported). On day 533 his ALT was 72U/L. Concomitant medications included C-bioflavin, chondroiton, kyolic, glucosamine, acetaminophen, multivitamins, and iodine.
031-222013 This 48 year old male with chronic pain, osteoarthritis, seasonal allergies, insomnia, and headaches, discontinued pregabalin treatment for abnormal LFTs. Baseline labs included ALT 37U/L, AST 26U/L, and total bilirubin 0.7mg/dL. On study day 7, his ALT was 206U/L, AST was 73U/L and total bilirubin was 0.7mg/dL. Repeat labs on day 9 included ALT 318U/L, AST 122U/L, and total bilirubin 0.6mg/dL. Study drug was stopped on day 10 and labs that day included ALT 292U/L, AST 106U/L, and total bilirubin 0.7mg/dL. On day 17 labs results included an ALT 109U/L, AST of 29U/L and a total bilirubin of 0.6mg/dL. The last available follow up labs from day 42 included an ALT of 35U/L, and AST of 24U/L and a total bilirubin of 0.6mg/dL. Concomitant medications included etodolac, tramadol, and Sweet Annie Herbs.
104-419026 This 46 year old male with a history of back pain, anaphylaxis, and migraine headaches, discontinued pregabalin treatment for abnormal LFTs. His baseline ALT was 103U/L, AST was 56U/L and total bilirubin was 0.7mg/dL. These repeated on day -1 and the abnormalities persisted. The patient had been randomized to pregabalin but was discontinued on study day 1.

Cholestatic Jaundice

149-369001 Summarized with SAEs
009-011006 Summarized with SAEs

Jaundice

034 021014 This 35 year old male with partial seizures, tuberous sclerosis, cardiac rhabdomyoma, experienced euphoria, jaundice, lethargy, and thinking abnormal (slowness to respond) on study day 1 of pregabalin. Study medication was stopped on day 2 and jaundice, somnolence, thinking abnormal, and euphoria resolved that day. Total bilirubin one day before starting pregabalin was 0.3mg/dL and on study day nine (seven days after stopping pregabalin) was 0.4mg/dL with an AST of 22U/L and an ALT of 20 U/L.

Pancreatitis

030-131005 Summarized with the SAEs
034-036006 Summarized with the SAEs

Leukopenia

040-017013 This 52 year old male with diabetes mellitus and neuropathy, discontinued from pregabalin treatment for leucopenia. This subject enrolled in an RCT where he received amitriptyline. His baseline labs included a WBC count of 4 x10E9/L, (ANC of 1.31), a hemoglobin of 14g/dL, and a platelet count of 237 x10E9/L. Repeat pretreatment labs included a WBC count of 6.4 x10E9/L, (ANC of 4.42), a hemoglobin of 15g/dL, and a platelet count of 199 x10E9/L.He discontinued from the RCT for vertigo on day 21. His day 8 and day 15 hematological results were normal. His day 22 (termination visit) labs included a WBC count of 4.2 x10E9/L, (ANC of 1.32), a hemoglobin of 15g/dL, and a platelet count of 216 x10E9/L. He enrolled in an open label trial and on day one of open label pregabalin he had neutropenia and was discontinued from the trial on day 8. The CRT included no lab results from the open label trial so this determination was likely based on the termination values from the previous trial. Concomitant medications included benazepril, triamterene/hydrochlorothiazide, allopurinol, and insulin.
009 006002 This 18 year old male with partial seizures developed neutropenia on study day 14 of pregabalin treatment and discontinued from the trial on study day 38. Selected hematological lab values are

provided below. Baseline labs demonstrated a low WBC and ANC prior to starting study medication. There appeared to be slight declines across all three cell lines during the study. Follow up off study medication labs suggested that the subject improved.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-92	4.4	1.86	14.3	211
-1	3.8	1.7	15.3	201
14	3.9	1.4	14.9	175
29	3.2	1.08	14.4	168
32 (last study)	3.1	1.06	13.7	174
63 (follow up)	3.5	1.3	14.6	199

Concomitant medications included fluticasone propionate, azelastine, and cephalexin.

009 006004 This 30 year old female with partial seizures developed neutropenia on study day 14 of treatment with pregabalin. This event led to discontinuation on study day 67. Below I summarize selected hematological test results for this subject.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-64	3.4	1.88	15.6	219
-1	3.8	1.95	14.8	233
14	2.9	1.45	13.7	188
35	3.5	1.4	13.7	194
63	2.3	0.81	12.4	176
65 (last on drug)	2.1	0.73	13.2	189
70	2.3	1.07	13.2	210
72	3.3	1.54	13	206
105	3.0	1.35	12.2	179

Concomitant medications included carbamazepine and clonazepam.

010 006113 This 31 year old female with partial seizures developed neutropenia on day 117 of open label pregabalin treatment (did not participate in preceding RCT). She began a taper of pregabalin on study day 136 and last dose was taken on day 142. Below I summarize selected hematological test results for this subject.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-10	3.9	1.72	13.5	193
33	3.4	1.69	14	214
61	3.3	1.34	13.3	202
117 (last on drug)	3.0	1.16	12.6	230
152	3.6	1.44	13.1	195

Concomitant medications included carbamazepine, valproate, paxil, and prn medications including ibuprofen, ercaf, and cor-a-fed tablets.

012 065100 This 48 year old male with partial seizures, and a history of hyponatremia, sensitive lower limbs neuropathy, and psycho-organic syndrome experienced leucopenia on open label study day 170 and neutropenia on study day 231 (first exposure to pregabalin was in this study). Study medication was stopped on day 254. Below I summarize selected hematological results for this subject.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-1	5.6	3.64	14.0	246
29	3.1	1.74	14.2	234
70	3.5	2.21	14.7	214
112	3.0	1.71	14.0	234
196	2.4	1.66	13.7	224
252 (last on drug)	2.3	1.20	13.9	220
261	2.3	1.27	14.1	229
307	2.3	1.10	15.4	246

Concomitant medications included lamotrigine, oxcarbazepine, and primidone.

034 054009 This 33 year old female with partial seizures had leucopenia that was present one day prior to starting pregabalin (WBC count 2.6 x 10 E 3/uL). Her WBC count remained low during treatment and pregabalin was stopped (taper began on day 22). Thirty-five days after stopping pregabalin, her WBC count was similar to her baseline (WBC count 2.5 x 10 E 3/uL). Concomitant medications included valproate, primidone, fexofenadine, paracetamol, prenatal vitamins and enzyme preparations.

Pancytopenia

029-015001 Summarized with SAEs

Thrombocytopenia

010 008125 This 62 year old male with partial seizures, diabetes mellitus, colon cancer s/p radiation and chemotherapy, hypercholesterolemia, coronary artery disease s/p CABG, arthritis, peptic ulcer disease, and atrial flutter withdrew from the study for thrombocytopenia and hematochezia. This subject had his first pregabalin exposure during this open label trial and on study day 140 he underwent cardioversion and on study day 201 he had an intestinal polyp removed. On day 259 he had an AE of thrombocytopenia. On day 296 he experienced rectal hemorrhage. Study medication was stopped on study day 296 for these two events. The rectal hemorrhage was reported as resolved on day 336 and the thrombocytopenia was ongoing. I summarize selected hematological results for this subject n the following table.

Study day	WBC x10E9/L	ANC x10E9/L	Hgb g/dL	PLT x10E9/L
-15	5.7	4.1	14.2	147
28	8.2	6.4	12.9	162
56	8.1	6.38	12.1	161
119	6.2	4.51	13.6	123
182	6.7	4.54	12.5	121
259 (last on drug)	5.4	3.96	11.1	107
301	9.2	7.51	10.3	131
336	8.0	5.86	11.6	175

Concomitant medications included simvastatin, furosemide, ranitidine, aspirin, insulin, warfarin, sorbitol, atenolol, dilantin, and lamictal.

030-131014 This 81 year old male with post herpetic neuralgia, questionable mild idiopathic thrombocytopenia (stable platelet count around 110,000), hypothyroidism, heart murmur, and leg cramps, discontinued pregabalin treatment for worsening thrombocytopenia and PVCs. The subject participated in an RCT where he received pregabalin and his baseline platelet count for that study was 123,000. His visit 4 platelet count was 105,000 and at the end of the RCT his platelet count was 87,000. On open label study day 14 (day 50 of pregabalin), his platelet count was 58,000. He was discontinued from the study on open label study day 25 (day 61 of pregabalin) and his platelet count was 121,000 that day. Thirteen days post treatment he developed bruising and swelling of the forearm, but refused to seek care. The next day he was seen at the study site and was found to have frequent PVCs, an arm and knee bruises, and petechiae on the arms, shoulder, shins, and knees. His platelet count that day was 13,000. He went to an emergency department and a repeat platelet count was 8,000. He was hospitalized and was treated with gamma globulin and recovered. Concomitant medications included aspirin, quinine, and amitriptyline. A consulting hematologist raised the possibility of a relationship of the decline in platelet count to quinine which the subject took on day 36. He had taken this medication as needed over the preceding four years without a similar associated event.

031-216009 This 72 year old male with chronic pain, osteoarthritis, diabetes mellitus, and slight thrombocytopenia discontinued pregabalin treatment for worsening thrombocytopenia. His baseline platelet count was 145x10E9/L. On day 7, his platelet count dropped to 109x10E9/L and on day 14 it was 106x10E9/L. Study medication was discontinued on day 14 and the AE was reported as resolved on day 18 (platelet count 120 x10E9/L). A follow up platelet count on day 50 was 159 x10E9/L.

Pulmonary Hypertension

104-439008 Summarized with SAEs

Lung Fibrosis

014-013006 Summarized with SAEs
082-225008 Summarized with SAEs

Anaphylactoid reaction

196-011008 Summarized with SAEs

Angioedema

014-013022 This 70 year old female with diabetes mellitus, neuropathy, restless leg syndrome, hypotension, and hypothyroidism discontinued from pregabalin treatment for angioedema. She received pregabalin in a previous RCT for 44 days and received pregabalin in the open label trial for 524 days when the event occurred (total duration of treatment 568 days). The narrative reported that the subject experienced breathing problems and was told at an emergency department that she had angioedema and was treated with diphenhydramine and famotidine. Concomitant medications included enalapril, furosemide, simvastatin, levothyroxine, aspirin, and insulin. In addition to stopping pregabalin, enalapril, which she had been taking for several years, was stopped. The event was resolved by open label day 577.

Urticaria

034 041011 This 45 year old female developed hives on day 160 of pregabalin treatment (91 days in the RCT and 69 days of the open label study). Pregabalin was stopped the same day and the hives were resolved ten days later. Concomitant medications included clonazepam, carbamazepine, amitriptyline, nizatidine, fluoxetine, and salbutamol.

029-036013 This 69 year old female with diabetes mellitus, neuropathy, hypertension, hypothyroidism, and hyperlipidemia, discontinued pregabalin treatment for urticaria. This event began on open label study day 50 and she was hospitalization on open label day 58 with urticaria of both arms, lower extremity edema and cellulitis (exposed to pregabalin for 36 days in RCT, total exposure 92 days). The cellulitis was treated with ampicillin/sulbactam. The narrative commented that the urticaria was attributed to the streptococcal cellulitis or furosemide. Concomitant medications included glipizide, hydrochlorothiazide/triamterene, atenolol, levothyroxine, and atorvastatin.

131-117008 This 57 year old male with diabetes mellitus, neuropathy, hypertension, and seasonal allergies, discontinued pregabalin treatment for urticaria. This subject had received pregabalin for 58 days in an RCT and for 69 days in the open label trial when this event occurred. The subject was treated with certirizine and discontinued from the open label trial on day 178. Concomitant medications were lisinopril, glipizide, metformin, aspirin, and rosiglitazone.

087-059009 This 75 year old female with generalized anxiety disorder, discontinued pregabalin treatment for urticaria. This subject received pregabalin for 56 days in the preceding RCT and for 97 days in the open label trial when this event occurred. She was treated with desloratidine, prednisolone, and clemastine. Concomitant medications included digoxin, acenocoumarol, ibuprofen, paracetamol, and zolpidem.

Tongue edema

132-145006 This 44 year old female with post herpetic neuralgia, endometriosis, and ulcers, discontinued pregabalin treatment for tongue disorder and tongue edema. The narrative noted that this subject withdrew on study day four due to tongue feeling hairy with swelling. She also experienced dizziness, altered consciousness, and numbness of the hands. The tongue disorder and tongue edema were resolved by day six. This was not an SAE and there was no mention of treatment for the event or respiratory compromise in the narrative.

Allergic Reaction

035 070101 This 41 year old female experienced an allergic reaction on study day 1. Pfizer reported that the subject experienced dizziness, swollen eyes, thick tongue, and pain in the center of her chest approximately seven hours after her first pregabalin dose (3/19/04 submission). She also felt tired and was unable to walk without assistance. The investigator rated the intensity as severe. Pregabalin was stopped and the event was resolved on day 3. The only concomitant medication was phenytoin.

Face Edema

014-017018 This 64 year old male with diabetes mellitus, peripheral neuropathy, hypertension and hyperlipidemia discontinued for face edema associated with peripheral edema and weight gain that was first reported on day 22. There was no mention of tongue edema or respiratory compromise.
149-366001 This 73 year old female with diabetes mellitus, peripheral neuropathy, hypertension, and hyperlipidemia, discontinued pregabalin treatment for face edema (no mention of peripheral edema) that was first reported on day 20. This subject recovered following discontinuation of pregabalin and without any other treatment. There was no mention of respiratory compromise or tongue edema.
149-483001 This 60 year old female with diabetes mellitus, neuropathy, hypertension, and coronary artery disease discontinued pregabalin treatment for periorbital edema (no mention of peripheral edema) that began on day 3. Study medication was stopped and the subject recovered. There was no mention of respiratory compromise or tongue edema.
045-046001 This 82 year old female with post herpetic neuralgia, Parkinson disease, and osteoarthritis discontinued pregabalin treatment for bilateral palpebral edema (no mention of peripheral edema). This was first noted on study day 4. There was no mention of peripheral edema, respiratory compromise or tongue edema.
132-107008 This 62 year old female with post herpetic neuralgia, heart murmur, hyperlipidemia, and hypertension discontinued pregabalin treatment for facial edema that was first noted on study day 3. There was no mention of peripheral edema, respiratory compromise or tongue edema.
132-145009 This 61 year old female with post herpetic neuralgia, hypertension, borderline hyperglycemia, and borderline hyperlipidemia, discontinued pregabalin treatment for confusion, dry mouth, dizziness, headache, and swelling around the eyes. The onset of face edema was day 14. There was no mention of peripheral edema, respiratory compromise or tongue edema.
196-206001 Summarized with the SAEs.
196-410022 This 60 year old male with post herpetic neuralgia, discontinued pregabalin treatment for dizziness, emotional lability, generalized edema, impotency, and periorbital edema. These events were noted on day 4. There was no mention of respiratory compromise or tongue edema.
087-065008 This 72 year old female with generalized anxiety disorder and nephrolithiasis discontinued pregabalin treatment for insomnia, anxiety, nervousness, headache, myalgia, tremor, and swollen eyes. The swollen eyes were noted on day 3. There was no mention of peripheral edema, respiratory compromise or tongue edema.
105-540004 This 45 year old female with chronic pain, fibromyalgia, and allergies discontinued pregabalin treatment for face edema and hand edema. This subject received pregabalin for 56 days in a previous RCT and the face and hand edema were noted on day 9 of open label pregabalin treatment. There was no mention of respiratory compromise or tongue edema.
105-541013 This 56 year old female with chronic pain, fibromyalgia, diabetes mellitus, and seasonal allergies, discontinued pregabalin treatment for visual blurring and swelling around the eyes. The facial edema was noted on day 17 of treatment. There was no mention of peripheral edema, respiratory compromise or tongue edema.

Acute kidney failure

149-430001 Summarized with SAEs

Kidney function abnormal

040-017017 Summarized with SAEs
040-062006 Summarized with SAEs
149-356024 Summarized with SAEs
045-053005 Summarized with SAEs
045-054008 Summarized with SAEs
127-004004 This 54 year old female with post herpetic neuralgia, hypertension, thyroid disease, and lupus, discontinued from pregabalin treatment for renal insufficiency, confusion, and visual hallucinations. Her baseline creatinine was 1.2mg/dL and BUN was 41mg/dL. On study day 21, her creatinine doubled to 2.4mg/dL and her BUN was 79mg/dL. Study drug was stopped on day 25. The hallucinations and confusion were reported as resolved on day 28. On day 49, her follow up creatinine was 1.4mg/dL and her

BUN was 32mg/dL.Concomitant medications included doxazosin, losartan/hydrochlorothiazide, prednisone, furosemide, thyroxine, estropipate and meperidine.

Creatinine Increased

040-026010 This 63 year old male with diabetes mellitus, neuropathy, hypertension, coronary artery disease, renal insufficiency, and hyperlipidemia, discontinued pregabalin treatment for increased creatinine. In a previous RCT where he received placebo, this subject's creatinine ranged from 1.7-2.3mg/dL. On day 9 of open label pregabalin, his creatinine was 1.9mg/dL. His creatinine ranged from 1.8-2.3mg/dL on days 30-296. On day 415, his creatinine was 3.2mg/dL and BUN was 49.5mg/dL. The CRT noted that on day 382, dosages of several concomitant medications including telmisartan and fosinopril were increased and hydrochlorothiazide was added. This subject discontinued from the trial on day 417.

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Appendix 4

Summary of All Malignant Tumors in the Integrated Safety Database Reported After Pregabalin Treatment (as of 14 February 2003)

Adverse Event Preferred Term *(Investigator term)*	**Number of Patients**	**Patient ID and Pregabalin Exposure [a] (in Days) when tumor began**	
		Patient ID	**Exposure in Days[b]**
Skin carcinoma (i.e., *Basal, Squamous cell, or NOS*)	17	029_017028	5
		029_009001	28
		127_008005	39
		032_320022	54
		104_403003	68
		034_058005	113
		149_396001	144
		031_222012	208
		030_111009	277
		029_021008	308
		029_007017	383
		032_315002	440
		029_006004	440
		030_115004	506
		045_065003	718
		014_009002	745
		030_103003	1393 & 1859
Breast carcinoma	8	045_052010	56
		031_215004	111
		009_037005	141 &148
		088_516015	152
		030_116004	461
		040_016005	519
		029_002003	698
		029_009005	733
Prostatic carcinoma	6	009_015001	28
		082_210025	71
		196_109001	170
		014_011008	323
		040_017008	351
		034_068004	559
Carcinoma NOS (*i.e., peritoneal carcinosis, brain metastases, liver metastases unknown primary site, spread of cancer, metastatic carcinoma*)	6	045_065002	180
		011_070011	211
		045_002003	288
		087_055009	344
		040_028006	616
		045_068001	1043
Bladder carcinoma	4	014_013014	105
		132_106009	293
		034_068004	481
		032_306012	354 & 572

Chronic Leukemia	1	030_131016	492
Kidney (*i.e., renal cell carcinoma, metastatic renal cell carcinoma*)	3	029_021003 045_068001 030_130005	208 467 744
Lymphoma like reaction (i.e., *Hodgkin's lymphoma, CNS Lymphoma*)	3	030_113004 030_125008 035_046100	26 254 432
Ovarian Cancer	1	088_516022	14
Skin Melanoma	2	014_015014 030_109005	364 414
Carcinoma of lung	1	040_017008	360
CNS Cancer (*Anaplastic astrocytoma RT temporal lobe*)	1	094_807001	375
Colon/Rectal (*Carcinoma colon*)	1	040_072002	470
Endometrial carcinoma (*Adenocarcinoma of the endometrium)*	1	030_130017	492
Head and Neck (*Throat cancer*)	1	030_126012	518
Hepatoma (*Adenocarcinoma of liver*)	1	040_017008	360
Myelodysplasia	1	029_015001	479
Pancreas (*Head of pancreas tumor [malignant])*	1	149_369001	433
Sarcoma	1	034_048001	91
Thyroid carcinoma	1	029_043036	99

Total Number of Unique Patients with Malignant Tumors In the Integrated Safety Database as of 14 Feb 2003 57

[a] Total exposure to pregabalin at time of event start [b] Some patients had multiple events of tumor, so patients may have more than 1 total for exposures to pregabalin at time of event start

Appendix 5
Summary of Data for Pregabalin Subjects with low platelet counts

Subject ID	Low PLT on PGB	Baseline PLT*	Comments
007-000709	43,000	71,000	BL on gabapentin, Day 16 PLT 84 (first on tx) remaining PLT ranged from 43-90
007-001003	77,000	176,000	Until day 751, PLT >120; Day 751: 107, Day 970: 95, Day 984: 77, After that all PLT >150
007-001703	97,000	163,000	Only 1 value <120, on day 1477
009-001006		57,000	Had PLT 57 on PBO, On PGB all PLT >120
009-001014	7,000	225,000	Single PLT value<120 (7) four days later 229 (? lab error)
009-008015	84,000	101,000	BL WBC 3.9, post treatment PLT 161
009-019011	85,000	187,000	BL WBC 2.6, BL HGB 11.9, During PGB RCT, PLT>120, During OL, day 897, only PLT <120 (85) WBC 2.4-5.1
009-027007	20,000	17,000	BL WBC 2.4 Missing PLT counts on PGB in RCT and most of OL. First OL PLT count day 1037 (20). Subject had post tx PLT 19
009-037001	98,000	124,000	BL PLT 124, Day 15 113, PLT>120 until day 114 (108). Lowest day 197 (98) only value <100
009-037005	76,000	212,000	RCT on PGB all PLT>120, OL day 499 only PLT <120 (76)
009-038008	98,000	161,000	RCT on PGB no PLT <120, OL all PLT >120 until Day 762 (98), Day 856 (103)
009-044002	58,000	186,000	RCT on PGB PLT>120, OL day 151 PLT 58, no other PLT<120 (1064 days tx total)
009-045005	53,000	144,000	RCT on PGB only PLT <120 day 84 (116), OL only PLT <120 day 196 (53) total tx 1155
009-045014	54,000	114,000	RCT on PGB 167 (13days), OL PLT >120 until day 713 (54), day 776 (103). Post tx day 844 (73)
010-003106	38,000	102,000	BL WBC 2.9. First on tx Day 51 PLT 52, Ranged from 63-85K, on Day 352 PLT 38, Post tx 69
010-008111	100,000	133,000	Day 252 PLT 112 (first <120), and PLT 100 on day 336, remaining on tx all >120.
010-021103	99,000	137,000	Day 280 PLT 99 (first<120), remaining on tx >120.
011-033004	100,000	154,000	BL and RCT on PBO low PLT 154, Day 329 PLT 113 (first<120), Day 666 PLT 100 (last on tx)
011-050006	97,000	214,000	Day 952 PLT 97 (first <120), Remaining on tx and post tx>120
011-055003	93,000	127,000	Day 147 PLT 117 (first <120) Day 210 PLT 114, Day 700 PLT 93 (first <100) Remaining on tx >=100
012-054103	79,000	161,000	Day 105 PLT 118 (first <120), remaining >120 until day 880 PLT 79, Day 960 PLT 131
012-065101	86,000	152,000	Day 172 PLT 86 (first <120), remaining PLT >120
012-084102	60,000	80,000	On tx PLT ranged from 60-80,000
014-004016	99,000	142,000	Day 14 PLT 117, Day 28 PLT 111, Day 42 PLT 128, Day 82 PLT 99, Day 117 PLT 129 (last on tx)
014-010002	89,000	138,000	Day 14 PLT 102, Day 28 PLT 89 Day 37 PLT 106. No other PLT <100
014-012013	96,000	171,000	BL and PBO PLT 171, Day 89 PLT 96 (first<120), remaining on tx>120
014-012016	89,000	131,000	Day 43 PLT 89 (first <120), remaining PLT >120 (868

			days total).
014-013008	99,000	95,000	Day 27 PLT 99 remaining PLT on tx>100
014-015013	89,000	109,000	Day 15 PLT 99 (first <100), Day 90 PLT 97, Day 253 PLT 89, remaining on tx>100
014-020005	89,000	84,000	On tx PLT ranged 89-120
014-025004	78,000	90,000	On tx PLT ranged from 78-115
014-026018	100,000	105,000	Day 43 PLT 100, No on tx<100, Post tx 103
017-002003	48,000	71,000	Day 14 PLT 48, on tx PLT range 48-145, Post tx PLT 52
029-001013	73,000	114,000	Day 22 PLT 100, Day 36 PLT 73, then PLT ranged from 78-245. Post tx PLT 78
029-007005	76,000	153,000	Day 644 PLT 76 (first <120) remaining on tx PLT 141
029-009005	88,000	146,000	Day 28 PLT 88, PLT >100 until Day 447 PLT 93, No other PLT<100
029-012010	91,000	110,000	Day 7 PLT 91, PLT >100 until Day 210 PLT 98, remaining PLT>100
029-015001	82,000	184,000	Day 92 PLT 116 (first<120) Day 197 100, Day 415 PLT 87, Day 450 PLT 82, Next PLT post tx PLT 90
029-028009	96,000	123,000	Day 26 PLT 109, Day 84 PLT 96 (first<100), >120 until Day 426 PLT 101, remaining PLT >100, post tx PLT 108
029-031012	33,000	255,000	PLT above 200 until day 196 PLT 33 (last on tx), post tx PLT 293
029-035011	84,000	118,000	Day 7 PLT 115, Day 21 PLT 106, Day 35 PLT 84, remaining PLT >120
029-036011	65,000	50,000	Day 35 PLT 68, Day 91 PLT 221, Day 119 PLT 76, Fluctuated from PLT 65-241. Post tx 293
029-037007	99,000	141,000	Day 203 PLT 99 (first <120), remaining PLT >120
029-041001	10,000	191,000	Day 119 PLT 10 (first<120), next Value Day 327 PLT 205, No other PLT <200
029-043014	70,000	108,000	Day 7 PLT 75, Day 21 PLT 84, Day 36 PLT 85, Remaining PLT ranged from 70-103, post tx 79
029-043024	93,000	147,000	Day 37 PLT 117 (first<120), PLT>100 until day 226 PLT 93, remaining PLT >120
029-043029	95,000	205,000	Day 21 PLT 95, Day 35 PLT 183 (last on tx)
030-118014	96,000	158,000	Day 294 PLT 114 (first<120), Day 682, PLT 96 (last on tx)
030-126002	7,000	219,000	Day 274 PLT 7 (first <200), six days later PLT 286, no other PLT <200
030-127027	59,000	126,000	Day 21 PLT 113 (first<120), Day 211 PLT 59 (first <100) Day 224 PLT 182 (last on tx)
030-127030	62,000	194,000	Day 7 PLT 90, Day 37 PLT 99, remaining PLT ranged 62-208, last on tx PLT 62, post tx PLT 49
030-130007	84,000	161,000	Day 22 PLT 84, Day 37 PLT 166, no other plt<150
030-131014	58,000	104,000	Day 9 PLT 117, Day 36 PLT 87 (first<100), day 50 PLT 58, Day 61 PLT 121, post tx day 75 PLT 13, post tx day 121 PLT 112
030-131017	45,000	232,000	Day 36 PLT 45 (first <120), Day 40 PLT 191, remaining PLT >190 (through day 494)
031-210019	99,000	140,000	Day 20 PLT 110, Day 41 PLT 99 (first <100), remaining PLT >100 (through day 615)
031-216010	95,000	105,000	Day 7 PLT 95, remaining PLT >100
031-217007	87,000	105,000	Day 6 PLT 107, Day 21 PLT 99, Day 42 PLT 87, remaining PLT ranged from 87-106
031-217017	45,000	189,000	Day 446 PLT 45 (first <120), Day 494 PLT 164 (last on tx)

032-306006		125,000	No on tx results, post tx Day 13 PLT 90
032-324002	52,000	142,000	Day 642 PLT 52 (first<120), post tx Day 686 PLT 166
032-331005	72,000	100,000	Day 22 PLT 87, remaining PLT ranged 72-135
034-001008	38,000	170,000	Day 149 PLT 38 (first <120), remaining PLT>120 through day 800
034-003001	87,000	158,000	Day 149 PLT 111 (first<120), Day 322 PLT 99 (first<100), Day 414 PLT 87, Day 506 PLT 176 (last on tx)
034-019004	99,000	104,000	Day 28 PLT 99, remaining PLT >100 through day 1213
034-025007	96,000	131,000	Day 56 PLT 96 (first<120), Remaining PLT>120 through day 1044
034-036001	89,000	68,000	Day 15 PLT 89, Day 30 PLT 99, Remaining PLT>110
034-036006	69,000	86,000	Day 13 PLT 219, Day 144 PLT 87 (first on tx<120), Day 256 PLT 69, Day 333 PLT 179 (last on tx)
034-040016	93,000	193,000	Day 630 PLT 93 (first <200), Day 638 PLT 194, no other on tx PLT<200
034-040021	67,000	87,000	Day 14 PLT 83, remaining PLT ranged 67-120 (PLT 67 on day 640)
034-047002	54,000	207,000	Day 15 PLT 54, Day 32 PLT 198 remaining PLT >150
034-056006	11,000	185,000	Day 88 PLT 11, Day 180 PLT 175, No other PLT <120
034-072006	98,000	150,000	Day 56 PLT 98 (first <120), No other PLT<120
034-075007	94,000	124,000	Day 11 PLT 109, Day 21 PLT 94, remaining PLT >100
034-077003	95,000	108,000	Day 520 PLT 96 (first<100), remaining PLT ranged from 95-118, post tx PLT 133
034-079002	96,000	193,000	Day 1171 PLT 96 (first<120), No other PLT<120
035-016104	14,000	300,000	Day 190 PLT 14 (first<250), Day 193 PLT 273, remaining on tx PLT>250
035-056105	75,000	152,000	Day 247, PLT 75 (first<150), remaining PLT>150
035-057100	76,000	234,000	Day 176 PLT 76 (first<200), remaining PLT >150
035-073108	86,000	104,000	Day 31 PLT 86, Day 65 PLT 98, remaining PLT >100
035-084102	100,000	150,000	Day 431 PLT 114 (first<120), Day 566 PLT 100, remaining PLT >120
040-020007	100,000	242,000	BL on Amitrip., Day 365 PLT 100 (first <200), Remaining PLT>190
040-020008	63,000	208,000	Day 638, PLT 63 (first <150), Day 729 PLT 208 (last on tx)
040-023001	59,000	119,000	Day 8 PLT 101, Day 15 PLT 73, Day 36 PLT 133, Above 100 until Day 128 PLT 59, then PLT ranged from 77 to 181
040-035006	78,000	92,000	Day 15 PLT 84, Day 59 PLT 78, Remaining PLT ranged from 80-110
040-072021	64,000	101,000	Day 36 PLT 101 (first on tx<120), Day 125 PLT 64 (first <100) Remaining PLT ranged from 83-86
040-082002	42,000	200,000	Day 8 PLT 42, Remaining PLT >150
045-003003	43,000	154,000	Day 56 PLT 110 (first<120), Day 574 PLT 43, remaining PLT ranged from 92-114
045-047003	90,000	116,000	Day 56 PLT 90 (first<120), remaining PLT >120
045-052002		170,000	All on tx PLT150, post tx Day 223 PLT 46
045-071001	87,000	134,000	Day 80 PLT 119 (first<120), Day 252 PLT 87 (first<100), remaining on tx PLT>120, Day 539 post tx PLT 114
080-108005	13,000	190,000	Day 14 PLT 13, Day 26 PLT 201(last on tx).
083-303012	95,000	184,000	Day 31 PLT 95 (only on tx value)
085-409005	77,000	268,000	Day 48 PLT 77 (first on tx), Day 55 PLT 253, remaining

			PLT >200
087-080009	96,000	147,000	Day 322 PLT 96 (first<120), Day 406 PLT 102 (last on tx)
088-504035	92,000	151,000	Day 48 PLT 92 (only on tx) Post tx PLT ranged from 83-125
092-618002	66,000		No BL PT, Day 7 PLT 74, Remaining PLT ranged from 66-84
104-403012		92,000	No on tx result, Day 32 post tx PLT 170
104-432005	99,000	110,000	Day 21 PLT 107, Day 126 PLT 99 (first <100) Day 182 post tx PLT 116
104-433022	68,000	235,000	Day 254 PLT 68 (first and only <200), Day 338 PLT 264
104-434006	95,000	129,000	Day 43 PLT 95 (first on tx), No other PLT <120
104-439032	0		No BL PLT, Day 75 PLT 0, Day 77 PLT 145, No other PLT <120
105-505018	21,000	238,000	Day 168 PLT 21 (first and only <200), Day 251 PLT 242,
127-002007	70,000	100,000	Day 56 PLT 107 (first on tx<120), Day 117 PLT 93 (first <100) remaining PLT ranged from 70-83
132-106004		167,000	On tx PLT>120, Day 85 post tx PLT 97
132-106014	95,000	125,000	Day 14 PLT 95 (first and only on tx)
132-118003	99,000	109,000	Day 10 PLT 99 (first on tx) remaining PLT >100
149-369001	92,000	104,000	Day 88 PLT 92 (first <100), remaining PLT >100
149-371005	99,000	180,000	Day 58 PLT 99 (first and only <120)
149-378004	95,000	122,000	Day 29 PLT 95 (first and only PLT <100)
149-378009	100,000	143,000	Day 85 PLT 100, Remaining PLT>100
149-379002	86,000	111,000	Day 100 PLT 86,000 (first and only on tx PLT<100) Day 351 post tx PLT 89
149-405003	84,000	95,000	Day 29 PLT 96 (first on tx<100), remaining PLT ranged 84-121
149-419006	83,000	83,000	Day 8 PLT 94, Day 57 PLT 83, Remaining PLT ranged 87-107
149-430003	37,000	153,000	Day 29 PLT 37 (first on tx), Day 56 PLT 196, Remaining PLT >150
149-483009	70,000	116,000	Day 22 PLT 108, Day 164 PLT 97 (first PLT<100), Day 241 PLT 70 (last on tx, no post tx)
149-484004	96,000	112,000	Day 57 PLT 114 (first on tx<120), Day 113 PLT 96 (first <100), remaining on tx>100
173-328015		104,000	Day 8 PLT 130 (only on tx) Day 29 post tx PLT 69, Day 31 post tx PLT 49
196-410019		101,000	Post tx Day 29 PLT 99 (no on tx PLT)
196-501002	88,000	131,000	Day 36 PLT 94 (first on tx) remaining on tx PLT ranged 88-119
196-808001	84,000	93,000	Day 28 PLT 89 (first on tx) Day 83 PLT 84 (last on tx, no post tx)

* For subjects with more than one platelet count prior to starting pregabalin, the lowest platelet count was selected as the baseline

Appendix 6
Adverse Events Occurring in =2% of Pregabalin-Treated Patients by Decreasing Frequency, Incorporating Safety Update Data; Controlled Trials in Integrated Safety Database (All Indications)

Preferred Term	Placebo original NDA data (n=2384); % (no.)	Placebo new data (n=65); % (no.)	Placebo updated data (n=2449); % (no.)	Pregabalin original NDA data (n=5508); % (no.)	Pregabalin new data (n=273); % (no.)	Pregabalin Updated data (n=5781); % (no.)
Any adverse event	64.7% (1542)	44.6% (29)	64.1% (1571)	79.3% (4369)	71.4% (195)	78.9% (4564)
Dizziness	8.7% (208)	4.6% (3)	8.6% (211)	29.2% (1606)	24.5% (67)	28.9% (1673)
Somnolence	7.7% (183)	0% (0)	7.5% (183)	22.2% (1225)	11.7% (32)	21.7% (1257)
Headache	13.0% (311)	6.2% (4)	12.9% (315)	11.3% (623)	5.9% (16)	11.1% (639)
Dry Mouth	3.4% (82)	4.6% (3)	3.5% (85)	9.1% (499)	4.4% (12)	8.8% (511)
Infection	7.7% (184)	3.1% (2)	7.6% (186)	8.2% (449)	2.9% (8)	7.9% (457)
Asthenia	5.2% (124)	1.5% (1)	5.1% (125)	7.2% (397)	8.8% (24)	7.3% (421)
Peripheral edema	1.8% (42)	6.2% (4)	1.9% (46)	6.1% (336)	13.2% (36)	6.4% (372)
Amblyopia	2.1% (49)	0% (0)	2.0% (49)	6.4% (351)	2.2% (6)	6.2% (357)
Nausea	7.0% (167)	1.5% (1)	6.9% 9168)	6.1% (334)	8.4% (23)	6.2% (357)
Weight gain	0.8% (19)	3.1% (2)	0.9% (21)	5.6% (311)	13.2% (36)	6.0% (347)
Thinking abnormal	1.6% (38)	0% (0)	1.6% (38)	5.4% (300)	1.8% (5)	5.3% (305)
Constipation	2.2% (53)	6.2% (4)	2.3% (57)	4.8% (262)	2.9% (8)	4.7% (270)
Ataxia	1.0% (24)	1.5% (1)	1.0% (25)	4.7% (260)	1.8% (5)	4.6% (265)
Accidental injury	2.9% (69)	4.6% (3)	2.9% (72)	4.2% (233)	5.9% (16)	4.3% (249)
Pain	3.8% (91)	3.1% (2)	3.8% (93)	3.9% (216)	4.8% (13)	4.1% (229)
Incoordination	0.7% (17)	0% (0)	0.7% (17)	4.0% (221)	0.7% (2)	3.9% (223)
Euphoria	0.5% (11)	0% (0)	0.4% (11)	3.7% (205)	0.4% (1)	3.6% (206)
Diarrhea	5.3% (126)	0% (0)	5.1% (126)	3.4% (187)	5.5% (15)	3.5% (202)
Flu syndrome	3.3% (79)	0% (0)	3.2% (79)	2.9% (159)	1.8% (5)	2.8% (164)
Amnesia	1.0% (24)	0% (0)	1.0% (24)	2.8% (156)	2.6% (7)	2.8% (163)
Nervousness	2.2% (52)	0% (0)	2.1% (52)	2.9% (160)	0.4% (1)	2.8% (161)
Confusion	0.5% (13)	1.5% (1)	0.6% (14)	2.7% (151)	1.8% (5)	2.7% (156)
Insomnia	3.7% (88)	1.5% (1)	3.6% (89)	2.7% (149)	1.1% (3)	2.6% (152)
Increased appetite	0.8% (20)	0% (0)	0.8% (20)	2.3% (128)	1.5% (4)	2.3% (132)
Flatulence	1.2% (29)	0% (0)	1.2% (29)	2.3% (127)	1.5% (4)	2.3% (131)
Tremor	1.3% (31)	0% (0)	1.3% (31)	2.3% (127)	1.1% (3)	2.2% (130)
Diplopia	0.5% (11)	0% (0)	0.4% (11)	2.0% (111)	1.5% (4)	2.0% (115)

From Pfizer Table 8 (page 19, Safety Update) and Appendix ALL.11 (pages 195-222, Safety Update).

Appendix 7
Adverse Events Occurring in =3% of Pregabalin-Treated Patients by Decreasing Frequency, Original NDA and Safety Update Data; Controlled and Uncontrolled Trials in Integrated Safety Database (All Indications)

Preferred term	Original NDA data; % (no.) N=8666	New data; % (no.) N=1617	Updated data; % (no.) N=9278
Any adverse event	89.0% (7711)	67.0% (1083)	89.0% (8254)
Dizziness	33.5% (2902)	12.3% (199)	33.1% (3070)
Somnolence	26.8% (2325)	7.9% (127)	26.3% (2438)
Infection	16.0% (1385)	9.0% (145)	16.1% (1496)
Headache	15.8% (1368)	6.2% (100)	15.7% (1457)
Weight gain	12.2% (1059)	6.5% (105)	12.4% (1154)
Accidental injury	11.6% (1003)	6.4% (103)	11.6% (1080)
Asthenia	11.2% (973)	4.3% (70)	11.2% (1037)
Peripheral edema	9.9% (860)	6.1% (99)	10.1% (935)
Nausea	9.5% (824)	5.5% (89)	9.7% (903)
Pain	9.4% (812)	6.4% (103)	9.5% (884)
Dry mouth	9.3% (806)	2.4% (39)	9.1% (840)
Amblyopia	8.9% (773)	2.5% (41)	8.7% (808)
Thinking abnormal	8.3% (716)	1.9% (30)	8.0% (741)
Flu syndrome	6.9% (601)	3.1% (50)	7.0% (645)
Ataxia	6.7% (577)	2.0% (32)	6.5% (602)
Constipation	6.3% (544)	2.7% (44)	6.3% (582)
Diarrhea	5.9% (510)	4.5% (72)	6.2% (576)
Insomnia	5.8% (501)	2.9% (47)	5.9% (545)
Incoordination	5.6% (482)	1.0% (16)	5.4% (497)
Back pain	4.8% (419)	3.8% (61)	5.1% (471)
Amnesia	5.1% (442)	1.6% (26)	5.0% (467)
Rash	4.6% (296)	3.0% (49)	4.8% (445)
Euphoria	4.9% (423)	3.0% (49)	4.8% (445)
Depression	4.6% (395)	2.5% (40)	4.6% (428)
Nervousness	4.6% (401)	1.2% (20)	4.5% (418)
Pharyngitis	4.1% (354)	2.0% (33)	4.1% (383)
Abdominal pain	4.0% (343)	2.4% (38)	4.1% (379)
Confusion	4.0% (344)	1.4% (22)	3.9% (364)
Sinusitis	4.0% (349)	1.2% (19)	3.9% (364)
Tremor	4.0% (344)	1.2% (19)	3.9% (363)
Dyspepsia	3.8% (325)	1.4% (23)	3.7% (345)
Urinary tract infection	3.5% (303)	2.8% (45)	3.7% (340)
Vomiting	3.4% (293)	2.1% (34)	3.5% (322)
Diplopia	3.5% (305)	0.5% (8)	3.4% (313)
Rhinitis	3.3% (283)	1.4% (22)	3.3% (305)
Chest pain	3.1% (270)	1.7% (28)	3.2% (296)

Flatulence	3.2% (277)	0.9% (15)	3.1% (291)
Increased appetite	3.2% (273)	0.9% (15)	3.1% (287)

From Pfizer Appendix ALL.13 (pages 256-287, Safety Update).

Appendix 8
Adverse Events Occurring in =3% of Pregabalin-treated Patients by Decreasing Frequency, Incorporating Safety Update Data; Controlled and Uncontrolled GAD Studies

Adverse event Preferred Term	Original NDA; % (no.) n=1962	New data % (no.) n=14	Updated data % (no.) n=1962
Any adverse event[41]	87.7% (1720)	85.7% (12)	87.7% (1720)
Dizziness	31.4% (617)	7.1% (1)	31.4% (617)
Somnolence	30.3% (595)	0% (0)	30.3% (595)
Headache	18.0% (354)	7.1% (1)	18.1% (355)
Infection	15.6% (307)	14.3% (2)	15.6% (307)
Dry mouth	15.1% (296)	0% (0)	15.1% (296)
Nausea	11.2% (220)	7.1% (1)	11.3% (221)
Weight gain	9.1% (178)	0% (0)	9.1% (178)
Incoordination	8.8% (173)	0% (0)	8.8% (173)
Euphoria	8.5% (166)	0% (0)	8.5% (166)
Amblyopia	8.2% (161)	0% (0)	8.2% (161)
Thinking abnormal	8.0% (157)	0% (0)	8.0% (157)
Asthenia	7.1% (139)	7.1% (1)	7.1% (140)
Insomnia	6.8% (134)	14.3% (2)	7.0% (137)
Constipation	6.3% (123)	0% (0)	6.3% (123)
Flu syndrome	6.2% (121)	0% (0)	6.2% (121)
Diarrhea	6.1% (119)	0% (0)	6.1% (119)
Nervousness	5.2% (102)	0% (0)	5.2% (102)
Accidental injury	5.0% (98)	21.4% (3)	5.1% (101)
Amnesia	5.1% (100)	0% (0)	5.1% (100)
Flatulence	4.9% (96)	0% (0)	4.9% (96)
Increased appetite	4.7% (93)	0% (0)	4.7% (93)
Pain	4.2% (83)	14.3% (2)	4.3% (84)
Depression	4.1% (80)	0% (0)	4.1% (80)
Dyspepsia	4.1% (80)	0% (0)	4.1% (80)
Pharyngitis	4.1% (80)	0% (0)	4.1% (80)
Libido decreased	3.7% (72)	0% (0)	3.7% (72)
Back pain	3.6% (70)	7.1% (1)	3.6% (70)
Rhinitis	3.5% (69)	0% (0)	3.5% (69)
Sinusitis	3.4% (67)	0% (0)	3.4% (67)
Abdominal pain	3.1% (61)	0% (0)	3.2% (62)

From Pfizer Appendix GAD.8 and GAD.9 (pages 3137-3171, Safety Update).

[41] Although 12 patients had new adverse events after the NDA cutoff date, they all had experienced adverse events prior to the cutoff date as well. As a result, the total number of patients with any adverse event is unchanged from the original NDA. Similarly, many of the patients experienced re-occurrences of adverse events that they had already experienced prior to the original NDA cutoff date. In these cases, the overall frequency of that adverse event is unchanged in the column summarizing updated data.

Appendix 9
Peripheral edema

Relative Risks for Peripheral Edema by Age and Study Grouping; Controlled Trials in NDA Integrated Safety Database

Study grouping	Age group	Placebo	Pregabalin; all doses and regimens	Relative risk
All Controlled Studies	All patients	1.8% (42/2384)	6.1% (336/5508)	3.4
	18-64	1.3% (23/1781)	4.3% (186/4289)	3.3
	65-74	3.3% (12/367)	12.1% (87/718)	3.7
	=75	3.0% (7/230)	12.9% (63/487)	4.3
Neuropathic pain	All patients	2.9% (25/857)	10.4% (190/1831)	3.6
	18-64	2.1% (8/376)	7.5% (64/851)	3.6
	65-74	3.6% (10/275)	12.5% (66/528)	3.5
	=75	3.4% (7/206)	13.3% (60/452)	3.9
Diabetic neuropathy	All patients	2.4% (11/459)	9.4% (92/979)	3.9
	18-64	1.7% (5/302)	7.9% (52/660)	4.6
	65-74	3.3% (4/122)	12.6% *31/246)	3.8
	=75	5.7% (2/35)	12.3% (9/73)	2.2
Postherpetic neuralgia	All patients	3.5% (14/398)	11.5% (98/852)	3.3
	18-64	4.1% (3/74)	6.3% (12/191)	1.5
	65-74	3.9% (6/153)	12.4% (35/282)	3.2
	=75	2.9% (5/171)	13.5% (51/379)	4.6
Epilepsy	All patients	2.0% (6/294)	4.2% (32/758)	2.1
	18-64	2.1% (6/280)	4.4% (32/732)	2.1
	65-74	0.0% (0/7)	0.0% (0/10)	*
	=75	0.0% (0/1)	0.0% (0/2)	*
GAD	All patients	0.4% (2/484)	1.9% (22/1149)	4.7
	18-64	0.2% (1/465)	2.0% (22/1123)	10
	65-74	5.6% (1/18)	0.0% (0/24)	*
	=75	0.0% (0/1)	0.0% (0/2)	*

From Pfizer Appendices ALL.207, ALL.209, and ALL.211 (pages 7496, 7498, and 7500, Summary of Clinical Safety).
*Relative risk could not be calculated given that there were no events in the pregabalin group.

Relative Risks for Peripheral Edema by Baseline BMI and Study Grouping; Controlled Trials in NDA Integrated Safety Database

Study grouping	BMI group	Placebo	Pregabalin; all doses and regimens	Relative risk
All Controlled Studies	All patients	1.8% (42/2384)	6.1% (336/5508)	3.4
	BMI<28	1.2% (16/1329)	4.3% (128/2968)	3.6
	BMI =28	2.4% (25/1047)	8.2% (208/2522)	3.4
Neuropathic pain	All patients	2.9% (25/857)	10.4% (190/1831)	3.6
	BMI<28	2.5% (10/407)	9.4% (76/812)	3.8
	BMI =28	3.1% (14/447)	11.3% (114/1013)	3.6
Diabetic neuropathy	All patients	2.4% (11/459)	9.4% (92/979)	3.9
	BMI<28	1.4% (2/147)	6.4% (18/282)	4.6
	BMI =28	2.6% (8/311)	10.6% (74/697)	4.1
Postherpetic neuralgia	All patients	3.5% (14/398)	11.5% (98/852)	3.3
	BMI<28	3.1% (8/260)	10.9% (58/530)	3.5
	BMI =28	4.4% (6/136)	12.7% (40/316)	2.9
Epilepsy	All patients	2.0% (6/294)	4.2% (32/758)	2.1
	BMI<28	0.5% (1/198)	3.3% (16/489)	6.6
	BMI =28	5.3% (5/95)	6.1% (16/262)	1.1
GAD	All patients	0.4% (2/484)	1.9% (22/1149)	4.7
	BMI<28	0.6% (2/313)	1.1% (8/729)	1.8
	BMI =28	0.0% (0/171)	3.4% (14/417)	5.9*

From Pfizer Appendices ALL.213 and ALL.215 (pages 7502 and 7504, Summary of Clinical Safety).
* To perform this relative risk calculation, I counted one event in the placebo group. The result is an underestimation of the relative risk for pregabalin.

Relative Risks for Peripheral Edema by Gender and Study Grouping; Controlled Trials in NDA Integrated Safety Database

Study grouping	Gender	Placebo	Pregabalin; all doses and regimens	Relative risk
All Controlled Studies	All patients	1.8% (42/2384)	6.1% (336/5508)	3.4
	Males	1.1% (13/1139)	4.4% (113/2557)	4.0
	Females	2.3%	7.6% (223/2951)	3.3

		(29/1245)		
Neuropathic pain	All patients	2.9% (25/857)	10.4% (190/1831)	3.6
	Males	2.2% (10/458)	8.2% (80/974)	3.7
	Females	3.8% (15/399)	12.8% (110/857)	3.4
Diabetic neuropathy	All patients	2.4% (11/459)	9.4% (92/979)	3.9
	Males	3.1% (8/260)	8.4% (48/573)	2.7
	Females	1.5% (3/199)	10.8% (44/406)	7.2
Postherpetic neuralgia	All patients	3.5% (14/398)	11.5% (98/852)	3.3
	Males	1.0% (2/198)	8.0% (32/401)	8.0
	Females	6.0% (12/200)	14.6% (66/451)	2.4
Epilepsy	All patients	2.0% (6/294)	4.2% (32/758)	2.1
	Males	0.6% (1/156)	2.2% (8/363)	3.7
	Females	3.6% (5/138)	6.1% (24/395)	1.7
GAD	All patients	0.4% (2/484)	1.9% (22/1149)	4.7
	Males	0.0% (0/206)	1.3% (6/474)	2.7*
	Females	0.7% (2/278)	2.4% (16/675)	3.4

From Pfizer Appendices ALL.203 and ALL.205 (pages 7492 and 7494, Summary of Clinical Safety).
* To perform this relative risk calculation, I counted one event in the placebo group. The result is an underestimation of the relative risk for pregabalin.

Appendix 10

Summary of Exposure to Pregabalin by Dosage Range
Combined Data For Controlled and Uncontrolled Epilepsy Studies (Studies 1008-007, -008, -009, -010, -011, -012, -034, -035, -145)

Pregabalin 4-Month Safety Update, Cutoff 10/10/2003

NDA Data

	Dosage of Pregabalin (mg/day)								
	0*	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	>=600	Any Dose>0+	Any Dose#
>=1 day to 1 week	127	95	502	407	272	91	46	43	41
>=1 week to <2 weeks	24	74	346	297	182	71	34	30	27
>=2 weeks to <4 weeks	15	47	98	144	179	137	44	35	37
>=4 weeks to <6 weeks	4	12	23	64	107	171	28	46	48
>=6 weeks to <8 weeks	0	4	13	44	69	80	21	21	22
>=8 weeks to <10 weeks	3	2	7	29	64	89	27	26	26
>=10 weeks to <12 weeks	1	26	7	34	34	49	37	31	30
>=12 weeks to <16 weeks	0	51	11	144	84	69	123	76	76
>=16 weeks to <20 weeks	0	1	2	18	58	57	50	56	57
>=20 weeks to <24 weeks	0	1	1	18	34	42	36	45	43
>=24 weeks to <36 weeks	1	2	4	33	80	94	80	145	147
>=36 weeks to <52 weeks	0	2	4	14	56	65	95	141	141
>=52 weeks to <65 weeks	0	0	2	13	45	21	51	129	128
>=65 weeks to <78 weeks	0	0	2	6	27	22	39	103	104
>=78 weeks to <91 weeks	0	0	2	4	15	21	48	63	63
>=91 weeks to <104 weeks	0	0	0	1	13	17	43	66	66
>=104 weeks to <117 weeks	0	1	2	4	13	13	36	83	81
>=117 weeks to <130 weeks	0	0	0	3	10	8	31	80	81
>=130 weeks to <143 weeks	0	0	0	2	9	11	34	67	68
>=143 weeks to <156 weeks	0	0	1	4	9	8	37	59	58
>=156 weeks to <169 weeks	0	0	0	0	9	12	31	57	56
>=169 weeks to <182 weeks	0	0	0	1	6	9	18	64	65

Summary of Exposure to Pregabalin by Dosage Range
Combined Data For Controlled and Uncontrolled Epilepsy Studies (Studies 1008-007, -008, -009, -010, -011, -012, -034, -035, -145)

Pregabalin 4-Month Safety Update, Cutoff 10/10/2003

NDA Data

	Dosage of Pregabalin (mg/day)								
	0*	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	>=600	Any Dose>0+	Any Dose#
>=182 weeks to <195 weeks	0	0	0	1	11	6	15	73	72
>=195 weeks to <208 weeks	0	0	0	0	0	6	6	34	35
>=208 weeks to <221 weeks	0	0	0	1	0	0	4	24	25
>=221 weeks to <234 weeks	0	0	0	0	0	0	4	9	9
>=234 weeks to <247 weeks	0	0	0	0	0	0	2	3	3
>=247 weeks to <260 weeks	0	0	0	0	0	0	2	4	4
>=260 weeks to <273 weeks	0	0	0	0	0	0	0	0	0
Total Patient-Days	1478	10991	17476	71251	190451	201468	405560	897197	898703
Total Patient-Weeks	211.14	1570.14	2496.57	10178.76	27207.24	28781.14	57937.14	128171.00	128386.14
Total Patient-Years	4.05	30.09	47.85	195.08	521.43	551.59	1110.36	2456.39	2460.51

* Indicates days off drug, i.e. day when pregabalin was not taken. Does not refer to days on placebo or days when pregabalin dose was unkno
+ Indicates days on all specified pregabalin doses. Does not include days off drug or days when pregabalin dose was unknown.
# Indicates total days on pregabalin, including days off drug and days when dose was unknown.
Note: Each patient is counted in only one row within a column, but patients who received more than one dose of pregabalin will appear in multiple columns.

Appendix 11

Summary of Exposure to Pregabalin by Dosage Range
Combined Data For Controlled and Uncontrolled Studies, Patients with Generalized Anxiety Disorder (Studies 1008-021, -025, -026, -083, -084, -085, -087, -088, -100, -181)

Pregabalin 4-Month Safety Update, Cutoff 10/10/2003

NDA Data

	Dosage of Pregabalin (mg/day)								
	0*	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	>=600	Any Dose>0+	Any Dose#
>=1 day to 1 week	496	208	549	651	854	395	20	116	114
>=1 week to <2 weeks	59	2	112	119	69	57	24	100	101
>=2 weeks to <4 weeks	8	0	13	249	116	130	225	158	154
>=4 weeks to <6 weeks	1	0	0	31	147	101	83	524	526
>=6 weeks to <8 weeks	0	0	1	64	107	205	15	235	225
>=8 weeks to <10 weeks	0	0	0	13	33	84	12	124	134
>=10 weeks to <12 weeks	0	0	1	3	21	46	12	40	38
>=12 weeks to <16 weeks	0	0	0	23	66	45	14	76	79
>=16 weeks to <20 weeks	0	0	0	11	39	26	11	68	66
>=20 weeks to <24 weeks	0	0	0	13	24	20	12	63	64
>=24 weeks to <36 weeks	0	0	2	20	68	67	20	133	132
>=36 weeks to <52 weeks	0	0	0	41	81	14	25	133	137
>=52 weeks to <65 weeks	0	0	0	15	18	3	5	149	146
>=65 weeks to <78 weeks	0	0	0	0	2	2	1	27	30
>=78 weeks to <91 weeks	0	0	0	0	2	0	0	3	3
>=91 weeks to <104 weeks	0	0	0	0	0	0	1	0	0
>=104 weeks to <117 weeks	0	0	0	0	1	0	0	1	1
>=117 weeks to <130 weeks	0	0	0	0	0	1	1	1	1
>=130 weeks to <143 weeks	0	0	0	0	3	0	1	3	3
>=143 weeks to <156 weeks	0	0	0	0	1	0	1	4	4
>=156 weeks to <169 weeks	0	0	0	0	0	0	0	4	4

Summary of Exposure to Pregabalin by Dosage Range
Combined Data For Controlled and Uncontrolled Studies, Patients with Generalized Anxiety Disorder (Studies 1008-021, -025, -026, -083, -084, -085, -087, -088, -100, -181)

Pregabalin 4-Month Safety Update, Cutoff 10/10/2003

NDA Data

	Dosage of Pregabalin (mg/day)								
	0*	>0 to <75	75 to <150	150 to <300	300 to <450	450 to <600	>=600	Any Dose>0+	Any Dose#
>=169 weeks to <182 weeks	0	0	0	0	0	0	0	0	0
Total Patient-Days	2325	817	3382	42401	87182	59228	33003	226013	228357
Total Patient-Weeks	332.14	116.71	483.14	6057.29	12454.57	8461.14	4714.71	32287.57	32622.43
Total Patient-Years	6.37	2.24	9.26	116.09	238.69	162.16	90.36	618.79	625.21

* Indicates days off drug, i.e. day when pregabalin was not taken. Does not refer to days on placebo or days when pregabalin dose was unknown. + Indicates days on all specified pregabalin doses. Does not include days off drug or days when pregabalin dose was unknown.
# Indicates total days on pregabalin, including days off drug and days when dose was unknown.
Note: Each patient is counted in only one row within a column, but patients who received more than one dose of pregabalin will appear in multiple columns.

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/s/

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