Review and Evaluation of Clinical Data
NDA Safety Review

NDA: 21-446, 21-723, 21-724, [redacted]
Drug: pregabalin (Lyrica)
Route: oral
Indications: [redacted] adjunctive therapy for partial seizures; neuropathic pain associated with diabetic peripheral neuropathy [redacted];
Sponsor: Pfizer
Reviewers: Gerald Boehm, MD, MPH and Alice T.D. Hughes, MD
Action Date: August 31, 2004

The Executive Summary-Safety Review

Pregabalin is an orally administered GABA analogue that interacts with the alpha$_2$-delta protein of voltage gated calcium channels in the CNS. Pfizer submitted pregabalin NDAs to HFD-170 for diabetic peripheral neuropathy and post herpetic neuralgia indications, and to HFD-120 for epilepsy. HFD-170 is reviewing the diabetic peripheral neuropathy NDA as a priority application, so their review will be completed prior to the reviews for the other indications.

Pregabalin has not yet been marketed in any country but it received a recommendation for marketing authorization for neuropathic pain and epilepsy from the European Union Committee for Proprietary Medicinal Products in March 2004.

There are FDA approved treatments for epilepsy and GAD. No approved epilepsy or GAD treatment is completely efficacious. Many epilepsy drug treatments are associated with substantial and in some cases life threatening toxicities whereas the approved GAD medications are generally well tolerated.

Pregabalin related hemangiosarcoma in mice was a major preclinical safety finding. In the United States, this finding resulted in partial clinical holds, termination of controlled trials and reassessment of the subjects in open label trials that were ongoing at the time. In addition, other countries placed restrictions on pregabalin studies and Pfizer discontinued its studies in Japan.

The pregabalin NDA included pooled safety data from 53 phase II/III controlled and uncontrolled trials from studies of a number of indications (diabetic peripheral neuropathy, post-herpetic neuralgia, epilepsy, GAD, other psychiatric indications, chronic pain, etc.) The pregabalin NDA controlled trials safety database pooled data from 30 controlled trials including 11 neuropathic pain studies, 3 epilepsy studies, 6 GAD studies, 4 chronic pain studies and 6 other psychiatry studies. In addition to the overall pooled safety databases that included data from studies of a number of different indications, Pfizer provided separate safety analyses for diabetic neuropathy, post herpetic neuralgia, neuropathic pain (diabetic neuropathy and post herpetic neuralgia pooled), epilepsy, and GAD studies. These separate analyses included the safety data from only those trials examining the specific indication(s). In addition to phase II/III safety data, Pfizer submitted safety data from twenty-eight phase I trials and from dental pain trials and pregabalin trials conducted in Japan.

The number of patients exposed to pregabalin in phase II/III combined controlled and uncontrolled trials exceeds ICH guidelines and Pfizer exposed adequate numbers of subjects to the intended recommended doses. The pregabalin NDA includes safety data for 440 subjects exposed to pregabalin in phase I trials, 9,278 subjects exposed to pregabalin in the combined controlled and uncontrolled trials through the safety update, 267 subjects exposed to pregabalin in dental pain studies, 51 subjects exposed to pregabalin in Japanese studies, and 20 subjects exposed to pregabalin in a platelet function study. In their phase II/III trials through the safety update, Pfizer reported that

1,304 subjects had been exposed to the pregabalin maximum recommended dose (600mg/day) for at least 24 weeks and that 751 subjects had been exposed to the maximum recommended dose for at least 1 year.

The safety testing, capture of adverse events, coding of investigator terms and analyses of safety data were generally adequate. The safety data were consistent across the submitted case report forms, electronic data sets, and summary tables. There were occasional problems with submission quality, some that were technical in nature (incorrect electronic bookmarks) and some that were the result of sponsor errors (inaccurate duration of treatment estimates, incorrect tables, etc.).

In the pooled controlled trials, the percentage of subjects who died was similar in the pregabalin and placebo treatment groups. The reported causes of death generally were those expected in the studied populations.

The overall SAE risk was similar for pregabalin and placebo subjects in the controlled trials. The most common SAE among pregabalin subjects in the safety database was accidental injury (0.9%, 78/8666) and this SAE was also more common among pregabalin subjects in the controlled trials (pregabalin 0.3%, 19/5508; placebo <0.1%, 1/2384). The pregabalin NDA included less frequent SAEs of potential concern. Six SAEs of pancreatitis were reported for pregabalin subjects through the safety update; one occurred prior to pregabalin exposure, one was associated with alcohol use, three were associated with stones (biliary lithiasis, vesicular lithiasis, and cholelithiasis) and one case had no identified confounding factors. Another pancreatitis SAE case was identified from an ongoing study and this subject had a negative re-challenge. Pfizer also reported two SAEs of myopathy and three of CK increased through the safety update. In the phase II/III trials there were no SAEs of liver failure or aplastic anemia.

Pregabalin subjects discontinued from controlled trials for AEs almost twice as frequently as placebo subjects. Through the safety update, dizziness, somnolence, ataxia, nausea, and confusion were the AEs leading to discontinuation of at least 1% of pregabalin subjects and more frequently when compared to placebo subjects.

Common AEs that occurred more frequently among pregabalin subjects and in some cases that exhibited evidence of a dose response relationship included dizziness, somnolence, dry mouth, asthenia, amblyopia, peripheral edema, weight gain, thinking abnormal, constipation, ataxia, accidental injury, incoordination, euphoria, amnesia, confusion, increased appetite, flatulence, tremor, and diplopia.

The safety data suggest a potential relationship between pregabalin and myopathy. Pregabalin subjects experienced a greater mean increase and greater high outlier risks for creatine kinase compared to placebo subjects in the controlled trials, and Pfizer reported three cases of rhabdomyolysis (coded to the term myopathy) among pregabalin subjects in their safety database (1 AEs, 2 SAEs). The pregabalin safety database included six pregabalin subjects with CK elevation of at least 5x ULN associated with muscle pain or muscle weakness AEs (three of which were AEs mentioned above). Another review of

subjects with CK outliers revealed that some subjects' CK result abnormalities were present at baseline and that CK elevations were present in the placebo treated subjects, both of which support that these events occur in the background and complicate interpretation of abnormal results. Although a number of subjects had their marked CK abnormality for their only on-treatment test or at their last on-treatment test, there were also subjects who developed marked CK elevations on pregabalin that resolved with continued treatment.

Pregabalin was associated with a greater mean decrease in platelet count as well as a higher risk for low platelet outliers compared to placebo in the controlled trials. Despite these differences in lab results, there did not appear to be differences in risk for bleeding related adverse events between the pregabalin and placebo treated groups in the combined clinical trials database.

Pregabalin was associated with weight gain. Although Pfizer reported that subjects in epilepsy trials were at greatest risk for weight gain, this finding appeared to be due to differences in the duration of observation in the controlled trials. When considering only the first six weeks, in epilepsy controlled trials, 6% (26/758) of pregabalin subjects and 1% (2/294) of placebo subjects gained at least 7% of their baseline body weight. In GAD controlled trials (5-7 weeks in duration), 4% (42/1044) of pregabalin subjects and 1.4% (6/428) of placebo subjects gained at least 7% of their baseline body weight. The mechanism of weight gain was not described but pregabalin subjects in controlled trials did experience increased risks for appetite increased and peripheral edema AEs. Neither of these AEs completely explained the weight gain differences between pregabalin and placebo subjects in the controlled trials. Based on an analysis of AE co-occurrence, Pfizer concluded that pregabalin associated weight gain was not associated with increased risk for blood pressure or cardiac adverse events. These conclusions are based on data from relatively short term trials and therefore cannot address the long term impact of pregabalin associated weight gain on cardiac disease or blood pressure outcomes.

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. 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's analyses of ECGs did not support that pregabalin was associated with QT prolongation but the ECG data were limited. Pfizer submitted no preclinical studies of the effect of pregabalin on ion channels and no clinical pharmacology studies specifically designed to evaluate the effect of pregabalin on the QT interval. Analyses of phase II/III trial data did not find evidence of pregabalin related QT prolongation although these data were limited because they compared a single baseline and a single on-treatment ECG.

Pfizer demonstrated that pregabalin was associated with prolongation of the PR interval. Pregabalin associated PR prolongation did not appear to be associated with notable increased risk for heart block related AEs in the pregabalin controlled trials database. Pfizer did not explore the effect of pregabalin when used concomitantly with other

medications that prolong the PR interval or in subjects with prolonged PR intervals at baseline.

Despite a preclinical signal of increased risk of hemangiosarcoma in mice, Pfizer provided no quantitative assessment of human cancer rates in the development program. The review team requested comparisons of the malignancy rates in the NDA to general population malignancy background rates. Pfizer had not submitted their review at the time of completion of this review.

Recommendations

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

Follow up on the request for quantitative analyses of the human cancer rates in the development program.

Add to the description of CK elevation that Pfizer proposed in labeling.

Add a section to product labeling that describes pregabalin's effect on platelets.

Revise the labeling descriptions of the findings for weight gain and peripheral edema as recommended in the review.

1. Materials Used in This Review

This safety review is based on the information included in the following submissions:

- October 30, 2003; NDA Summary of Safety electronic submission, Study reports for individual studies electronic submissions, electronic data sets, electronic Case Report Forms (CRFs), electronic case report tabulations
- February 23, 2004 submission, Safety Update electronic submission
- January 24, 2004, February 5, 2004, February 13, 2004, February 23, 2004, March 19, 2004, March 31, 2004, April 12, 2004, April 19, 2004, April 28, 2004, May 17,1004, May 19, 2004, June 4, 2004, June 9, 2004, July 6, 2004, and July 7, 2004 submissions; responses to reviewer safety questions-electronic submissions

2. Background

2.1 Name, Drug Class, Proposed Indication, Safety Related Regulatory Issues in the Development Program

Pregabalin (CI-1008, or (S)-3-(aminomethyl)-5-methylhexanoic acid) is a GABA analogue that interacts with the alpha$_2$-delta protein of voltage gated calcium channels in the CNS (NDA Clinical Overview, p.12, Pregabalin is administered orally. The sponsor, Pfizer, seeks FDA approval to market pregabalin for the treatment of patients with chronic pain disorders such as neuropathic pain, for partial seizures

Pregabalin is not yet marketed in any country. In March of 2004, the Committee for Proprietary Medicinal Products recommended granting marketing authorization for pregabalin for the treatment of neuropathic pain and epilepsy.

The pregabalin development program included clinical holds and termination of studies due to a safety related finding of increased hemangiosarcoma incidence in two mouse carcinogenicity trials. The FDA Division of Anesthetics, Critical Care, and Addiction Drug Products imposed a partial clinical hold on the pregabalin pain studies in February 2001. In addition, The FDA Division of Neuropharmacological Drug Products and the sponsor agreed that epilepsy controlled clinical studies would be terminated and that open label study subjects would be required to be refractory to other treatments and demonstrate response to pregabalin to continue in their studies.

2.2 State of Armamentarium- Safety

The approved AEDs are associated with significant toxicities including, but not limited to, serious skin reactions including Stevens Johnson Syndrome, liver toxicity, hematological toxicity, oligohydrosis, congenital malformations, pancreatitis, and cognitive neuropsychiatric abnormalities.

There are a number of FDA approved anti-anxiety drugs. Venlafaxine, paroxetine, and alprazolam include generalized anxiety disorder (GAD) in the Indications section of labeling. Alprazolam can be associated with development of dependence. Venlafaxine and paroxetine are generally well tolerated, although both are associated with discontinuation symptoms.

2.3 Proposed Pregabalin Label with Respect to Safety

This review is based on the pregabalin labeling proposal submitted 3/17/04.

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 3

2.4 Animal Pharmacology and Toxicology

In section 2.4.4.9 of their Non Clinical Overview Module of the pregabalin NDA, Pfizer summarized the major safety findings from animal studies. Pfizer identified the following five major findings in animals: hemangiosarcomas, reproductive effects, CNS effects, dermatopathy, and clinical lab (platelet) changes.

Pfizer reported that pregabalin was not carcinogenic in rats but that they observed an increased incidence of hemangiosarcoma in B6C3F1 mice at 1000 and 5000mg/kg with exposures 5 to 31 times the mean human exposures at the maximum recommended dose

(Non Clinical Overview, p.43). In addition, they observed a numerical but not statistically significant increased incidence of hemangiosarcoma in female B6C3F1 mice at 200mg/kg, with an exposure equivalent to human therapeutic exposure. Pfizer also observed an increased incidence of hemangiosarcoma in male CD-1 mice at 5000mg/kg with associated exposure 28 times the human mean exposure at the maximum recommended dose. The incidence of hemangiosarcoma was increased but not statistically significantly in female CD-1 mice at 5000mg/kg. Pfizer reported that no statistically significant increase in hemangiosarcoma was observed in CD-1 mice at =1000mg/kg with associated exposures =5 times the mean human exposure at the maximum recommended dose.

Pfizer attributed the increased incidence of hemangiosarcoma in B6C3F1 and CD-1 mice to increased platelet activation, bone marrow and splenic megakaryopoiesis, and circulating and tissue levels of endothelial growth factors. Pfizer reported that in one study of Wistar rats, platelet counts and bone marrow megakaryocyte counts were decreased and pregabalin was not carcinogenic. In a second Wistar rat study, dose related decreases in platelet count were observed and pregabalin was not carcinogenic (megakaryocytes not evaluated in this study). Pfizer reported that no endothelial cell proliferation or changes in bone marrow, spleen, platelet function, or growth factors similar to those observed in mice were observed in monkeys treated for up to 69 weeks.

Pfizer reported reduced sperm motility, morphology, and/or counts and decreased fertility and delayed mating in male rats at 27 times the maximum recommended human exposure (Non clinical summary, pp.45-46). Pfizer reported that the mechanism for the observed effects on sperm involved a direct effect on the epididymis or on sperm maturation in the epididymis. Pfizer did not observe similar findings in monkeys or mice.

Pfizer summarized the pregabalin animal findings related to female fertility, fetotoxicity, and development. In the female fertility study in rats, dystocia was noted at >= 47 times the mean human exposure. Pregabalin induced fetotoxicity in rats and rabbits at >=39 times the mean human exposure. In the prenatal/postnatal study, developmental toxicity was noted in offspring of rats at exposures >=5 times the mean human exposure. No developmental effects occurred at twice the mean human exposure. Pregabalin was not teratogenic in mice, rats, or rabbits at exposures 31 to 77 times the mean human exposure at the maximum recommended clinical dose. Pregabalin was present in milk of lactating rats.

Pfizer noted the following CNS effects in animals given pregabalin: hypoactivity, hyperactivity, and ataxia. Pfizer commented that these signs were seen in the initial days of exposure and decreased with continued exposure. Pfizer noted that the AUC values associated with these signs were = 1.4 times the mean human exposure at maximum recommended clinical dose (Non Clinical Overview, p.47).

Pfizer noted that pregabalin caused skin lesions (dermatopathy) of the tail of rats and monkeys that ranged from erythema to necrosis and that were characterized histologically by hyperkeratosis, acanthosis, fibrosis, and/or necrosis. Pfizer stated that these changes

were seen in rats and monkeys given = 2 times the mean human exposure at the maximum recommended dose, appeared within the first two weeks of exposure, and generally resolved with continued exposure. These changes were not observed in mice (Non Clinical Overview, p.48).

Pfizer reported that pregabalin was associated with platelet count decreases in rats but not monkeys. As detailed above, pregabalin caused platelet count increases in mice (Non Clinical Overview, p.48).

2.5 Human Pharmacokinetics

Pfizer reported that oral absorption of pregabalin was rapid and independent of dose. The mean bioavailability of pregabalin was =90% and was independent of dose. When pregabalin capsules were administered as single and multiple doses from 25-300mg, mean T_{max} (0.8–1.4 hours) occurred during the same interval as reported for single-dose administration and was shown to be independent of dose. Pfizer noted that linear pharmacokinetics were evident across a dose range which is broader than the intended dose range in clinical practice (Overview of Clinical Pharmacokinetics, p. 21-22).

Pfizer reported that pregabalin has a volume of distribution that is similar to that of total body water. Pregabalin does not bind plasma proteins at clinically relevant concentrations.

Pfizer commented that after oral administration to healthy subjects with normal renal function, more than 90% of ^{14}C labeled pregabalin was recovered in the urine and less than 0.1% in the feces.

Pfizer reported that *in vitro* studies document that at concentrations approximately 10 fold higher than observed in clinical trials, pregabalin does not inhibit cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4.

Pfizer noted that pregabalin's mean terminal phase half-life ($t_{1/2}$) was 6.3 hours and independent of dose. Mean renal clearance was estimated to be 72.7ml/min and was not dependent on dose following single dose administration within the dose range of 1 to 300mg. Steady state was achieved within 24 to 48 hours after the start of multiple dosing.

Pfizer reported that pregabalin pharmacokinetics are not affected by age, gender, or menopausal status. Pfizer recommends pregabalin dosage reductions in patients with renal insufficiency and in patients undergoing dialysis.

3. Approach to Safety Review/Methods

Pfizer submitted the pregabalin NDA to two CDER reviewing divisions to conside[illegible] indications. Dr. Boehm and Dr. Hughes in the Neuropharmacological drug products division, HFD-120, reviewed the overall safety data as well as the safety data specifically related to the indications that are overseen by this division (epilepsy [illegible]). As HFD-120

completed draft sections of the safety review, the division forwarded them to HFD-170, to keep them apprised of our findings. Pfizer used the Common Technical Document format for the pregabalin NDA safety data presentations.

HFD-120 reviewed the treatment emergent adverse events identified from the pregabalin development program using the electronic Summary of Safety, the Safety Update, and responses to specific reviewer questions. To examine the agreement of the data across sources, we cross checked data from the sponsor's listings, case report forms (CRFs), case report tabulations (CRTs), narrative summaries, and in some cases, electronic data sets for all deaths and serious adverse events summarized by the sponsor. To evaluate the adverse event (AE) coding procedures, we compared investigator verbatim terms with the corresponding preferred terms assigned by the sponsor. For selected events (e.g., liver related abnormalities, myopathy, rashes), we reviewed the coding in more detail by examining the CRFs, electronic data sets, narrative summaries, and study report listings to determine if the coded terms accurately reflected the described events. We reviewed the death narratives for all study subjects who died and summarized the clinical details for selected deaths. In addition, we reviewed the CRFs, narrative summaries, data sets and study reports for selected serious adverse events (SAEs), selected AEs leading to discontinuation from a study, and any AE preferred terms suggestive of events of particular interest. We reviewed the results of the sponsor's treatment emergent AE risk calculations. We reviewed the sponsor's lab and vital sign data analyses. We requested and reviewed additional analyses of lab outliers, CK results, and platelet results.

4. Review Findings

4.1 Description of Data Sources

4.1.1 Integrated Safety Database Data Sources

The pregabalin integrated safety database presentation includes analyses of information pooled from phase II/III controlled and uncontrolled trials. Pfizer's presentation of the overall safety data uses two main groupings, Controlled Studies and Combined Controlled and Uncontrolled Studies. In their Controlled Studies group, Pfizer included data from selected, but not all controlled trials from the pregabalin development program Safety data for pregabalin subjects from controlled trials not included in the Controlled Studies database were included in the Combined Controlled and Uncontrolled Studies presentations. The Controlled Studies database includes data from studies for the indication sought by Pfizer as well as studies for other indications (ex. other psychiatry, other chronic pain). In addition to Phase II/III safety data mentioned above, Pfizer also separately submitted (not included in the integrated safety data analyses) the safety data from clinical pharmacology studies and phase II/III trials for indications not sought in the NDA (dental pain, Japanese studies). Lastly, Pfizer submitted limited safety information for studies that were ongoing at the time of the integrated safety database lock date. These studies are summarized in Table 135 (Summary of Safety, p. 241; see Appendix Table 1). Data from patients in these ongoing studies were not integrated into Pfizer's analyses, although Pfizer does provide limited information regarding deaths and SAEs for

these patients. The following table provides a list of the studies included in Pfizer's NDA integrated databases.

Pfizer Summary of Safety Table 2. Study Groupings for Safety Data Summarization Phase 2/3 Studies

Study Grouping	Studies Included
30 Controlled Studies	**11** Neuropathic Pain: 014, 029, 030, 040, 045, 127, 131, 132, 149, 173, 196 **3** Epilepsy: 009, 011, 034 **6** Generalized Anxiety Disorder: 021, 025, 026, 083, 085, 087 **4** Other Chronic Pain: 031, 032, 104, 105 **6** Other Psychiatry: 017, 022, 080, 081/153[a], 092[b], 094[b]
Combined Data: All 53 Controlled Studies and Their Uncontrolled Extensions	**Controlled:** **11** Neuropathic Pain: 014, 029, 030, 040, 045, 127, 131, 132, 149, 173, 196 **2** Other Neuropathic Pain: 060[c], 160[c] **5** Epilepsy: 007[c], 009, 011, 034, 145[c] **4** Other Chronic Pain: 031, 032, 104, 105 **8** Generalized Anxiety Disorder: 021, 025, 026, 083, 085, 087, 088[c], 181[c] **7** Other Psychiatry: 017, 022, 080, 081/153, 082[c], 092, 094 **Open-Label Extension:** **9** Neuropathic Pain/Other Chronic Pain: 015, 033, 061, 074, 134, 165, 174, 197[d], 198 **1** Other Neuropathic Pain: 183 **4** Epilepsy: 008, 010, 012, 035 **2** Psychiatry: 084, 100

[a] Study 081 (conducted in Europe/South Africa/Israel) and Study 153 (conducted in the US) were twin studies summarized in one research report and therefore are counted as 1 study.

[b] Studies 092 and 094 were summarized in 1 report, per protocol amendment, but were originally planned as separate studies and therefore are counted as 2 studies.

[c] Controlled studies not integrated with the 30 controlled studies because of differences in study design or indication, or because they were terminated early with minimal enrollment.

[d] Patients who completed Study 015 or who were ongoing in Studies 015, 033, 132, 134, 173, and 174 at the time they were closed by Pfizer were eligible to enroll in Study 197.

The safety update included data from studies 155 (controlled, neuropathic pain), 093/132 (controlled, psychiatry), 093 (open label, psychiatry) and 166 (open label, pain), which were not included in the NDA databases. The Safety Update also included safety data for subjects continuing in ongoing studies.

In addition to the integrated safety data analyses that pooled data from the different indication populations, Pfizer made indication-specific presentations of safety data that followed the same format as the integrated safety data presentations.

4.1.2 Epilepsy Safety Database Data Sources

The pregabalin development program included three completed adjunctive controlled studies of twelve weeks duration (1008-009, 1008-011, 1008-034) and their open label extensions (1008-010, 1008-012, 1008-035). The open label extension studies also enrolled subjects who did not participate in the previous RCT (referred to by Pfizer as De Novo subjects). In addition, the NDA includes a completed eight day RCT (1008-007 monotherapy proof of concept study) and its extension (1008-008) and a titration study

that was terminated prior to completion (145). Pfizer presented pooled analyses for controlled studies 1008-009, 1008-011, and 1008-034. Separately, Pfizer provided analyses of combined controlled and uncontrolled studies that included the data from all of the epilepsy studies. The following table summarizes information from the epilepsy trials analysis groups.

FDA Table 1. Epilepsy trials in the Pregabalin Safety Database

Trial	PGB Dose/Duration	Number enrolled
Controlled Adjunctive Therapy Trials		
1008-009	600mg/day BID or TID/12 weeks	PGB=214, PBO=98
1008-011	150mg, 600mg/day, TID/12 weeks	PGB=191, PBO=96
1008-034	150mg/day, 300mg/day, 600mg/day BID/12 weeks	PGB=353, PBO=100
Monotherapy Epilepsy Controlled Trial		
1008-007	600mg/day TID/ 8 days	PGB=42, GAB*=51
Titration Study		
1008-145	Terminated	PGB=3
Open Label Extensions		
1008-008	150-600mg/day TID, Open-ended	Continued[1]=40 New[2]=42
1008-010	225-600mg/day BID or TID, Open-ended	Continued[1]=171 New[2]=88 De Novo[3]=195
1008-012	75-600mg/day BID or TID, Open-ended	Continued[1]=151 New[2]=81 De Novo[3]=89
1008-035	100-600mg/day BID, Open-ended	Continued[1]=308 New[2]=87 De Novo[3]=228

*Gabapentin
[1]Continued PGB from previous controlled trial
[2]Received comparator in controlled trial and switched to PGB in OL EXT
[3]Enrolled into OL EXT without participation in previous RCT
Data from Pfizer Table 88, p.171

4.1.3 GAD Safety Database Data Sources

The integrated pregabalin GAD safety database consisted of six controlled studies of four to six weeks duration[1] (1008-021, 1008-025, 1008-026, 1008-083, 1008-085, 1008-087) and a randomized withdrawal design relapse prevention study (1008-088) in which patients received open-label pregabalin therapy for eight weeks followed by up to six months of randomized, double-blind therapy with pregabalin or placebo. In addition to these studies, the GAD safety database included a placebo-controlled flexible dose study (1008-181) that was terminated soon after initiation. The safety database also included two open-label extension studies. Open-label Study 1008-100 enrolled patients from Study 087. Open-label Study 1008-084 enrolled patients from Studies 083, 085, and 088; it also enrolled patients who had not previously participated in a randomized controlled

[1] The durations of four to six weeks specified by Pfizer include the titration period but not the taper period that each study also had; the durations I specify in the table include both the titration and the taper periods.

trial. Both open-label studies also enrolled patients from controlled studies not in the integrated safety database. Throughout their NDA, Pfizer presented pooled analyses for GAD controlled trials that included data from controlled studies 021, 025, 026, 083, 085, and 087. Safety data from Studies 088 and 181 were not pooled with these controlled studies but were included in presentations of combined data from controlled and uncontrolled studies.

The following table summarizes information regarding the GAD trials included in the integrated safety database:

FDA Table 2. GAD Trials in the Pregabalin NDA Safety Database

Trial	Status	Pregabalin dose/duration (including titration and taper)	Open-label extension study following	Number enrolled		
Randomized, Double-blind, Placebo-controlled Short-term Studies				Pregabalin	Pla-cebo	Active Comparator
1008-021	Completed	150 mg/day, 600 mg/day tid/5 weeks	None	139	69	68 (lorazepam)
1008-025	Completed	150 mg/day, 600 mg/day tid/5 weeks	None	142	70	70 (lorazepam)
1008-026	Completed	150 mg/day, 600 mg/day tid/5 weeks	None	136	67	68 (lorazepam)
1008-083	Completed	300 mg/day, 450 mg/day, 600 mg/day tid/5 weeks	1008-084	270	91	93 (alprazolam)
1008-085	Completed	200 mg/day, 400 mg/day, 450 mg/day tid/6 weeks	1008-084	255	86	None
1008-087	Completed	400 mg/day, 600 mg/day bid/7 weeks	1008-100	207	101	114 (venlafaxine)
1008-181	Terminated early	200-600 mg/day (flexible dose) bid/6 weeks	None	4	2	None
Randomized Withdrawal Design Study						
1008-088	Terminated early	450 mg/day tid/34 weeks: 8 weeks OL, 26 weeks double-blind, placebo-	1008-084	624 enrolled in open-label phase; 168 enrolled in double-blind	170	None

		controlled		phase		
Uncontrolled Studies						
1008-084	Ongoing	200-600 mg/day bid or tid/open-ended	n/a	Reexposure: 413 [2] New: 78 [3] De Novo: 12 [4]	n/a	n/a
1008-100	Ongoing	200-600 mg/day bid/open-ended	n/a	Reexposure: 108 [2] New: 95 [3] De Novo: 0	n/a	n/a

From Pfizer Table 5.2 (Clinstat, pp. 9-11 and 18), Figure 16, and Table 107 (Summary of Safety, pp. 196-197,).

4.2 Exposure

4.2.1 Exposure, Integrated Safety Database

Pfizer included the following table summarizing the exposure in their NDA safety database.

Pfizer Table 1. Overview of Source and Number of Participants (Participants Who Received Study Medication)

	Placebo	Pregabalin	Comparator
Clinical Phase 2/3 Integrated Safety Database			
30 Controlled Studies	***2384***	***5508***	***671***
Neuropathic Pain	*857*	*1831*	*87*
Diabetic Neuropathy	459	979	87
Postherpetic Neuralgia	398	852	--
Epilepsy (Adjuvant Therapy in Partial Seizures)	*294*	*758*	--
Generalized Anxiety Disorder	*484*	*1149*	*412*
Other[a]	*749*	*1770*	*172*
Other Chronic Pain	416	1068	--
Other Psychiatry	333	702	172
53 Controlled and Uncontrolled Studies	--	***8666***	--
Neuropathic Pain	--	*2524*	--
Diabetic Neuropathy	--	1413	--
Postherpetic Neuralgia	--	1111	--
Epilepsy (Adjuvant Therapy in Partial Seizures)[b]	--	*1613*	51
Generalized Anxiety Disorder[c]	170	*1962*	--
Other[a]	--	*2567*	--
Other Chronic Pain	--	1364	--
Other Neuropathic Pain[d]	9	28	7
Other Psychiatry[e]	73	1175	--
Clinical Pharmacology (Phase 1) Studies			

[2] These patients received pregabalin in a preceding trial
[3] These patients received placebo or an active comparator in a preceding trial and switched to pregabalin in the open-label extension.
[4] These patients entered the uncontrolled trial without having previously participated in a controlled trial.

Integrated Clinical Pharmacology Database	134	440	140
Study A0081022 (Platelet Function)[f]	22	20	--
Phase 2/3 Studies Not in Integrated Safety Database			
Acute Dental Pain	120	267	114
Studies Conducted in Japan	14	51	--

[a] Other includes chronic pain, other neuropathic pain, and other psychiatry studies that are not summarized separately but are included when all indications are combined (overall profile of pregabalin).

[b] Includes comparator-controlled, 8-day monotherapy trial (Study 007) and its adjunctive therapy open-label extension (Study 008).

[c] Includes Study 088, a long-term, placebo-controlled, relapse prevention/sustained efficacy study in GAD.

[d] Other NeP includes [illegible]

[e] Includes Study 082, a long-term, placebo-controlled, relapse prevention/sustained efficacy study in social anxiety disorder (SAD).

[f] This study completed May 2003, after the 14 February 2003 cutoff date for this application, and therefore was not integrated.

Exposure by Number of Subjects, Integrated Safety Database

In the NDA, 5508 subjects were exposed to pregabalin and 2384 to placebo during the controlled trials included in the Controlled Studies Database (Summary of Safety P.21). In their safety update, Pfizer added safety data for 273 pregabalin and 65 placebo subjects from controlled study 155 (a neuropathic pain study). This resulted in an updated expose total of 5781 pregabalin subjects and 2449 placebo subjects in the Controlled Studies database (Safety Update, p.13).

Pfizer reported that 8666 subjects were exposed to pregabalin in their NDA Combined Controlled and Uncontrolled Studies database (Summary of Safety, p.21). After the integration of data for an additional 1617 pregabalin subjects in the safety update, the total pregabalin exposure in the Combined Controlled and Uncontrolled Studies database was 9278 (Safety Update, p.16).

Exposure by Duration, Integrated Safety Database

Pfizer reported that through the safety update 4,379 subjects were exposed to pregabalin for over 24 weeks and that 2,701 subjects were exposed to pregabalin for over 52 weeks in the Combined Controlled and Uncontrolled Studies safety database (Table 4, p.17, Safety Update). The pregabalin exposure exceeds ICH exposure recommendations.

Exposure by Dose and Duration, Integrated Safety Database

Pfizer reported that after integrating the data from the safety update, 1,304 subjects were exposed to a pregabalin dose of at least 600mg/day for at least 24 weeks and that 751 subjects were exposed to a pregabalin dose of at least 600mg/day for at least 52 weeks (Safety Update, Appendix ALL.5).

Person Time Exposure, Integrated Safety Database

In the NDA controlled trials included in the Controlled Studies safety database, Pfizer reported 760 person years exposure to pregabalin and 336 person years exposure to placebo (Summary of Safety p. 21). Pfizer did not update the controlled trials person time exposure in the Safety Update.

Pfizer reported a total of 6394 person years exposure to pregabalin in the NDA Combined Controlled and Uncontrolled Studies safety database (Summary of Safety, Table 6, p.23). After integrating the data from the Safety Update, Pfizer reported a total of 7162 person years exposure to pregabalin in the Combined Controlled and Uncontrolled Studies safety database (Safety Update, Appendix ALL.5).

Exposure by Sex, Integrated Safety Database

In the Safety Update, Pfizer reported that for the Controlled Studies database, 53% (3078/5781) of subjects exposed to pregabalin were females compared to 52% (1273/2449) of placebo subjects (Safety Update, Table 6, p.17). For the Combined Controlled and Uncontrolled Studies database, approximately 53% (4889/9278) of the pregabalin exposed study subjects were female.

Exposure by Age, Integrated Safety Database

Through the Safety Update, the mean age of pregabalin subjects enrolled in the Controlled Studies database was 50.1 yrs (SD 17) compared to 50.9 years (SD17.1) for placebo. For the Combined Controlled and Uncontrolled Studies database, the mean age of pregabalin exposed subjects was 48.3 yrs (SD16.9). The following table summarizes through the Safety Update the exposure by subject age categories for the Controlled and Combined Controlled and Uncontrolled Studies databases.

FDA Table 3. Exposure by Age, Controlled and Combined Controlled and Uncontrolled Studies Databases through the Safety Update

Controlled Trials Database		
Age Group	Pregabalin (n=5781)	Placebo (n=2449)
17 to 64 years	76.8% (4439)	74.2% (1817)
65 to 74 years	14% (812)	16.1% (394)
=75 years	9% (520)	9.7% (237)
Combined Controlled and Uncontrolled Studies		
	Pregabalin (n=9278)	
17 to 64 years	79.9% (7411)	
65 to 74 years	12.3% (1145)	
=75 years	7.6% (702)	

From Safety Update, Tables 6 and 7, p.17

Exposure by Study Drug Formulation, Integrated Safety Database

A majority of subjects in the NDA were exposed to the immediate release formulation (IR) of pregabalin. Pfizer noted that 9469 subjects were exposed to the IR formulation (8666 from integrated phase II/III database, 51 from Japanese phase II/III studies, 267 from dental pain studies, 419 subjects in phase I clinical pharmacology studies, 46 in Japanese phase I clinical pharmacology studies, and 20 from a platelet function clinical pharmacology study). Twenty one subjects were exposed to pregabalin modified release formulation or solution (Summary of safety P.16). Pfizer did not update the exposure by formulation in the Safety Update.

4.2.2 Exposure, Epilepsy Studies

Pfizer identified 1613 subjects exposed to pregabalin in their NDA epilepsy studies (controlled and uncontrolled). Pfizer noted that 758 subjects were exposed to pregabalin and 294 subjects to placebo during the controlled trials included in the pooled epilepsy safety analysis. Another 45 subjects were exposed to pregabalin in the eight day monotherapy trial (n=42) and the terminated titration study (n=3). Pfizer reported that 810 subjects were exposed to pregabalin for the first time in uncontrolled trials, including 298 who received the comparator treatment in the prior RCT and 512 who were enrolled in an uncontrolled trial de novo (Summary of Safety, p.171). Pfizer did not identify any newly exposed subjects from epilepsy trials in the safety update.

Pfizer reported a total of 151 person years exposure to pregabalin and 64 person years exposure to placebo in the epilepsy studies included in the NDA Epilepsy Controlled Trials database (2/13/04 Submission). For the NDA Combined Controlled and Uncontrolled Epilepsy Trials database, Pfizer reported a total of 2460 person years exposure to pregabalin (Summary of Safety, Table 92, p.174).

Epilepsy subjects identified in the NDA database who continued in open label pregabalin epilepsy studies accrued an additional 177 person years (Safety Update total person time exposure 2637 PY) at the time of the safety update (Safety Update, p.57). Appendix 10 includes a detailed description of exposure by dose and duration in epilepsy trials through the safety update.

Exposure by Sex, Epilepsy Studies

For the epilepsy studies included in the controlled studies safety database, 52% (395/758) of subjects exposed to pregabalin and 47% of subjects exposed to placebo were female (Appendix Epilepsy.007, Summary of Safety). For the epilepsy Combined Controlled and Uncontrolled Studies database, 50.5% (815/1613) of the subjects exposed to pregabalin were female (Appendix Epilepsy.008, Summary of Safety).

Exposure by Age, Epilepsy Studies

In the epilepsy studies included in the NDA Controlled Studies Database, the mean age of the pregabalin exposed subjects was 37.9 yrs (SD 11.6) compared to 39.1 yrs (SD 12.2) for placebo exposed subjects (Appendix Epilepsy.007, Summary of Safety). In the

Combined Controlled and Uncontrolled Studies database, the mean age of pregabalin exposed subjects was 38.2 yrs (SD 11.7) (Appendix Epilepsy.008, Summary of Safety). The following table summarizes the exposure by subject age categories for the epilepsy Controlled and Combined Controlled and Uncontrolled Studies databases.

FDA Table 4. Summary of Exposure by Age, Epilepsy Controlled and Combined Controlled and Uncontrolled Studies Databases

Controlled Trials Database		
Age Group	Pregabalin (n=758)	Placebo (n=294)
12 to 16 years	1.3% (10)	0.3% (1)
17 to 64 years	97.1% (736)	96.9% (285)
65 to 74 years	1.3% (10)	2.4% (7)
=75 years	0.3% (2)	0.3% (1)
Combined Controlled and Uncontrolled Studies		
	Pregabalin (n=1613)	
12 to 16 years	1.2% (20)	
17 to 64 years	96.8% (1562)	
65 to 74 years	1.5% (25)	
=75 years	0.4% (6)	

From Appendix Epilepsy, Tables 007, 008

4.2.3 Exposure, GAD Studies

Pfizer reported that 1962 patients were exposed to pregabalin in the controlled and uncontrolled GAD trials included in the safety database. 1149 patients were exposed to pregabalin in the short-term controlled trials that were included in the pooled analyses of GAD controlled trial data. 484 patients were exposed to placebo and 412 patients to an active comparator during these trials. 624 patients were exposed to pregabalin in Study 088, in which an eight week open-label period was followed by up to six months of randomized, double-blind pregabalin or placebo treatment; 170 patients were exposed to placebo during this study. Four patients were exposed to pregabalin and two to placebo in Study 181, a controlled study that was terminated early. An additional 185 patients were newly exposed to pregabalin in uncontrolled Studies 084 and 100; 173 of these patients had participated in a preceding trial during which they had received placebo or an active comparator and 12 entered without previously having participated in a controlled study.

In the Safety Update, Pfizer reported that there were no additional patients newly exposed to pregabalin in GAD trials.

Pfizer reported a total of 108.78 person-years exposure to pregabalin and 45.25 person-years exposure to placebo in the GAD controlled trials database (2/18/04 submission). They reported a total of 626.45 person-years exposure to pregabalin in the NDA combined controlled and uncontrolled GAD studies (Table 111, Summary of Safety, p.197). Pfizer reported that an additional 8.39 person-years were accrued in the combined controlled and uncontrolled study database between the NDA and the Safety

Update cutoff dates. This person-time was accrued exclusively in uncontrolled studies, since there were no controlled studies ongoing at the time of the NDA cutoff date. They reported that total person-time of exposure to pregabalin accrued through the Safety Update in the controlled and uncontrolled GAD studies was 633.52 patient-years. Appendix 11 includes a detailed description of exposure by dose and duration in GAD trials through the safety update.

Exposure by Sex, GAD Studies

In the GAD controlled trials database, 58.7% (675/1149) of patients exposed to pregabalin and 57.4% (278/484) of patients exposed to placebo were female. 41.3% (474/1149) of patients exposed to pregabalin and 42.6% (206/484) of patients exposed to placebo were male (Appendix GAD.007, page 13201, Summary of Clinical Safety). In the GAD combined controlled and uncontrolled trials database, 58.5% (1147/1962) of patients exposed to pregabalin were female and 41.5% (815/1962) were male (Appendix GAD.008, Summary of Safety, p. 13212).

Exposure by Age, GAD Studies

Pfizer reported that mean age in the GAD controlled trials database was 39.7 years (SD 12.2) for placebo-treated patients and 38.9 years (SD 11.8) for pregabalin-treated patients (Appendix GAD.007, Summary of Safety, pp. 13200-13201). In the GAD combined controlled and uncontrolled trials database, mean age was 38.7 years [SD 12.0] (Appendix GAD.008, Summary of Safety p. 13212). The following table summarizes exposure by age categories in the GAD trials included in the integrated safety database:

FDA Table 5. Summary of Exposure by Age, Controlled GAD Trials Database and Combined Controlled and Uncontrolled GAD Trials Database

Controlled Trials Database		
Age group	Placebo (n=484); % (no.)	Pregabalin (n=1149); % (no.)
18-64	96.1% (465)	97.7% (1123)
65-74	3.7% (18)	2.1% (24)
=75	0.2% (1)	0.2% (2)
Combined Controlled and Uncontrolled Trials Database		
18-64	n/a	97.5% (1912)
65-74	n/a	2.3% (46)
=75	n/	0.2% (4)

From Pfizer Appendix GAD.007 (Summary of Safety, pp. 13200-13211,) and GAD.008 (Summary of Safety pp. 13212-13215,).

4.3 Review of AE Surveillance, Coding of AEs, and Approach to Evaluating Safety

Pfizer summarized the deaths, other SAEs, AEs leading to discontinuation and common AEs from the pregabalin development program. Adverse Events were defined as "any untoward medical occurrence in a patient enrolled in a clinical study". Treatment

emergent adverse events were defined as "any event not seen during screening or baseline and not recorded as continuing on Medical History, or, any event that has worsened relative to screening, baseline, or Medical History" (Appendix ALL.11, p.1146). Adverse events were identified by investigators using non-specific questions (Appendix ALL.11, p.1141). Investigator verbatim terms for AEs were mapped to preferred terms using the COSTART IV Dictionary (Appendix ALL.11, p.1147).

SAEs were initially defined as "any event that required or prolonged hospitalization; was severely or permanently disabling, immediately life-threatening, or fatal; cancer; congenital anomaly; overdose; or any medically significant event." Pfizer commented that the SAE definition was later changed to be in accordance with ICH E2A and that SAE definition was "any event that required or prolonged hospitalization, resulted in a persistent or significant disability or incapacity; was life-threatening or resulted in death; was a congenital anomaly or birth defect; or was a medically significant event." Pfizer noted that hospitalizations not considered SAEs included admissions for diagnostic or elective surgical procedures for a pre-existing condition; admissions for therapy of the target disease of the study or for efficacy measurements defined by the protocol(Appendix ALL.11, p.1146).

Pfizer identified SAEs from two databases, their Oracle clinical trials safety database and their Adverse Reaction Information System, global (ARISg) database. The Oracle clinical database provides summaries and listings of SAEs that occurred in the completed, double blind studies and their open-label extensions. The ARISg database provides summaries and listings for SAEs that occurred in the ongoing, double blind studies and their open-label extensions. In addition, ARISg contains data from open-label extensions of completed double blind studies that did not get entered into Oracle as of the data cutoff for the NDA or Safety Update (Safety update, p.24).

In their NDA presentation of SAEs and AEs leading to withdrawal Pfizer noted that they included all recorded AEs (treatment emergent and non-treatment emergent). In their Safety Update presentation of SAEs and AEs leading to withdrawal, Pfizer summarized the treatment emergent AEs. Pfizer's Common AE presentations included treatment emergent AEs in both the NDA and Safety Update (Appendix ALL.11, p.1147).

Pfizer provided analyses of laboratory data collected during the pregabalin development program. Laboratory samples collected during pregabalin studies were analyzed by one of four central laboratories. Lab data presentations included mean changes from baseline to end of study, and Pfizer explained that end of study results could have been measured up to 14 days after discontinuation of pregabalin. Pfizer provided laboratory result outlier analyses. In one outlier analysis, Pfizer identified the percentage of subjects that changed to pre-specified low or high results at endpoint. In a separate outlier analysis, Pfizer identified the percentage of subjects with pre-specified clinically important changes from baseline to any time in the study. In yet another outlier analysis, Pfizer identified subjects with pre-specified very low, low, high, or very high lab results at any time during treatment. These outlier analyses did not exclude subjects with abnormal results at baseline (Appendix ALL.11, pp.1157-1160).

Pfizer provided analyses of vital sign data collected during pregabalin studies. Weight and heart rate data were collected in all studies. Epilepsy and GAD studies measured seated BP, while pain studies measured first supine, then standing blood pressure to check for orthostatic changes. Respiratory rate was collected in epilepsy and some GAD studies (Appendix ALL.11, p.1156).

The results of ECG data from the pregabalin phase II/III trials were presented in two separate memos referenced in the pregabalin NDA. The methods used to collect and analyze those data are reviewed in the EGG results section of this review.

4.4 Audit Findings, Evaluation of AE Coding, and Quality of the Submission

We reviewed the investigator actual/verbatim terms listed in the CRFs of selected pregabalin subjects with serious AEs or who discontinued for AEs and the terms were accurately summarized in the narrative summaries, and the electronic data sets. We repeated these comparisons for lab and vital sign data across the available data sources and found agreement among the sources.

Using the listing of adverse preferred terms and the verbatim terms that they subsumed (Appendix ALL.10), we reviewed the results of the coding process. The coding of investigator verbatim adverse event terms to preferred terms was generally acceptable. Although we found infrequent inconsistencies that resulted from the coding process, none would markedly impact the safety assessment of the pregabalin NDA.

There were occasional occurrences of splitting similar verbatim terms to different preferred terms. For example, the verbatim terms "Chest pain (?angina)" and "Chest pain (cardiac)" were coded to the to the preferred term chest pain under the Body as a Whole system rather than to the preferred term angina, under the Cardiovascular system. The verbatim terms "Long QT on ekg" and "prolong qt wave" were coded to the preferred term Electrocardiogram abnormal even though there was a preferred term QT interval prolonged. Upper respiratory tract infections were coded to both infection and pharyngitis preferred terms without an apparent reason for the different coding. Pfizer coded the verbatim terms slight edema, water retention, worsening edema to the preferred term generalized edema but coded the verbatim terms swelling diffusely, swelling, oedema worsening, fluid retention worsening, edema/water retention to the preferred term edema.

In several cases lumping of dissimilar verbatim terms to a single preferred term occurred, resulting in a preferred term that was essentially uninformative. For example, the preferred term cyst was not useful since it subsumed a variety of potentially unrelated events including epidermoid cysts, ovarian cysts, Baker cysts, ganglion cysts, and Bartholin cysts. The preferred term infection included a wide variety of unrelated processes including H pylori, cold, infected toe, gum infection, fungal toenail infection, bacterial skin infection (despite having a preferred term cellulitis), airway infection, and staph infection. The preferred term pain subsumed verbatim terms such as dental pain, extremity pain, testicular pain, pelvic pain, post surgical pain, pressure, and burning. The

preferred term gastrointestinal disorder subsumed acute appendicitis, biliary dyskinesia, diverticula, and GERD. The preferred term eye disorder subsumed verbatim terms of heavy eyes, eye infection, itchy eyes, nervous eye movement, blisters in both eyes, eye lashes falling out, stye, chalazion and drooping eyelids (despite ptosis being a preferred term).

In rare cases the use of a particular preferred term did not appear justified. For example, the preferred term personality disorder included the verbatim event terms clenching of teeth, biting lip during meals, repeating self, and sighing, which do not appear to represent personality disorders.

We encountered quality and content deficiencies with the NDA and Safety Update that were impediments to the safety review. There were technical problems with the NDA including electronic links to CRFs that were incorrect and therefore required requests to Pfizer in order to locate necessary documents. The bookmark links in the Safety Update were also incorrect, complicating the navigation of that document. We occasionally encountered instances where Pfizer did not identify study subjects by their NDA identification system but by another patient ID numbering system, complicating the location of information necessary for review. Pfizer's data set submissions were generally too large resulting in data sets that required too much time to open and therefore were too cumbersome to be useful. Pfizer used different approaches to present the data in the NDA and Safety Update in some cases complicating the comparison of data from the two sources. For example, the SAE and discontinuation due to AEs risks in the NDA were based on all known AEs while the Safety Update calculated risks using only treatment emergent events. The result, while internally consistent for a given submission, left the reviewer unable to compare the same types of risks across submissions. In their presentation of common AEs for GAD trials in the Safety Update, Pfizer presented incorrect data requiring a request for a corrected presentation. In some cases the durations of exposure to drug provided in narratives were incorrect due to incorrect calculations performed by Pfizer. In one case, the appendix tables referenced by Pfizer as supporting a conclusion about blood pressure changes among subjects who gained weight were incorrect and required request to the sponsor for the correct tables.

4.5 Safety in the Phase I Trials

4.5.1 Phase I Trials Exposure

Pfizer summarized the safety data for subjects that participated in 28 Phase I trials. These trials included 19 immediate release formulation studies, a drug interaction study, a modified release bioavailability study, 4 studies using pregabalin solution and modified release formulations, and 3 special safety studies. These studies included 472 subjects, 440 of whom were exposed to pregabalin (Summary of Safety, p. 226). Pfizer did not include information from two Japanese Phase I studies in their summary but they reported that there were no deaths, serious adverse events, or discontinuations due to adverse events in either of these two studies.

The pregabalin Phase I studies included mostly healthy volunteers (n=385), but also included a smaller number of individuals with epilepsy (n=55), renal dysfunction (n=20), and dialysis patients (n=12).

4.5.2 Phase I Trials, Deaths

Pfizer reported that there were no deaths during clinical pharmacology trials (Summary of Safety, p. 230).

4.5.3 Phase I Trials, Serious Adverse Events

Pfizer reported that 10 clinical pharmacology study subjects experienced 12 SAEs. The most common SAE was seizures (7 subjects), with all of these events occurring in subjects with histories of seizures. The remaining Phase I study SAEs were myocardial infarction (n=1), post-ictal confusion (n=1), and cholecystitis (n=1). Pfizer noted that for the subject with the cholecystitis SAE, the symptoms were first noted during the gabapentin washout phase of a drug interaction study and the subject was withdrawn prior to receiving pregabalin (Summary of Safety p.231).

4.5.4 Phase I Trials, Discontinuations for Adverse Events

Pfizer reported that 16 pregabalin subjects discontinued from phase I studies for AEs. Seven subjects discontinued for AEs included among the SAEs listed above, and nine subjects discontinued for AEs that were not SAEs. For the nine non-SAEs leading to discontinuation, one, an elevated amylase test result was considered not treatment emergent. A subject had baseline amylase results of 81 and 97 U/L (ULN 81U/L), followed by an elevated amylase of 124 U/L approximately ten days after a single pregabalin dose. This subject also had a slightly elevated lipase of 36 U/L (ULN 24U/L). The study report noted that the investigator felt these results were related to an unspecified underlying medical condition (Study report for Study 003, p.20). For the remaining eight non-SAEs leading to discontinuation, two were for stupor (verbatim term: intoxicated sensation), and one for each of the following: rash, rash and pruritis, twitching, hypotension, vertigo, and flu syndrome (Summary of Safety, p.231). The study report for Study 36 stated that the subject withdrawn for hypotension was withdrawn for a low baseline blood pressure (86/52 mmHg) prior to dosing (Study 36 study report, p.21).

4.5.5 Phase I Trials, Adverse Events

Pfizer reported that 86% (378/440) of pregabalin subjects in Phase I trials experienced one or more adverse events.

In the single dose studies, the AE risk for the placebo group was 30% (17/57) and for the pregabalin subjects the AE risk ranged from 29% (5/17) for the 450mg group (highest single dose) to 100% (14/14) for the 150mg dose group (Appendix CP.5).

In the multiple dose studies, the AE risk for the placebo group was 63% (56/89) and for the pregabalin subjects the AE risk ranged from 13% (4/30) for the 50mg group q8h regimen to 95% (20/21) for the 300mg q8h regimen (highest dosing regimen) (Appendix CP.5).

For the pooled single and multi dose data, I identified the AEs occurring in at least 2% of pregabalin subjects and at least twice as frequently compared to placebo. Those AEs are listed in the following table.

FDA Table 6. AEs Occurring in at Least 2% of Pregabalin Subjects and at Least Twice as Frequently Compared to Placebo, Pooled Single and Multiple Dose Clinical Pharmacology Trial Data

AE	Placebo (n=134)	Pregabalin (n=440)	AE	Placebo (n=134)	Pregabalin (n=440)
Dizziness	5.2% (n=7)	44.8% (n=197)	Confusion	0	3.4% (n=15)
Somnolence	11.2% (n=15)	37.5% (n=165)	Nervousness	1.5% (n=2)	3.0% (n=13)
Stupor	0	13.2% (n=58)	Nystagmus	0	3.0% (n=13)
Thinking abnormal	3.0% (n=4)	13.2% (n=58)	Vomiting	0.7% (n=1)	3.0% (n=13)
Nausea	3.7% (n=5)	11.6% (n=51)	Paresthesia	0.7% (n=1)	2.5% (n=11)
Euphoria	0	9.8% (n=43)	Abnormal vision	0	2.3% (n=10)
Amblyopia	0	8.6% (n=38)	Ataxia	0	2.3% (n=10)
Abnormal gait	0	8.2% (n=36)	Amnesia	0	2.0% (n=9)
Dry Mouth	0	6.6% (n=29)	Diplopia	0	2.0% (n=9)
Incoordination	0.7% (n=1)	5.2% (n=23)	Rash	0.7% (n=1)	2.0% (n=9)
Insomnia	0	3.9% (n=17)			

From Appendix CP.7

Data from both single and multi dose studies support that for many of the AEs listed above, the risk among pregabalin subjects increased with increasing doses of pregabalin.

The list of AEs from clinical pharmacology trials did not include events suggestive of rhabdomyolysis, acute hepatic failure, acute renal failure, aplastic anemia, or serious skin reactions. The list included an AE of tongue edema (verbatim term: tongue feels thick) that was not serious, not associated with respiratory compromise and that resolved without intervention. The list included seven subjects (1.6%, 7/440) with liver function abnormal AEs.

Pfizer described Phase I LFT abnormality AEs in more detail. In study 001, one subject had mild AST and ALT elevations three days after a single placebo dose. In study 002,

seven subjects experienced increases in hepatic enzymes that were reported as AEs. Pfizer stated that the increases were =3 times the ULN and were not associated with increases in bilirubin. In study 023, three pregabalin subjects (25%, 3/12) and two placebo subjects (66%, 2/3) experienced increases in hepatic enzymes that were not reported as AEs. None of these hepatic enzymes elevations were associated with increases in bilirubin. Pfizer reported that the increases in hepatic enzymes resolved within one to two weeks for all subjects but one. The exception was a subject with positive serology for hepatitis C and CMV.

I reviewed the study report for study 002 to better characterize the hepatic elevation AEs noted above. Study 002 included seven groups of subjects exposed to pregabalin or placebo. Group One received the lowest pregabalin dose (25mg, single dose days 1 and 22, multiple dose q8h days 8-21) and group seven received the highest pregabalin dose (300mg, single dose days 1 and 22, multiple dose q8h days 8-21).

I reviewed the lab results included in Appendix D.21 of the Study report for study 002. I identified ten subjects (nine pregabalin, one placebo) with an elevated AST, ALT, or both. None of the subjects with transaminase elevations had associated total bilirubin results =2mg/dL. For three subjects (one placebo, two pregabalin) the abnormal result was a single ALT abnormality that exceeded the ULN, but did not reach 2xULN. Five subjects had more than one elevated transaminase result but no results that reached 2x ULN. The remaining two subjects had one or more transaminase elevations that were at least 3xULN. Below, I summarize selected lab data for these three subjects.

Test	ULN	Subject 02, 42 year old female, Dose 25mg q8h										
		Study Day										
		-12	1	8	10	12	15	18	22	23	24	29
AST	40	14	13	18	13	11	21	31	88	76	41	43
ALT	45	12	12	19	15	10	21	40	148	149	67	72
T bili	1.2	0.9	0.7	0.7	0.7	0.5	0.6	0.5	0.6			0.5
ALP	140	52	51	53	50	51	50	62	64			60
GGT	45	22	19	21	21	16	22	32	50	49	20	39
		Subject 04, 35 year old female, Dose 25mg q8h										
		Study Day										
		-12	1	8	10	12	15	18	22	23	24	29
AST	40	22	23	24	24	25	38	33	48	43	66	49
ALT	45	19	29	28	28	30	49	45	71	70	140	77
T bili	1.2	0.6	0.7	0.9	0.6	0.5	0.7	0.5	0.8			0.8
ALP	140	62	57	61	55	64	57	64	62			63
GGT	45	20	17	16	18	17	19	19	22			23

Pfizer commented that one of the above two subjects was subsequently found to have positive serology for Hepatitis C and CMV (Study 002 Study report, p.39).

I reviewed the results from Study 023, where 3 of the 12 subjects exposed to pregabalin 300mg q8h had mild transient elevations of hepatic enzymes compared to 2 of 3 placebo subjects. Two of these pregabalin subjects had increases of ALT that were above the ULN, but none of these results reached 2x ULN. The third pregabalin subject had

increases in ALT, AST, and GGT that exceeded ULN but did not reach 3xULN. One placebo subject experienced an increase in ALT that exceeded ULN but did not reach 2x ULN. The second placebo subject experienced increases in AST and ALT that exceeded ULN but that did not reach 2x ULN (Study report 023, Table 8, p.31). None of these subjects had a total bilirubin result that was above the ULN (total bilirubin ULN 1.2mg/dL).

Pfizer reported that no elevations of hepatic enzymes >3x ULN occurred in any other clinical pharmacology trials (Summary of Safety, p. 230).

4.5.6 Phase I Trials, Laboratory Results

Pfizer commented that lab abnormalities from clinical pharmacology trials were sporadic, transient, and considered unrelated to study medication (Summary of Safety, p.232). They provided a summary listing of possibly clinically important lab results. For these tables, they calculated the outlier risk in two ways. They provided the outlier risk in terms of the number of subjects (the number of subjects with abnormal test results divided by the number of tested subjects) and in terms of the number of tests (the number of abnormal test results divided by the total number of tests performed). This second analysis was done to take into consideration the differences in the numbers of tests performed which was related to differences in study designs and durations of exposures. Pregabalin subjects had a higher risk of abnormal platelet results (1%, 16 abnormal results/1649 tests) compared to placebo (0/310) but interestingly, all of the abnormal platelet results were above the ULN. Table CP.18 had creatinine results listed twice with different results and creatine kinase was not listed. I reviewed the listing of individual lab abnormalities and determined that the second creatinine result listing was actually the creatine kinase abnormalities. For pregabalin, the risk for abnormal CK result was 0.6% (6 abnormal results /948 tests, all above ULN) compared to 0 (0/258) for placebo. Three of the abnormal CK results (2 subjects) occurred at baseline. The highest post baseline CK for this group was 850 U/L (Appendix CP.19).

4.5.7 Phase I Trials, Vital Signs

Using the same outlier criteria used in analyzing the Phase II/III trial data, Pfizer analyzed the vital sign data from the single and multi-dose clinical pharmacology studies. Few vital sign measurements met the outlier criteria and there did not appear to be notable differences between pregabalin and placebo or among the different pregabalin dose regimens (Appendix CP.20).

4.5.8 Phase I Trials, ECGs

There were no clinical pharmacology studies specifically designed to evaluate the effect of pregabalin on cardiac repolarization. ECGs were performed as part of the safety monitoring in selected studies. Pfizer reported that ECGs were performed on 164 clinical pharmacology subjects (Summary of Safety, p.233). This total included fifteen placebo subjects, seventy-seven pregabalin only subjects, fourteen pregabalin plus carbamazepine

subjects, twelve pregabalin plus lamotrigine subjects, sixteen pregabalin plus valproate subjects, ten pregabalin plus phenytoin subjects, and twenty pregabalin plus gabapentin subjects (Appendix CP.24).

Pfizer provided the mean QTc changes from baseline using Bazzett's, Fridericia's and a linear model correction for the clinical pharmacology studies. For subjects who received only pregabalin, the QTc mean changes from baseline were generally negative and similar to placebo. Pregabalin only subjects experienced mean increases in PR interval that ranged from 1.6 to 8.1 msec. Placebo treated subjects also experienced increases in PR in these studies (3.9msec, n=12; 9.3msec, n=3).

Pfizer reported that none of the study subjects had a corrected QT interval that exceeded the ULN (for males >450msec, females >470msec).

Pfizer provided estimates of the slopes resulting from the regression of QTc change from baseline and PR change from baseline against pregabalin Cmax. The effect of a 1 μg/mL increase in pregabalin Cmax on the change from baseline QTc was -0.453msec (linear based correction). For the PR interval, the effect of a 1μg/mL increase in pregabalin Cmax on the change from baseline PR was 0.349msec. Pfizer noted that the largest observed Cmax in this group was 18μg/mL, leading to a predicted 6 msec increase in PR based on their regression analysis (Summary of Safety, p.234).

4.5.9 Phase I Trials, Other Safety Results

Pfizer noted that selected clinical pharmacology studies captured safety data not summarized above. Pfizer commented on visual data captured in clinical pharmacology studies and I will defer to our ophthalmologic consultant for interpretation of the results. Pfizer reported that study 002 included platelet evaluation (number, volume, morphology, and in vitro aggregation), cardiac telemetry, and echocardiogram monitoring. In this two week study, one subject experienced two brief (less than six beat), asymptomatic runs of ventricular tachycardia within a 30 second interval. This occurred five hours after the 43rd and last pregabalin dose. Pfizer reported that no clinically important changes occurred in platelets, or echocardiograms. I reviewed the study report for this study to further evaluate these claims.

Pfizer reported that no clinically significant changes in platelet count, volume, in vitro aggregability and morphology were observed in study 002 (Study report 002, p.39). I reviewed the results of the platelet aggregation studies that were performed in study 002. Pfizer provided the results but the listing did not include the normal limits for the lab that performed the tests. In general there did not appear to be systematic changes in aggregation from baseline to the on-treatment results (Study report 002, Appendix D.19). The platelet morphology evaluation did not identify any consistent abnormalities and the majority of smears were reported as normal (Study report 002, Appendix D.20).

I reviewed the echocardiogram result listings and compared the screening ejection fractions to the on-treatment ejection fractions and these results were similar for the individual subjects (Study report 002, Appendix D.14).

4.6 Safety in Phase II/III Studies

4.6.1 Deaths

Deaths in the Overall Integrated Database

As of the cutoff date for the NDA integrated safety database (2/14/03), there were 55 deaths in subjects treated with pregabalin. The mortality risk was 0.63% (55/8666) and the mortality rate was 8.6/1000PY (55/6393PY). Pfizer noted that not all of these deaths occurred within 30 days of last pregabalin exposure (Summary of Clinical Safety p.38). Considering only those deaths occurring within 30 days of last pregabalin exposure, the mortality risk was 0.5% (43/8666) and the mortality rate was 6.7/1000PY (43/6393PY).

From completed controlled trials, six pregabalin subjects (0.1%, 6/5508) and one placebo subject (0.04%, 1/2384) died. Considering only the deaths that occurred within 30 days of last study treatment dose, the mortality risk for pregabalin was 0.04% (2/5508) and for placebo was 0.04% (1/2384). Considering all identified deaths from controlled trials, the mortality rate for pregabalin subjects in controlled trials was 7.9/1,000PY (6/790 PY) compared to 3/1,000PY (1/336PY) for placebo subjects. For deaths within 30 days of last study treatment dose the mortality rate for pregabalin subjects in controlled trials was 2.5/1,000PY (2/790 PY) compared to 3/1,000PY (1/336PY) for placebo subjects.

Forty-nine deaths occurred during uncontrolled trials. The mortality rate for uncontrolled trials was 8.7/1,000PY (49/5633PY). Pfizer applied the age specific death rates from the US population (2001) to the open label study population to calculate a standardized mortality ratio (SMR). The SMR was 0.85 (95% CI 0.74, 1.32) which Pfizer interpreted as supporting the conclusion that the number of deaths observed in the open label study population was similar to that expected given the patients age, gender and follow up time (NDA Section 2.5.5.2.2, p.94).

Deaths by Indication
Pfizer provided the following table that summarizes the deaths by indication for the integrated safety database.

Pfizer Table 15. Summary of Deaths by Indication: Combined Controlled and Uncontrolled Studies All Indications

	DPN	PHN	Epilepsy	GAD	All Studies[a]
Data in the Integrated Clinical Safety Database (All Chronic Controlled and Uncontrolled Studies)					
Median Age (Years)	60	73	38	38	47
% of Patients ≥65	32.3%	79.1%	1.9%	2.5%	19.3%
N Treated With PGB	1413	1111	1613	1962	8666
Number (%) of Deaths	17 (1.2%)	19 (1.7%)	14 (0.9%)	1(0.05%)	55(0.6%)
Patient-Years of Exposure	1421	649	2461	626	6394
Deaths/1000 Patient-Years	11.9	29.3	5.6	1.6	8.6

[a] Includes patients from non-neuropathic pain studies and other psychiatric disorders.

This table demonstrates that the mortality risk was not uniform across indications, with the highest mortality risk observed in the post-herpetic neuralgia and diabetic neuropathy study groups. This table also demonstrates the differences in ages of the different study populations. The pain indication study groups were comprised of older individuals compared to the epilepsy and anxiety study populations.

Deaths from Ongoing Studies/not Included in the Integrated Safety Database

Pfizer identified nine additional pregabalin deaths that were not included in the integrated safety database at the time of the NDA submission (from ongoing blinded studies or reported to the sponsor's serious adverse event database but not entered into the clinical trial safety database, Summary of Clinical Safety p.39). The reported causes of death for these nine patients are summarized below.

155 074020 52 year old male, cause of death: cardiac arrest, decompensation of diabetes mellitus, third degree heart block, metabolic acidosis, hypovolemic shock.
155 106008 81 year old male, cause of death: worsening of COPD.
155 033004 67 year old female, cause of death: myocardial infarction.
155 038003 74 year old male, cause of death: apoplexia cerebri.
155 132002 67 year old male, cause of death: myocardial infarction.
009-003004 Impaired gait, personality disorder, thinking abnormal, cerebral hemorrhage, brain herniation (120 days post-treatment)
009-045013 accidental injury, confusion, abnormal gait, hostility, depression, convulsion, cardiac arrest
196-008002 Aortic aneurysm, myocardial infarction
029-015001 pancytopenia (bone marrow biopsy diagnosis-myelodysplastic syndrome), thinking abnormal, cholecystitis, diarrhea, malaise, leukemoid reaction. Pancytopenia SAE occurred prior to database lock, death occurred after lock date.
(Appendices ALL.51, ALL.289)

Deaths in the Safety Update

Pfizer's safety update included information about thirteen new deaths not previously identified. Five of the new deaths are from studies that have been completed since the NDA submission and prior to the Safety Update lock date. I provide additional information about those five deaths below. There is an apparent inconsistency since one of the deaths identified as new (012-084102) was included among the deaths presented in the NDA. In a July 6, 2004 submission responding to the division request for more information about this death, Pfizer responded that "this patient was inadvertently carried forward to the list of "new deaths" in Table 10 of the SU. This inconsistency will be corrected in future safety update reports."

012-084102 This subject was identified as dying in a study completed since the safety update but was also included in a listing of deaths in the integrated safety database at the time of the NDA lock data. Narrative included below in epilepsy death section.
034-027017 This 45 year old female with a history of refractory epilepsy, asthma, chronic bronchitis, seasonal allergies, and panic attacks, was found dead at home on study day 1355. This subject did not have an autopsy and the cause of death listed on the death certificate was aspiration due to intractable seizures. She was hospitalized three times during the study for status asthmaticus, with the last hospitalization on study day 870. Concomitant medications at the time of death included hydrochlorothiazide/triamterene, naproxen, levosalbutamol, ipratropium bromide, fluticasone, omeprazole, carisoprodol, estradiol, ranitidine, tocopherol, budesonide, formoterol, hydroxyzine, prednisone, guaifenesin, alendronate, calcium,

vitamin D, paroxetine, ipratropium bromide/salbutamol, diphenhydramine, theophylline, cephalexin, fexophenadine, lamotrigine, and phenytoin.
149-484003 This 71 year old male with diabetic neuropathy, diabetes mellitus, coronary artery disease, hypertension, and nephrolithiasis experienced an anterior wall MI that led to discontinuation of pregabalin on study day 317. The next day the subject developed cardiogenic shock and died. Concomitant medications at the time of the event included isosorbide dinitrate, molsidomine, diltiazem, magnesium, and insulin.
155-136003 This 88 year old male with post herpetic neuralgia, arthritis, parkinsonian symptoms, orthostatic hypotension, and first degree heart block was hospitalized on study day 500 for a chest infection. He received no study medication after study day 500. Eight days later he died and death was attributed to a cerebrovascular accident. Concomitant medications at the time of the event included calcium, retinol, loratidine, furosemide, ramipril, and risedronate.
196-705001 This 79 year old male with post herpetic neuralgia was admitted to a hospital with fever and was initially treated with antibiotics for a presumed unspecified infection. The subject developed unspecified lab abnormalities that were evaluated with an abdominal CT. The CT found a pancreatic mass, a nodular hepatic lesion that was presumed metastatic, and nodules in the lung bases. A liver biopsy found a "little differentiated" adenocarcinoma compatible with a pancreatic origin. The subject developed cholestasis, hepatic cytolysis, and died 3 days after the liver biopsy (seventeen days after stopping pregabalin) and his death was attributed to cardiac arrest.

Pfizer is aware of eight additional deaths from either completed or ongoing studies that have not yet been entered into the clinical trials database at the time of the Safety Update. Seven of these deaths were in pregabalin treated subjects and one in a subject who received blinded treatment (blind not yet broken). The causes of death for the pregabalin treated subjects include aspiration, cardiomyopathy/sepsis, head injury, unknown, seizures/drowning, coronary artery atherosclerosis and astrocytoma. For the subject who received blinded treatment, the death was a suicide (Safety update, p.23).

Deaths in Epilepsy Trials

Pfizer reported that no deaths occurred during epilepsy controlled trials. Fourteen pregabalin subjects died during epilepsy uncontrolled trials (0.9%, 14/1613). The mortality rate for these trials was 5.6/1000PY (14/2461PY).

Four of the epilepsy uncontrolled trial deaths were not witnessed and the subjects were found dead. These deaths were coded to the preferred terms heart arrest, sudden death, apnea, and cardiomyopathy. Three deaths were associated with seizure activity, with two of these events involving aspiration (preferred terms respiratory disorder, lung disorder). Two deaths were cerebrovascular accidents (intracranial hemorrhage, cerebral hemorrhage), and the remaining deaths were attributed to cardiovascular disorder (possible MI), carcinoma, pulmonary embolism, accidental injury, and septicemia. Using the patient narratives, CRFs, datasets, and patient profiles, I constructed summaries of the clinical details for the epilepsy study deaths. Those summaries are provided below.

007-000601 This 68 year old female with partial seizures was taking pregabalin 200mg/d and had a total of 1098 days of pregabalin when she experienced a seizure, fell down, aspirated, and died. The coded cause of death was respiratory disorder. She was found dead in her home and the death certificate listed aspiration and seizure disorder as causes of death. An autopsy was not performed. Concomitant medications included phenytoin, rofecoxib, and ibuprofen.
007-001704 This 24 year old male who was taking pregabalin 600mg/d and had a total of 511 days of pregabalin at the time of the event died and death was attributed to airway obstruction. The coded cause of

death was lung disorder. The narrative noted that the subject experienced a seizure followed by vomiting and difficulty breathing. This was followed by another episode of vomiting and a second seizure and he was noted to be cyanotic. CPR was begun and he was transported to an ED. He was unresponsive and asystolic. It was one day from last dose until death.

009-004001 This 84 year old male with a history of coronary artery disease, atrial fibrillation, hypertension, diabetes, congestive heart failure and stomach cancer who was taking pregabalin 600mg/d and had a total of 713 days of pregabalin exposure when he experienced cerebral artery occlusion, pneumonia, and brainstem hemorrhage. The coded cause of death was intracranial hemorrhage. The subject was admitted to a hospital for pneumonia with hemoptysis, cerebral artery occlusion, and corticoadrenal insufficiency. While hospitalized he experienced a brainstem hemorrhage and exam noted he was unresponsive with fixed, dilated pupils. Concomitant medications included levetiracetam, fludricortisone acetate, furosemide, hydrocortisone, omeprazole, and acetylsalicylic acid. It was 3 days from last dose until death.

009-042003 This 56 year old female with a history of rheumatic fever, myokymia (involuntary rippling of the muscles at rest), hypertension, atrial fibrillation, and seizure disorder was taking pregabalin and had a total of 545d exposure. She experienced staph endocarditis, sepsis, respiratory failure, and cerebral hemorrhage. The coded cause of death was cerebral hemorrhage. It was nine days from last dose until death. She had a history of rheumatic fever and underwent mitral and aortic valve replacement surgery on study day 407. She subsequently presented with fever, chills and nausea and had positive blood cultures. She was treated with vancomycin and gentamicin. Vancomycin was switched to cefazolin due to lack of improvement and a declining mental status. On open label study day 459 she experienced cerebral hemorrhage and died.

010-045102 This 42 year old male with a history of partial seizures, hypertension, hypercholesterolemia, cervical spondylosis, back pain, and migraine was taking pregabalin 600mg/d and had been taking pregabalin for 974 days. He died and death was attributed to a heart attack. The coded cause of death was cardiovascular disorder. The subject was taking pregabalin at the time of death. The narrative noted that the subject had a brother who died of a heart attack (age "30's"). Concomitant medications included carbamazepine, oxcarbazepine, tiagabine, levetiracetam, lisinopril, simvastatin, cyclobenzaprine, diazepam, amitriptyline, ranitidine, butalbital with aspirin and caffeine. The narrative noted that this subject experienced elevated liver enzymes (ALT, AST in 300's) that were attributed to simvastatin and that resulted in discontinuation of simvastatin.

011-066001 This 47 year old male with a history of complex partial seizures, with secondary generalization, intelligence deficit, cerebral malformations, basal cell carcinoma, cutaneous abscesses, guanine/thymine elevation, anemia, fibromas, Sprengel's deformity corrected (congenital elevation of the scapula), macroglossia, and hypoalbuminemia was taking pregabalin 300mg/d and had been taking pregabalin for 607 days. He experienced somnolence, cough, fever, bronchitis, and cardiovascular arrest. The coded cause of death was heart arrest. He was taking pregabalin on the day of death. The narrative noted that on study day 582 the subject experienced fever, increased cough, wheezing and rhonchi that were treated with amoxicillin/clavulanate and acetylcysteine. On open label study day 583 he was found dead in bed by his caregiver. No autopsy report was provided. Concomitant medications included valproic acid, carbamazepine, clobazam, hyoscine, phenolphthalein, and paraffin.

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 days. 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 the lung had metastases bilaterally. He withdrew from the open label study on day 170 and died 21 days later.

012-084102 This 68 year old male with a history of partial seizures, closed head injury and hypertension was taking pregabalin 600mg/d and had been taking pregabalin for 828 days. He died and the coded cause of death was fall. It was 45 days from last dose until death. He was assessed at a hospital following a fall on study day 828. There was no information about the events preceding the fall and no description of the distance or circumstances of the fall itself. He was sent home but returned to the hospital two days later and was diagnosed with a perinephric hematoma and a pericardial effusion. He underwent a pericardiocentesis.

His condition deteriorated and two days later he developed bilateral pleural effusions that were treated by thoracentesis. On study day 833 he was treated with external ventilation (BIPAP). He developed a large pleural effusion and abdominal distension. The effusion was drained. He developed renal failure. Study medication was stopped. He died on study day 875 and the investigator felt the death was due to renal failure. An autopsy documented chronic liver disease, ileus, bilateral adrenal hemorrhage, bilateral pleural effusion, possible ARDS, fibrous pericarditis with cardiomegaly, left renal infarct with massive perinephric hematoma.

012-084108 This 74 year old male with epilepsy, hyperlipidemia, angina, hypertension and s/p CABG was taking pregabalin 300mg/d and had been taking pregabalin for 34 days. On study day 7 he was hospitalized for weakness, inability to stand, disorientation, hallucinations, and reduced alertness. His pregabalin dose was reduced from 450mg/d to 300mg/d. On study day 10 he was diagnosed with a urinary tract infection and possible pulmonary edema. He was treated with ampicillin and gentamicin. He developed septicemia and died on study day 34. The cause of death listed on the death certificate was pulmonary embolism.

012-084122 This 77 year old female with a history of epilepsy, hypertension, arrhythmia, pulmonary emboli, angina, diabetes mellitus, cerebral hemorrhage, and digitalis toxicity was taking pregabalin 375mg/d and had been taking pregabalin for 495 days. She died and the coded cause of death was sepsis. She was taking pregabalin on the day of death. During the study she was hospitalized for digitalis toxicity (screening phase) myocardial infarction (study day 8), DVT (study day 42), fall (study day 111) and loss of consciousness (study day 418). On study day 495 she experienced life threatening sepsis of unknown origin. The narrative noted that she lost consciousness that evening. Hospital labs included a WBC count of 19.6 neutrophils of 17.54 and AST=65U/L. Two days later, WBC count was 24.4 neutrophils 20.15 and AST 3100U/L. The listed cause of death was septicemia.

034-001008 This 52 year old female with mental retardation, spastic cerebral palsy, bilateral benign breast cyst removal, hypothyroidism, migraine headaches and constipation was taking pregabalin 600mg and had been taking pregabalin for 931 days. She died and the coded cause of death was sudden death. It was one day from last dose until death. This adult home resident returned to the home from vacation and went to bed. A caregiver heard her get up and go to the bathroom several times during the night. She was found dead in her bed the next morning. Concomitant medications included carbamazepine, tiagabine, alendronate sodium, citalopram, docusate, ergocalciferol, levothyroxine, paracetamol/dichloralphenazone/isometheptene, polycarbophil, and urea hydrogen peroxide.

034-015002 This 44 year old male with intractable partial seizures, status epilepticus, post ictal psychosis, and incomplete right bundle branch block was taking pregabalin 600mg and had been taking pregabalin for 1174 days. He died and the coded cause of death was convulsion. The subject was taking pregabalin on the day of death. The narrative noted that this subject experienced a witnessed prolonged generalized tonic clonic seizure that resulted in death. No autopsy was performed. Concomitant medications included phenytoin and levetiracetam.

034-025004 This 23 year old male with a history of partial seizures, sickle cell anemia, and thrombocytopenia died and the narrative listed sudden unexpected death in epilepsy as the cause of death. This subject had received a total of 605 days of pregabalin (92 in RCT, 513 in open label). The subject was found dead on the floor by his father. An autopsy noted mild concentric LVH. Concomitant medications were valproate, topiramate, hydrochlorothiazide/triamterene, desonide, clindamycin, and ketoconazole.

035-022105 This 55 year old male with a history partial seizures, myocardial infarction 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.

Deaths from Ongoing Epilepsy Studies/Deaths not included in the Integrated Safety Database

Two of the nine pregabalin deaths that are not included in the integrated safety database (from ongoing blinded studies or reported to the sponsor's serious adverse event database but not entered into the clinical trial safety database-Summary of Clinical Safety p.39) occurred in pregabalin treated subjects from epilepsy trials (009-003004, 009-045013).

Subject 009-003004 experienced a cerebral hemorrhage 120 days after stopping pregabalin. Subject 009-045013, a 68 year old male, experienced four seizures on study day 1,046 of open label pregabalin treatment and never regained consciousness. He was pronounced brain dead nine days later.

Deaths from Epilepsy Studies in the Safety Update
The safety update included one additional death from an epilepsy trial that was not included in the NDA. A narrative summary for that death (Subject 034-027017) is provided above, in the section that discusses all new deaths in the safety update.

SUDEP
I calculated the rate of sudden unexplained deaths in the pregabalin development program and it appeared slightly lower than SUDEP rates observed in other AED development programs. Through the safety update, there appeared to be two pregabalin deaths that were definitely sudden and unexplained. Subject 034-025004 died and the listed cause of death was SUDEP and subject 034-001008 was found dead in bed with no obvious cause reported. There were three additional deaths that were possible SUDEP deaths. Subject 007-00601 was found dead, and the narrative reported that the subject appeared to have a seizure and aspirated but there was no autopsy and the event was not witnessed so the provided information does not seem sufficient to rule out SUDEP. Subject 010-045102 died and the death was attributed to MI but the narrative provided no evidence (e.g. autopsy) to support this diagnosis. The safety update included subject 034-027017 who was found dead, and the death certificate listed intractable seizures and aspiration as the cause of death but the subject did not have an autopsy. There were two additional deaths where patients were found dead, but in one case (035-022105) an autopsy documented cardiomyopathy and congestive heart failure as the cause of death and in the second case, the subject (011-066001) began antibiotic treatment for a respiratory illness associated with fever on the day before death. Considering the definite (n=2) and possible (n=3) SUDEP cases, the SUDEP rate in the pregabalin development program through the safety update was 1.9/1,000PY (5/2,637PY). This SUDEP rate is slightly lower than SUDEP rates reported in the labeling for tiagabine (2.6/1,000PY), topiramate (3.5/1,000PY), lamotrigine (3.5/1,000PY), gabapentin (3.8/1,000PY), and zonisamide (7.7/1,000PY)

Deaths in GAD Studies

The sponsor reported one death that occurred during or after participation in one of the six controlled GAD studies. One death occurred in a pregabalin-treated patient (patient 181_002003) whereas no deaths occurred in patients who were receiving or had received placebo or a comparator as of the termination date for data collection (February 14, 2003). Based on that information, I calculated that the proportion of deaths observed in pregabalin-treated patients in controlled studies was .087% (1/1149) compared with 0% (0/484) in placebo-treated patients and 0% (0/412) in patients treated with an active comparator. I estimated that the death rate in controlled studies in patients treated with pregabalin was .9/100 patient-years (1 death in 108.8 patient-years) compared with 0/100 patient-years (0 deaths in 45.2 patient-years) in patients treated with placebo.

The death that occurred after pregabalin exposure in a controlled study was a result of suicide (self-inflicted gunshot wound) committed 42 days after patient 181_002003, a 54 year old man with GAD and a history of major depression as well as hypertension and type 2 diabetes mellitus, had received his last dose of pregabalin. The patient had received just two days of treatment at 400 mg/day before study 1008-181, a double-blind placebo-controlled flexible-dose study, was terminated early by the sponsor. Concomitant medications included venlafaxine, gabapentin, glibenclamide, and diltiazem.

No deaths occurred in GAD open-label extension studies. Among the 1962 patients with GAD exposed to pregabalin in the ten controlled and uncontrolled studies, the proportion of deaths observed and reported by the sponsor was 0.05% (1/1962); this indication had the lowest proportion of deaths observed compared with the other indications for which the sponsor is seeking approval. The rate of death observed in this population was also the lowest compared with the other populations—1.6 deaths/1000 patient-years (calculated by the sponsor based on one death observed in 626 patient-years exposure to pregabalin).

Deaths from Ongoing GAD Studies/Deaths not included in the Integrated Safety Database

None of the nine pregabalin deaths that are not included in the integrated safety database (from ongoing blinded studies or studies reported to the sponsor's serious adverse event database but not entered into the clinical trial safety database; Summary of Safety, p.39) occurred in pregabalin treated subjects from GAD trials.

Deaths in the Safety Update

In the 4-month Safety Update, Pfizer reported no additional deaths occurring in GAD studies.

4.6.2 Serious Adverse Events

Serious Adverse Events in the Integrated Database

Pfizer reported in the NDA that there were 726 (8.4%, 726/8666) pregabalin subjects with one or more serious adverse events in the integrated safety database (Summary of Clinical Safety, p.40). The rate of experiencing on or more SAEs in the NDA integrated safety data base is 113/1000PY (726/6393PY).

Pfizer reported that 129 pregabalin subjects (2.3%, 129/5508) and 49 placebo subjects (2.1%, 49/2384) experienced one or more SAEs during NDA controlled trials. The rate of experiencing one or more SAEs was 163.3/1000PY (129/760PY) for pregabalin subjects and 145.8/1000PY (49/336PY) for placebo subjects. There was no specific SAE that occurred at a frequency of at least 1% in pregabalin subjects in the integrated safety database controlled trials. The most commonly occurring SAE among pregabalin subjects

in controlled trials was accidental injury (pregabalin 0.3%, 19/5508, placebo 0.0%, 1/2384). The other SAEs occurring in at least five pregabalin subjects in controlled trials were chest pain (pregabalin 0.2%, 9/5508, placebo 0.1%, 3/2384), pneumonia (pregabalin 0.1%, 6/5508, placebo 0.1%, 2/2384), congestive heart failure (pregabalin 0.1%, 5/5508, placebo 0.1%, 2/2384), and myocardial infarction (pregabalin 0.1%, 5/5508, placebo 0.1%, 2/2384) (Appendix ALL.53).

In the Safety Update, Pfizer provided the treatment emergent SAE risks from the NDA and compared these to the risks after including new data through the Safety Update cutoff date. Since the Safety Update included the treatment emergent SAE risks and the NDA presentations included all SAEs, the numbers of SAEs that Pfizer presents in the Safety Update cannot be compared to the numbers from the NDA presentation. Instead, one must rely on the comparisons included in the Safety Update. In the Safety Update, Pfizer reported that the treatment emergent SAE risk based on the NDA data was 2.2% (121/5508) for pregabalin subjects and was 1.8% (42/2384) for placebo subjects. After the addition of the new SAEs reported through the Safety Update cutoff date, the treatment emergent SAE risk for pregabalin subjects was 2.4% (138/5781) compared to 1.8% (44/2449) for the placebo subjects. The safety update included seventeen additional pregabalin subjects with treatment emergent SAEs that were not in the NDA total (SU, p.24).

In the NDA combined controlled and uncontrolled trials database, there was no SAE that occurred at a frequency of at least 1% in pregabalin subjects. The most commonly reported SAEs in the combined controlled and uncontrolled trials database were accidental injury (0.9%, 78/8666), pneumonia (0.5%, 39/8666), chest pain (0.3%, 29/8666), congestive heart failure (0.3%, 29/8666), myocardial infarction (0.3%, 29/8666) and angina pectoris (0.3%, 22/8666)(Appendix ALL.60). Pfizer reported in the safety update that in their clinical safety database there are a total of 854 pregabalin treated subjects with treatment emergent SAEs from the combined controlled and uncontrolled trials. The updated treatment emergent SAE risk for the combined controlled and uncontrolled studies in the Safety Update is 9.2% (854/9278) compared to 8.2% (714/8666) for the NDA data.

In the NDA, Pfizer provided a listing of all SAEs experienced by pregabalin treated subjects in any of their safety databases (Appendix ALL.62), and we reviewed this list to identify subjects with SAEs coded to preferred terms of potential importance. The list included the following SAEs: Kidney function abnormal (5) acute kidney failure (4), kidney failure (1), creatinine increased (1), nephrosis (1), nephritis (1), glomerulitis (1), pancreatitis (4), necrotizing pancreatitis (1), cardiomyopathy (3), cholestatic jaundice (2), jaundice (1), abnormal LFT (3), allergic reaction (2), anaphylactoid reaction (2), rash (2), Stevens Johnson Syndrome (1), CK increased (3), myopathy/rhabdomyolysis (2), acidosis (1), face edema (1), leucopenia (1), pancytopenia (1), lung fibrosis (3), and pulmonary hypertension (1). I provide summaries for these events in an appendix to this review. In addition, some of these events are summarized below in sections that review safety by indication.

The safety update list of new SAEs did not include cases of aplastic anemia, pancytopenia, thrombocytopenia, pancreatitis, acute hepatic failure, Stevens Johnson syndrome, CK increased, myopathy, rhabdomyolysis, lung fibrosis or pulmonary hypertension. There were several SAEs of potential concern in the safety update including five new SAEs of acute kidney failure, one case of angioedema, one case of myalgia, one case of petechial rash and one case of liver damage. I summarize details from those cases in an appendix to this review.

The following SAEs were present in the safety update but were not reported in the NDA: aggravation reaction (n=1), moniliasis (n=1), constipation (n=4), ileus (n=2), biliary pain (n=1), carcinoma of the mouth (n=1), hepatic neoplasia (n=1), liver damage (n=1), diabetic acidosis (n=1), chronic lymphocytic leukemia (n=1), hypovolemia (n=1), purpura (n=1), BUN increased (n=1), gout (n=1), hypernatremia (n=1), bone necrosis (n=1), leg cramps (n=1), tendon disorder (n=1), acute brain syndrome (n=1), dysarthria (n=1), myoclonus (n=1), angioedema (n=1), petechial rash (n=1), breast neoplasm (n=1), fibrocystic breast (n=1), PSA increase (n=1), unintended pregnancy (n=1), vaginal moniliasis (n=1).

In the Safety Update, Pfizer also separately reported four new SAEs occurring in patients who entered open-label study 100 from studies 091 and 190/152, ongoing double-blind studies not included in the integrated safety database. These serious adverse events were coded to the preferred terms transient ischemic attack, ovarian adenoma, prostate cancer, and palpitations.

SAEs by Indication

In the NDA, Pfizer provided the following table that summarized overall SAEs by indication for the integrated safety database. I provided the relative risks[5] that compare pregabalin to placebo for the completed controlled trial data.

FDA Table 7. Overview of Serious Adverse Events by Indication

	[n (%) of Patients With Serious Adverse Events]				
	DPN	PHN	Epilepsy	GAD	All Studies[a]
Completed Controlled					
Placebo	**N=459**	**N=398**	**N=294**	**N=484**	**N=2384**
All Subjects with SAEs	11(2.4)	10(2.5)	13(4.4)	6(1.2)	49(2.1)
PGB	**N=979**	**N=852**	**N=758**	**N=1149**	**N=5508**
All Subjects with SAEs	38(3.9)	28(3.3)	29(3.8)	7(0.6)	129(2.3)
Relative Risk	*1.63*	*1.32*	*0.86*	*0.5*	*1.10*
Combined DB/OL	**N=1413**	**N=1111**	**N=1613**	**N=1962**	**N=8666**
All Subjects with SAEs	244(17.3)	145(13.1)	210(13.0)	38(1.9)	726(8.4)

N = Total number of patients in the patient population.

[a] Includes serious adverse events in nonneuropathic pain studies and other psychiatry studies.

From Pfizer Table 16, Summary of Safety, p.40

[5] Relative risk =%pregabalin/%placebo

The table above illustrates that the overall SAE risks were similar for pregabalin treated subjects in the pain and epilepsy trials, and that the SAE risk was lowest for pregabalin subjects in GAD trials. The SAE relative risks (pregabalin compared to placebo) were >1.0 for the pain indication studies and <1.0 for the epilepsy and GAD indication studies.

Serious Adverse Events in Epilepsy Trials

Epilepsy Controlled Trials

Pfizer summarized serious adverse event risk for the controlled epilepsy trials included in the NDA integrated database in Appendix Epilepsy .048. Pfizer reported that 3.8% (29/758) of pregabalin subjects and 4.4% (13/298) placebo subjects reported one or more SAEs. Accidental injury was the only SAE reported by more than 1% of pregabalin subjects (pregabalin 1.2%, 9/758, placebo 0.3%, 1/294). There were no SAEs of acute hepatic failure, acute renal failure, pancreatitis, rhabdomyolysis or aplastic anemia in the epilepsy controlled trials.

Since there was an increased risk for accidental injury SAEs among pregabalin subjects compared to placebo subjects in the epilepsy controlled trials, I read the narrative summaries for these events. Of the nine pregabalin subjects who experienced accidental injury SAEs during controlled trials, two (009-035008, 011-002001) had their events during the baseline phase, prior to study drug administration. One subject experienced a burn from a cooking accident (034-003001). Two of the accidental injury SAEs were falls that occurred following a seizure (009-002006, 011-060001) and two were falls that appeared to have explanations (009-029003 lost footing and fell from ladder, 011-083007 fell from an icy roof). The two remaining accidental injury SAEs were both falls without obvious explanation for the events but also without evidence to suggest a relationship to study drug. Those events are summarized below.

009-004012, This 63 year old male with a history of osteoporosis and static encephalopathy (cerebral palsy) fell on study day 44 while taking pregabalin 600mg/day BID. He was hospitalized for a leg fracture and withdrew from the study. He subsequently re-enrolled in the open label extension.
011-073012, This 37 year old male was hospitalized for a painful swollen leg that developed one day after a fall at work. The event occurred on study day 34 and the subject was taking pregabalin 600mg/day at the time. The circumstances surrounding the fall were not described. The subjects did have an AE of "drowsy" at a visit prior to the fall. Concomitant medications included lamotrigine, carbamazepine, and clobazam.

Epilepsy Combined Controlled and Uncontrolled Trials

In the NDA, Pfizer reported that 13% (210/1613) of subjects exposed to pregabalin in combined controlled and uncontrolled epilepsy studies experienced one or more SAEs. I reviewed Pfizer's table 2.74 Appendix Epilepsy.053 to examine the types of serious AEs reported during the epilepsy studies. Pregabalin subjects most frequently experienced SAEs from the Body as a Whole body system (5.6%, 90/1613). Accidental Injury was the only SAE reported by more than 1% of pregabalin subjects in the combined controlled and uncontrolled trials (2.9%, 46/1613). There were no SAEs of acute hepatic failure, acute renal failure, rhabdomyolysis or aplastic anemia in the epilepsy combined

controlled and uncontrolled trials. There were several SAEs coded to preferred terms of interest including ventricular tachycardia (1), LFT abnormal (2), cholestatic jaundice (1), pancreatitis (1), CK increased (3), psychosis (6), psychotic depression (2) hallucinations (1), schizophrenic reaction (1), Stevens Johnson syndrome (1), maculopapular rash (1), and kidney calculus (5). Below I summarize SAEs of interest.

Ventricular tachycardia

034-004004 This 35 year old male who had received 1189 days of pregabalin treatment developed ventricular ectopy, ventricular tachycardia and ventricular fibrillation during a craniotomy for a planned temporal lobectomy. Treatment included lidocaine, amiodarone, magnesium, electrical cardioversion/defibrillation and AICD placement. The narrative reported that an EP study demonstrated ventricular dysfunction possibly due to the cardiac arrests.

LFT abnormal

011-070011 (See above, deaths)

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.

Cholestatic jaundice

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 but the narrative included no hospital lab results. 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.

Pancreatitis

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.

Increased CK

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 CK 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 CK was 1031U/L. Other study CKs were: Day 14=150U/L, Day 28=187U/L, Day 56= 193U/L. On day 91 the subject's CK 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 CK results

009-008015 This 26 year old male with refractory seizures experienced elevated CK 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 CK four days later was 1,805U/L and seven days after that it was 203U/L. During the preceding double blind study, his CKs 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 CK 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 CK was 292U/L. She continued in the trial with no additional elevated CK results. Concomitant medications were topiramate and lamotrigine. The event was attributed to strenuous exercise. This subject had no recorded AEs of myalgia.

Psychosis

010-002103 This 19 year old female was hospitalized for psychosis after 282 days of pregabalin (63 days in a controlled trial and 219 days in the open label extension). On day 281 she experienced confusion and worsening seizures. The narrative noted unusual behavior but did not provide details. The narrative did not note if she was treated with an antipsychotic. She was discharged on day 299, considered recovered with sequelae due to mental slowness. Concomitant medications were lamotrigine, oxcarbazepine, zolpidem, and ethinylestradiol/norgestimate.

010-033101 This 39 year old female with a history of postictal hallucinations was hospitalized for visual and sensory hallucinations and postictal psychosis on study day 415. The subject had 3 secondary generalized tonic clonic seizures on study day 403. She began experiencing post-ictal hallucinations on study day 405. Pregabalin was stopped on study day 410 because the subject did not meet re-qualification criteria. She reported a number of complaints including the feeling that something had slipped inside her chest and that she could not talk. She felt she had to walk on the outer parts of her feet, she felt like drooling, and she felt that her fingers were snapping on a wire near her ear. She also felt that the wires and subdural grid from her vagal nerve stimulator were getting tangled outside her body and that she felt them in her throat. She was treated with risperidone and the symptoms were reportedly improved. She was discharged from the hospital on day 422.

010-045113 This 52 year old male with a history of postictal psychosis was hospitalized for postictal psychosis eight days after stopping open label pregabalin. Study medication was discontinued on day 224 for administrative reasons. Seven days later he experienced a secondary generalized tonic clonic seizure and the next day two more. Following those seizures he experienced postictal psychosis described as overwhelming feelings and emotions. He was also noted to be experiencing delusions, and agitation. His mental status returned to baseline and he was discharged on day 236.

012-037107 This 42 year old female was hospitalized for psychosis on study day 369. There were no details about this event in the narrative. Concomitant medications were oxcarbazepine, valproate, and levetiracetam. The patient profile reported that she was treated with olanzapine and the narrative reported that she recovered.

012-059115 This 42 year old male with a history of postictal psychosis was hospitalized on study day 73 for postictal delirium. He experienced a prolonged complex partial seizure followed by confusion. He was treated with lorazepam, clonazepam, and risperidone. He recovered on study day 78 and continued in the

study. He was hospitalized again on study day 277 for postictal psychosis. He withdrew from the study due to this event. Following a one month period of no seizures, he experienced eight seizures from study day 275 to 277. He awoke on study day 278 and exhibited messianic delirium. Pregabalin was down titrated and he was treated with clonazepam, risperidone, and haloperidol. The narrative reported that the subject recovered.
035-036108 This 19 year old female was hospitalized for postictal psychosis 119 days after stopping treatment with pregabalin. She recovered from the event.

Psychotic depression

009-035004 This 28 year old male with refractory partial seizures was hospitalized for psychotic depression after a total of 792 days of pregabalin (90 days in controlled trial, 702 days open label). Concomitant medications included paroxetine, carbamazepine, tiagabine, and levetiracetam. He displayed aggressive behavior and attention seeking behavior (not further described). He was treated with olanzapine and recovered.
007-001104 This 36 year old female with a history of right temporal lobectomy/hippocampectomy developed depression with suicidal ideation and was hospitalized on study day 369. She was taking pregabalin 600mg/day at the time of the event. The narrative noted that she had social problems and that she was treated with citalopram and discontinued from the study. The narrative also noted that she recovered without sequelae.

Hallucinations

010-033101 (See Above under psychosis)

Schizophrenic reaction

007-001601 This 43 year old male with intractable seizures was hospitalized for schizophrenia and depression on study day 311. The narrative noted that he experienced stress and behaved strangely following a move to a new home facility. This included threatening behavior. He was treated with fluoxetine and risperidone. Study medication was continued. Concomitant medications included carbamazepine, tiagabine, ranitidine, and chloral hydrate. The narrative reported that the subject recovered from depression but that schizophrenia was ongoing at the last follow up.

Stevens Johnson syndrome

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 26), 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.

Maculopapular rash

011-037001 This 33 year old female with no history of drug sensitivities developed a maculopapular rash on her face on day 2 of pregabalin treatment (150mg/day). Study drug was stopped, the blind broken, and she was treated with an antihistamine (clemastine). She recovered by study day 8. Concomitant medications were valproic acid and lamotrigine and the CRF stated that these were begun — while the start date of the rash was ——

Kidney calculus

011-072009 This 21 year old female with no history of nephrolithiasis was hospitalized for suspected nephrolithiasis on study day 34. She was taking pregabalin 150mg/day at the time of the event. An abdominal x-ray was reported as negative; there was no mention of a renal ultrasound having been done.

The pain resolved on study day 36 and she was discharged the next day. She continued in the study. Her concomitant medications included topiramate and carbamazepine.
034-059006 This 49 year old male was hospitalized for nephrolithiasis during the baseline phase of the study, prior to receiving study medication.
009-015003 This 27 year old male with refractory seizures and a history of kidney stones was hospitalized for nephrolithiasis after 111 days of pregabalin treatment (93 days in controlled trial, 18 days in open label extension). Concomitant medications were levothyroxine, sertraline, and topiramate. The narrative stated that he recovered two days later.
011-066002 This 36 year old male was diagnosed with pyelonephritis on study day 835 and nephrolithiasis on study day 836. He had a history of a motorcycle accident with resulting tetraplegia, s/p right kidney rupture with a solitary kidney and multiple urinary tract infections. Concomitant medications included carbamazepine, tizanidine, paraffin, trimethoprim, acyclovir cream, nitrofurantoin, phenolphthalein, and sulfamethoxazole. During hospitalization for nephrolithiasis he was found to have a 4cm renal concretion with urethrostenosis and urine culture was positive for proteus mirabilis. The nephrolithiasis was felt likely due to previous urinary tract infections.
011-075008 This 58 year old male developed a left ureteral calculus on study day 843. This subject's CRF did not include kidney calculus as part of his past medical history. He underwent cystoscopy and ureteral stent placement. Concomitant medications included carbamazepine, lamotrigine, diclofenac, paracetamol, paramol-118, flucloxacillin, hyoscine, ketoconazole, lactulose, miconazole, oxytertracycline, senna, and trimethoprim.

SAEs from Ongoing Epilepsy trials/ SAEs not included in the Integrated Safety Database

Pfizer provided listings of SAEs from ongoing trials not included in the integrated safety database (ALL.066) or events identified from the sponsor's serious AE database but not entered into the clinical trial safety database by the cutoff date (ALL.289). Review of these two tables identified 25 additional subjects who received either pregabalin or blinded treatment in epilepsy trials who experienced SAEs. The SAEs in this list were similar to those identified above. There were no events of hepatic failure, acute renal failure, rhabdomyolysis, blood dyscrasias or serious skin reactions for pregabalin treated or blinded therapy treated subjects from these epilepsy trials.

SAEs in Epilepsy Trials, Safety Update
The safety update included 24 subjects from ongoing epilepsy uncontrolled trials with SAEs since the NDA cutoff date. Inclusion of these SAEs with those identified in the NDA resulted in no meaningful differences in SAE risks. I reviewed the list of new SAEs reported in the safety update (Appendix Epilepsy 10) to look for SAEs of potential interest. There were no SAEs of liver failure, pancreatitis, myopathy, CK increased, pancytopenia, aplastic anemia, renal failure, or skin rash among the newly reported SAEs from epilepsy trials in the safety update.

Serious Adverse Events in GAD Trials

GAD Controlled Trials

The sponsor lists SAEs experienced by patients in controlled GAD studies in Appendix GAD.048 (p. 14245). In this table, the sponsor lists SAEs by body system and calculates SAE risk for placebo patients, all pregabalin-treated patients, and patients assigned to each dose of pregabalin individually. The SAE risk among patients assigned to any dose of pregabalin during controlled GAD studies was 0.6% (7/1149), which was half of the

risk of SAEs among patients assigned to placebo (1.2%, [6/484]). The SAE rate in the pregabalin group of 6.4/100 person-years (7/108.8 person-years) was also about half the SAE rate in the placebo group (13.3/100 person-years; [6/45.2 person-years]).

The sponsor presents SAE risks by indication and in all studies in table 16 (Summary of Safety, p. 40). The overall risk of SAEs in the pregabalin treated GAD population was considerably lower than the risk for pregabalin treated subjects in all controlled studies combined (2.3%; 129/5508) or the risk for pregabalin treated subjects in controlled studies for any of the other indications individually (SAE risk in DPN studies was 3.9% [38/979]; SAE risk in PHN studies was 3.3% [28/852]; SAE risk in epilepsy studies was 3.8% [29/758]).

The seven pregabalin-treated patients who experienced SAEs in controlled GAD studies experienced a total of eight SAEs (one patient experienced two concomitant events both coded as SAEs to the preferred terms dizziness and accidental injury). The only SAE that occurred in more than one patient was "accidental injury," which occurred in two patients (0.2%; 2/1149 patients). 0.2% (1/484) assigned to placebo experienced an SAE of accidental injury.

Of the SAEs coded as accidental injuries that were experienced by pregabalin-treated patients, one was a fall leading to a right wrist fracture that occurred in the setting of dizziness, and one was an injury of a finger with an axe that occurred while the patient was chopping wood. Patient 087_015013, a 71 year old female, developed dizziness and sustained a fall and right wrist fracture on study day five while in the dose titration phase; she was on pregabalin 300 mg/day at the time of the event. Concomitant medications taken by the patient at the time of the event were fluticasone, ipratropium, salbutamol, nystatin, domperidone, ranitidine, and mebeverine. Pregabalin was discontinued on study day 6. Patient 087_032009, a 34 year old male, sustained an injury to his finger with an axe on study day 31, the last day of his taper; he had been taking pregabalin 400 mg/day but was on 300 mg/day at the time of the finger injury, which required surgery. Prior to the finger injury, the patient had developed difficulty concentrating (which was coded as "thinking abnormal") on study day 13.

Other SAEs reported by the sponsor that were experienced by one pregabalin-treated patient each were cardiomyopathy, myocardial infarction, appendicitis (coded to the preferred term "gastrointestinal disorder"), left iliac fossa pain (coded to the preferred term "bone pain")[6], and worsening of underlying GAD. No pregabalin-treated patient in a controlled GAD study had an SAE due to hepatic failure, renal failure, rhabdomyolysis, serious skin reaction, blood dyscrasia, or pancreatitis.

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[6] Patient 087_017004 was a 37 year old woman hospitalized for four days beginning on study day 36 of pregabalin treatment; she was receiving 600 mg/day at the time of her SAE. She was treated with hydration and analgesics and discharged with a diagnosis of abdominal pain. Three months later, the patient was diagnosed with diverticulitis of the sigmoid colon. This information was obtained by the sponsor after follow-up with the investigative site on 2/2/04.

I reviewed the patient narratives and case report forms for all the patients with SAEs, and will discuss the SAEs involving cardiac events in more detail here. Patient 025_004031, a 39 year old male with a history of GERD and major depressive disorder as well as GAD, was diagnosed with cardiomyopathy on study day 9 after presenting with chest pain and shortness of breath while being treated with pregabalin 600 mg/day. Medications at the time of the event included only omeprazole. Of note, the patient had had a viral syndrome beginning 12 days and ending five days before the event. He underwent angioplasty and was treated with furosemide, lisinopril, and digoxin. As of study termination, he had not recovered from the SAE. No information is provided regarding the etiology of the cardiomyopathy.

Patient 085_401004, a 30 year old female with no significant past medical history other than GAD and on no medication other than pregabalin, was diagnosed with a myocardial infarction based on a routine EKG on study day 45 while receiving pregabalin 450 mg/day. This event was later considered by the sponsor to have been misreported, although it was not reclassified within the database. The patient, who had gained 8 kg since the study's inception (initially 98.0 kg, her weight had increased to 106 kg at the time of the SAE), had a routine EKG on study day 45 which was machine-read as being consistent with a recent anterior myocardial infarction. Upon questioning, she reported that she had experienced recent chest pain. She was sent to the Emergency Room and was seen by a cardiologist, who considered her chest pain to be atypical and her EKG to be "within normal limits." The case report form mentions that cardiac enzymes were ordered but no results are provided by the sponsor. The sponsor states that the cardiologist's opinion was not obtained until the database had been closed and locked, and therefore the event remains classified as an SAE.

GAD Combined Controlled and Uncontrolled Trials

The overall risk of SAEs in the GAD controlled and uncontrolled studies combined in the NDA database was 1.9% (38 /1962). According to the sponsor, no individual SAEs were experienced by more than two patients. Accidental injury, bone pain, dizziness, gastrointestinal disorder (appendicitis in both instances), myocardial infarction, neoplasm, and overdose were each experienced by two patients (0.1%; 2/1962).

There were no cases of serious skin rashes, blood dyscrasias, renal failure[7], hepatic failure, renal calculi, or rhabdomyolysis. Of note, there was one SAE of pancreatitis, one SAE of syncope, one SAE of urinary tract disorder (verbatim term was "urinary obstruction"), one patient who experienced concurrent SAEs of gastrointestinal hemorrhage and myocardial infarction, one patient with concurrent SAEs of cholelithiasis and cholecystitis, one SAE of grand mal convulsion and one of convulsion (the investigator had termed this SAE "acute possible seizure"), and three (non-cardiac) vascular SAEs—one left leg thrombosis (coded to the preferred term thrombosis), one

[7] Patient 083_305017 had an SAE of renal infarction after 37 days of exposure to placebo in study 83. The patient was enrolled in the subsequent open-label study 84 and received pregabalin 300 mg/day for 22 days in that study. The patient's renal function remained stable while receiving pregabalin. Serum creatinine, which was 2.6 on the day of the SAE, was 2.5 after 22 days of pregabalin treatment.

cerebrovascular accident, and one pulmonary embolism. I summarize below, to the extent possible based upon the information provided by the sponsor, selected events of potential interest.

Pancreatitis

Patient **088_516021**, a 49 year old female with GAD and a history of cholecystectomy, major depression, and hypothyroidism, was hospitalized on study day -31 of study 88, a relapse prevention study with an eight week phase of open-label pregabalin treatment followed by a six month phase at the beginning of which patients were randomized either to placebo or to (continuing) pregabalin treatment. She was entering the open label phase of that study but had not yet taken any pregabalin at the time of her SAE. The patient recovered from her pancreatitis and commenced pregabalin treatment, completing the initial open-label phase and withdrawing from the study after three days of double-blind placebo-controlled treatment because of worsening of her anxiety. She subsequently entered open label study 84. She continued in this study for 252 days without recurrence of her pancreatitis.

Seizures

Patient **088_508030**, a 47 year old male with GAD, asthma, and no documented prior history of seizures, experienced seizures classified as SAEs on days 89 and 91 of treatment with pregabalin in study 88, during which he had received pregabalin at 450 mg/day prior to a taper. The first seizure occurred six days after the patient's last day of exposure to pregabalin in study 88 and two days prior to resuming open-label pregabalin treatment in study 84. The patient's second seizure SAE occurred on the first day of treatment with pregabalin in study 84 [redacted]. The patient's other medications included aspirin, salmeterol, and salbutamol. The patient experienced another seizure (classified as an AE rather than an SAE) during study 84 or [redacted] while being treated with pregabalin at 500 mg/day. The sponsor reported that the patient had a single episode of "heavy alcohol abuse" on study day 88 of study 88, and that the investigator considered the patient's seizures to be secondary to alcohol withdrawal. No mention is made of whether alcohol use preceded the patient's [redacted] seizure. The patient continued on pregabalin (at a reduced dose) through [redacted] when he withdrew his consent for continued participation on the study.

Patient **085_417020**, a 29 year old Native American female with no history of prior seizures, experienced an SAE coded to the preferred term "convulsion" (from the verbatim term "acute possible seizure") on study day 354 of open-label pregabalin in study 84 after a total of 403 days of exposure to pregabalin. She was on pregabalin 400 mg/day at the time of the event, and had received pregabalin 400 mg/day for 49 days in the previous controlled study (85); concomitant medications were zinc, calcium carbonate, paracetamol, and ibuprofen. The patient experienced an unwitnessed loss of consciousness while at work in a medical setting; her loss of consciousness was preceded by a burning sensation in her chest and a feeling of wooziness. She was disoriented upon regaining consciousness. Vitals signs at that time were BP 155/90; P 123; RR 18. Head CT, EKG, and labs were unremarkable. She underwent two EEGs; the first was "noted as borderline due to a cold" while the second was normal. The patient's pregabalin was discontinued and she recovered without additional treatment.

Syncope

Patient **087_068001**, a 54 year old female with a history of total hip replacement, appendectomy, and cholelithotomy, was hospitalized with syncope after 62 days of exposure to pregabalin in open-label study 100. She was receiving 400 mg/day at the time of her syncopal episode in addition to oxazepam, paroxetine, trazodone, tetrazepam, tizanidine, and estradiol. She had received venlafaxine for 49 days during the previous controlled study 87. The patient had a syncopal episode after swimming and was hospitalized with suspected sick sinus syndrome. A pacemaker was "proposed" according to the patient narrative but is not mentioned in the case report form. The investigator did write "cardiac problems" in the comment section of the AE report form. A carotid artery doppler, MRI, and 24-hour cardiac monitoring were performed; the results are not reported. The patient recovered and pregabalin was continued at a reduced dose until the following month when "pregabalin treatment was discontinued due to a request from the Ministry of Health of Austria," according to the patient narrative.

SAEs from Ongoing GAD trials/ SAEs not included in the Integrated Safety Database

Five patients enrolled in ongoing controlled GAD studies not in the integrated safety database[8] experienced SAEs that were reported to Pfizer by February 14, 2003. These SAEs are listed in Appendix All066 (Summary of Safety, p. 3916). The SAEs are listed by Pfizer as chest pain; ventricular tachycardia; proctorrhagia, anemia, and intermittent second degree atrioventricular block (all experienced by one patient); fall, dizziness, and drowsiness (all experienced by one patient); and right big toe ulcer, progression of chronic arteritis, and right great toe infection (all experienced by one patient). Since treatment of patients in these studies was still blinded, Pfizer does not report whether the patients who experienced these SAEs were receiving pregabalin or placebo. Case report forms and patient narratives are available for each of these patients, but not patient profiles or case report tabulations. I briefly summarize the SAEs experienced by each patient below based on the limited information available:

003001 (study 1008-090) This 79 year old male with a history of hypertension, left bundle branch block, and diabetes mellitus in addition to GAD was hospitalized on study day 2 of treatment with pregabalin 150 mg/day or placebo with ventricular tachycardia (VT) that was discovered during Holter monitor assessment on study day 1. Two adverse event forms reporting VT were completed for this date; it is not clear whether these represent one episode or two different episodes of VT. Concomitant medications included metformin, glipizide, alprazolam, atenolol, lansoprazole, quinapril, acetylsalicylic acid, clopidogrel, and vitamins. Evaluation of the patient included a cardiac catheterization that demonstrated four coronary artery blockages and an EP study that was unsuccessful at inducing VT. Study medication was discontinued on study day 8. Neither the case report form nor the patient narrative notes whether the patient experienced any further episodes of VT while on the study drug. A pacemaker was inserted on study day 15, and Pfizer reports that the patient subsequently recovered.

005004 (study 1008-090) This 69 year old female with GAD in addition to a history of hypertension, hyperlipidemia, coronary artery disease, angina, breast cancer s/p mastectomy, history of TAH-BSO, history of cholecystectomy, and history of pacemaker insertion (per patient narrative, although this history is not mentioned on the CRF) was hospitalized with chest pain on study day 5 of treatment with pregabalin or placebo. Study medication was temporarily stopped but restarted and continued for a total of 59 days. Concomitant medications included Tylenol, Tums, Niacin, triamterene/hydrochlorothiazide, diltiazem, fluvastatin, aspirin, Metamucil, nitroglycerin, potassium chloride, celecoxib, and multivitamins. The patient's chest pain was relieved by nitroglycerin. Details of any subsequent work-up are few; the narrative notes only that results of a cbc, EKG, and blood chemistry were negative and that the patient's chest pain resolved but returned after hospital discharge, although no additional adverse event forms reporting chest pain were completed.

984006 (study 1008-152) This 89 year old male with GAD and a history of Crohn's disease, ulcerative colitis, diverticulosis, hypertension, and lumbar and cervical arthrosis (per the patient narrative; the case report form excludes diverticular disease and also lists polyneuritis, prostatic adenoma, peptic esophagitis, and rheumatoid arthritis) was hospitalized with proctorrhagia on study day 47 of treatment with pregabalin or placebo. He was subsequently diagnosed with anemia requiring transfusion of 6 units of packed red blood cells. Colonoscopy performed on study day 58 suggested that the patient's underlying Crohn's disease and diverticular disease were responsible for his proctorrhagia. Concomitant medications at the time of his GI bleed included mesalazine and amiloride/hydrochlorothiazide. On study day 59, intermittent

[8] Study 090/152, a placebo-controlled study being conducted among elderly patients with GAD, is the only ongoing GAD study not in the integrated safety database described by Pfizer in table 135 (Summary of clinical safety, p.241; see attached table 2), in which ongoing studies not in the phase 2/3 integrated safety database are listed. Two additional studies for psychiatric indications are also described in this table—study 091 for panic disorder and study 093/192 for panic relapse prevention.

second degree AV block (also reported as an SAE by the investigator) was discovered during a cardiac check-up and a pacemaker was placed. The patient was discharged from the hospital back to his nursing home on study day 65; he was considered recovered from all adverse events. He continued study medication during this time, completing taper of his study medication two days prior to diagnosis of second degree AV block. He subsequently entered open label study 100.

984007 (study 1008-152) This 76 year old male with GAD and chronic arteriopathy, hyponatremia, hypokalemia, prostatic adenoma s/p resection, and diabetes mellitus (per patient narrative but not case report form) developed an ulcer of his right great toe (on study day 49) which worsened and required hospitalization on study day 53 of treatment with pregabalin or placebo. Doppler demonstrated stage 4 arteritis. The patient underwent a femero-popliteal bypass and right great toe amputation on study day 64. He was discharged from the hospital and later re-admitted (on study day 79) with a stump infection requiring a higher amputation. He was ultimately discharged on study day 91, at which point he was considered recovered. During the patient's SAE he continued his study medication, completing his taper seven days before his vascular bypass and initial toe amputation and entering open label study 100; details of the patient's participation in this study, including date of study entry, are not provided. Concomitant medications at the time the patient's SAE began included potassium chloride and sodium chloride per the case report form (the patient narrative also lists Diosmin, tramadol, clonazepam, and nadroparin).

152_988005 (study 1008-152) This 73 year old female with Parkinson's disease and history of a CVA in addition to GAD sustained a fall on study day 11 of treatment with pregabalin or placebo. She was subsequently admitted to the hospital with a fractured arm on study day 14, at which time her study medication was discontinued. Preceding her fall were drowsiness and dizziness; these adverse events were reported as beginning on study days 1 and 3, respectively, and continuing through her hospital admission. Fall leading to arm fracture was reported by the investigator as an SAE, while dizziness and drowsiness were reported as AEs. Sinemet CR was the patient's only concomitant medication at the time of her SAE.

In addition, there were six patients with SAEs in open-label GAD studies that were reported to the sponsor's ARISg database but not the Oracle Clinical Database as of February 14, 2003. According to patient narratives and case report forms, all of these SAEs occurred in patients who had previously been enrolled in study 090/152, an ongoing study not in the integrated safety database being conducted among elderly patients with GAD. Their treatment assignments in this preceding study remain blinded. The SAEs, which are listed in Appendix ALL289 (Summary of Safety, p. 7674), were coded to the WHOART preferred terms atrial fibrillation; bronchiectasis (investigator's term: worsening of bronchiectasis); hypoxia and other and unspecified neoplasms (investigator's terms: hypoxemia and pancreatic mass); synovitis (investigator's term: inflamed Baker's cyst right knee); dizziness (investigator's term: faintness); and angioedema (investigator's term: Quincke's disease). Below, I briefly discuss three patients with SAEs of interest:

Atrial fibrillation

433001 (study 100) This patient, an 85 year old female with GAD and a history of hypertension, was hospitalized with atrial fibrillation with fast ventricular response on study day 380 of open-label pregabalin treatment. She had no previous history of atrial fibrillation. At the time of her hospitalization, she was receiving pregabalin 300 mg/day; she had received doses ranging from 150 mg/day to 300 mg/day during the study. Captopril was her only concomitant medication. The arrhythmia was discovered on a routine EKG at her final study visit according to the patient narrative. This description of the time course of events is not consistent with the patient's case report form, which notes that the atrial fibrillation occurred from [redacted] whereas the patient's termination visit, for which "rhythm-conduction" disturbance is checked in the EKG results section of the visit report, occurred on [redacted] Pregabalin was discontinued on [redacted] according to the case report form. The patient narrative states that she spontaneously reverted to normal sinus rhythm and was considered to have recovered.

Pancreatic neoplasm

434005 (study 100) This 76 year old male with hypothyroidism, type 2 diabetes mellitus, adrenal insufficiency (listed as suprarenal cortex insufficiency on the case report form), renal cysts, hypertension, and hypercholesterolemia in addition to GAD was diagnosed with hypoxia and a newly discovered pancreatic mass after presenting to the hospital with asthenia on study day 145 of open-label pregabalin treatment, at which time he was receiving 300 mg/day. Concomitant medications included enalapril, hydrocortisone, thyroxine, and lovastatin. After being treated with oxygen, the patient was discharged from the hospital on study day 162 and re-admitted four days later with breathing difficulties and a deterioration in his level of consciousness. The patient was again hypoxic with a pO_2 of 47 mm Hg. Abdominal CT revealed a 5.8 cm multicystic pancreatic lesion consistent with a cystadenoma or cystadenocarcinoma that was felt to be unresectable. No information regarding work-up for lung pathology is discussed. The patient stabilized and was discharged on study day 174. Pregabalin was continued, although the dose was reduced to 75 mg/day on study day 254 because of the patient's "delicate health status" and ultimately discontinued on study day 276 at the study manager's request because, according to the case report form, "it's not possible to prescribe only 75 mg/d of pregabalin." He had not recovered from his SAEs at the time of exiting the study.

Angioedema/ Quincke's disease

571001 (study 100) This 67 year old female with a history of hypertension, "many allergies and sensitivities," and venous insufficiency was diagnosed with Quincke's disease (coded to the WHOART preferred term angioedema) on study day 140 of open-label pregabalin treatment; she was receiving 225 mg/day at the time of the SAE. After a visit to the dentist, she experienced swelling of her face and tongue and subjective shortness of breath. She was treated with corticosteroids and recovered later that day. Pregabalin treatment was continued. Concomitant medications at the time of the SAE included labetolol, Moduretic MSD (amiloride/hydrochlorothiazide), rofecoxib, pravastatin, and diosmin.

SAEs in the Safety Update

Pfizer reported no additional SAEs in the Safety Update for patients enrolled in GAD studies (Safety Update, p.67).

4.6.3 Discontinuations for Adverse Events

Discontinuations for Adverse Events in the Integrated Safety Database

In the controlled trials included in the NDA integrated safety database, 13.5% (741/5508) of pregabalin subjects discontinued for adverse events compared to 6.8% (162/2384) of placebo subjects (Table 21, Summary of Clinical Safety, p.52). The following table summarizes the discontinuation due to AE risk by pregabalin dose for the controlled trials in the NDA integrated safety database.

FDA Table 8. Discontinuation Due to AE Risks by Pregabalin Dose, Combined Controlled Trials

Placebo	150 mg/day	200 mg/day	300 mg/day	400 mg/day	450 mg/day	600 mg/day	All DB
N=2384	**N=1164**	**N=208**	**N=1224**	**N=360**	**N=501**	**N=1802**	**N=5508**
162(6.8)	85 (7.3)	21(10.1)	164(13.4)	38(10.6)	65(13.0)	358(19.9)	741(13.5)

Taken from Pfizer Table 21, Clinical Summary of Safety, p.52.

As was noted for SAEs, Pfizer presented all AEs leading to discontinuation in the NDA presentations and treatment emergent AEs leading to discontinuation in the Safety Update. Pfizer reported in the Safety Update that the risk for discontinuation

due treatment emergent AEs in controlled trials was 13.7% (794/5781) for pregabalin compared to 6.6% (161/2449) for placebo.

Dizziness (pregabalin 4.1% [224/5508]; placebo 0.6% [15/2384]), somnolence (pregabalin 3.5% [193/5508]; placebo 0.3% [8/2384]), and ataxia (pregabalin 1% [55/5508]; placebo 0.0% [1/2384]) were the AEs leading to discontinuation of at least 1% of pregabalin subjects in controlled trials included in the NDA integrated safety database (Appendix ALL.074). After adding newly available data in the safety update, and considering only treatment emergent AEs, nausea (pregabalin 1%, 57/5781, placebo 0.7%, 18/2449) and confusion (pregabalin 1%, 57/5781, placebo 0.2%, 4/2449) also led to the discontinuation of at least 1% of pregabalin subjects (Safety Update, Table 20, p.31).

Pfizer reported in the NDA that 19% (1647/8666) of pregabalin subjects withdrew from studies in the NDA integrated safety database for adverse events (Summary of Clinical Safety p.51).

Pfizer reported in the Safety Update that after the addition of the new data, and considering only treatment emergent AEs leading to discontinuation, 19.3% (1787/9278) of pregabalin subjects in the combined controlled and uncontrolled trials database discontinued for AEs (Safety Update, p.31).

In the combined controlled trials and uncontrolled trials NDA database, the AEs that led to discontinuation of at least 1% of pregabalin subjects were dizziness (3.8% [333/8666]), somnolence (3.5% [307/8666]), thinking abnormal (1.2% [104/8666]), weight gain (1.1% [96/8666]), peripheral edema (1% [89/8666]), asthenia (1% [87/8666]) and headache (1% [85/8666])(Appendix ALL.078). After adding the newly available data, and including only the treatment emergent AEs leading to discontinuation, the Safety Update also included nausea (1%, 96/9278) as an AE leading to discontinuation of at least 1% of pregabalin subjects (Appendix ALL.39, Safety Update).

Pfizer provided a listing of AEs leading to discontinuation for pregabalin treated subjects in their NDA safety databases (Appendix ALL.80). I reviewed this list to identify subjects with AEs leading to discontinuation of potential importance. I identified subjects with the following AEs leading to discontinuation: Kidney function abnormal (6), acute kidney failure (1), creatinine increased (1), pancreatitis (2), cholestatic jaundice (2), jaundice (1), LFTs abnormal (8), SGOT increased (4), SGPT increased (9), allergic reaction (1), anaphylactoid reaction (1), urticaria (4), angioedema (1), CK increased (11), myopathy/rhabdomyolysis (2), face edema (11), leucopenia (6), pancytopenia (1), lung fibrosis (2), and pulmonary hypertension (1). I read the narratives for these events. Some of these events were discussed previously with the SAEs. I provide summaries for these events in an appendix to this review. In addition, some of these events are summarized below in sections that review discontinuations for AEs by indication.

I reviewed the updated listing of discontinuations for AEs included in the Safety Update (ALL.36). There were no discontinuations for CK increased, myopathy,

thrombocytopenia, pancreatitis, pancytopenia, aplastic anemia, acute liver failure, or Stevens Johnson Syndrome in the Safety Update data.

Discontinuations for Adverse Events by Indication

The following table summarizes the risk of discontinuation due to adverse events by indication for the integrated safety database.

FDA Table 9. Overview of Discontinuations Due to Adverse Events by Indication

	DPN	PHN	Epilepsy	GAD	All Studies[a]
Completed Controlled Trials					
Placebo	**N=459** 18(3.9)	**N=398** 26(6.5)	**N=294** 18(6.1)	**N=484** 48(9.9)	**N=2384** 162(6.8)
PGB	**N=979** 86(8.8)	**N=852** 123(14.4)	**N=758** 116(15.3)	**N=1149** 138(12)	**N=5508** 741(13.5)
Relative risk	2.26	2.22	2.51	1.21	1.99
Combined DB/OL	**N=1413** 229(16.2)	**N=1111** 256(23)	**N=1613** 284(17.6)	**N=1962** 309(15.7)	**N=8666** 1647(19)

[a]Includes nonneuropathic pain studies and other psychiatry studies.
Data from Pfizer Table 21, Summary of Safety, p.52

The relative risks for discontinuation due to adverse events were similar (2.2-2.5) for the pain and epilepsy trials while the relative risk for discontinuation due to adverse events was lower for the GAD trials (1.2)

Discontinuations for Adverse Events in Epilepsy Trials

Epilepsy Controlled Trials

Pfizer reported that 15.3% of pregabalin subjects (116/758) and 6.1% of placebo subjects discontinued from epilepsy controlled trials for adverse events (Table 102, p.190). Overall discontinuation for AEs risk exhibited dose response (see below). In the following table, I summarize the events leading to discontinuation of at least 1% of pregabalin epilepsy subjects and at least twice as frequently when compared to placebo.

FDA Table 10. Adverse Events Leading to Discontinuation of at least 1% of Subjects in the Pregabalin Group and at Least Twice as Frequently Compared to the Placebo Group, Epilepsy Controlled Trials

Event	PBO	50mg/d	150mg/d*	300mg/d	600mg/d*	All PGB
	N=294	N=88	N=185	N=90	N=395	N=785
Overall	6.1% (18)	6.8% (6)	5.9% (11)	14.4% (13)	21.8% (86)	15.3% (116)
Dizziness	0.3% (1)	0	2.7% (5)	4.4% (4)	7.8% (31)	5.3% (40)
Somnolence	0	2.3%	0	2.2%	5.3%	3.3%

		(2)		(2)	(21)	(25)
Ataxia	0.3% (1)	0	0.5% (1)	2.2% (2)	5.1% (20)	3% (23)
Asthenia	0.3% (1)	0	1.6% (3)	2.2% (2)	2.3% (9)	1.8% (14)
Amblyopia	0	0	0.5% (1)	1.1% (1)	2.5% (10)	1.6% (12)
Diplopia	0.7% (2)	0	0.5% (1)	2.2% (2)	2.3% (9)	1.6% (12)
Tremor	0	0	0.5% (1)	1.1% (1)	2.3% (9)	1.5% (11)
Confusion	0.3% (1)	0	0	1.1% (1)	2.3% (9)	1.3% (10)
Thinking abnormal	0	0	0	3.3% (3)	1.8% (7)	1.3% (10)
Headache	0	1.1% (1)	0.5% (1)	1.1% (1)	1.5% (6)	1.2% (9)

From table 2.7.4 Appendix Epilepsy.064
*Combines BID and TID dosing regimens

Epilepsy Combined Controlled and Uncontrolled trials

Pfizer reported that 17.6% (284/1613) of pregabalin subjects in combined controlled and uncontrolled epilepsy trials discontinued for adverse events (2.7.4 Appendix Epilepsy.066). In the table below I identify the AEs that led to discontinuation of at least 1% of pregabalin subjects in epilepsy trials.

FDA Table 11. Adverse Events Leading to Discontinuation of at least 1% of Pregabalin Subjects in the Epilepsy Combined Controlled and Uncontrolled Trials

AE leading to Discontinuation	Frequency (n=1613)
Overall	**17.6% (n=284)**
Dizziness	3.5% (n=56)
Somnolence	3% (n=48)
Ataxia	2.2% (n=35)
Weight gain	2% (n=33)
Asthenia	1.8% (n=29)
Thinking abnormal	1.3% (n=21)
Amblyopia	1.1% (n=17)
Confusion	1.1% (n=17)
Headache	1.1% (n=17)

No subjects discontinued from epilepsy trials for acute hepatic failure, acute renal failure, rhabdomyolysis, aplastic anemia, toxic epidermal necrolysis, or Stevens Johnson syndrome. Eight subjects discontinued for rash, five for leucopenia, three for generalized edema, three for hallucinations, two for CK increased, and one each for allergic reaction, cholestatic jaundice, jaundice, liver function tests abnormal, maculopapular rash, pancreatitis, thrombocytopenia, urticaria and ventricular tachycardia. I summarize those events below.

Rash

009 045005 This 47 year old male reported an adverse event of rash on open label study day 875 (also received pregabalin for 85 days in the preceding RCT). The rash was not described. Pregabalin was held for 14 days with no improvement in the rash. He restarted pregabalin and then discontinued for rash on study day 1123. Concomitant medications were lamotrigine, cerivastatin, and valsartan.
009 045006 This 61 year old female developed a rash on her hands, arms, trunk, and legs on day 65 of open label treatment (also received pregabalin for 34 days in the preceding RCT). Study medication was discontinued on day 1462 for rash. Concomitant medications at initial presentation of the rash were phenytoin, tiagabine, and tamoxifen.
011 005009 This 49 year old male developed a facial rash on study day 5 of an open label trial (first pregabalin exposure, received placebo in preceding RCT). Study medication was stopped on day 84 for rash. Concomitant medications included carbamazepine, lamotrigine, phenytoin, gabatril, and urgenin (sabalae, an herbal extract). The investigator classified the rash as mild intensity.
011 070008 This 35 year old female developed a rash on both hands on study day 4. She began a taper on study day 8 and her last pregabalin dose was on study day 14. The rash was resolved on day 22. The investigator classified the rash as moderate intensity. Concomitant medications included carbamazepine and bendrofluazide.
034 026007 This 46 year old female developed a rash on her legs and abdomen that was associated with pruritis. These events developed on day 84 of a double blind study and continued during the open label extension. Three days after appearance of the rash, she developed nausea and ataxia. Pregabalin was stopped two days later for all of these events. Eleven days after stopping pregabalin, she was hospitalized for altered level of consciousness. She was found unresponsive. She was dehydrated and although a chest x-ray found a right lower lobe pneumonia, the only reported treatment administered was intravenous fluids. All adverse events were reported as resolved on follow up. The altered level of consciousness was attributed to a post ictal state although the narrative did not mention seizure activity.
035 002100 This 55 year old female with a history of allergic rash to phenytoin, carbamazepine and lamotrigine developed a pruritic rash on study day 63. She discontinued pregabalin on study day 78 and the rash was resolved on study day 95. Concomitant medications included carbamazepine, topiramate, sertraline, estradiol, naprosyn, ibuprofen, pericolace, and citrocel.
035 028101 This 71 year old male developed a red rash on study day 84. This subject experienced additional AEs including blurred vision, unsteady gait, dizziness, insomnia, slurred speech, word finding difficulty, diarrhea, dry mouth, and upset stomach. Study medication taper began on day 85 to discontinue from the study for all of these AEs. The rash was resolved on day 146. The investigator rated the rash intensity as mild.
035 067103 This 42 year old male with a history of rheumatic fever and headache developed a rash on his chest and back on study day 43. Pregabalin was stopped for the rash and the last dose was taken on day 51. At follow up on day 79 the rash had not resolved. His only concomitant medication was carbamazepine. The investigator rated the intensity of rash on the chest as moderate and on the back as severe.

Leucopenia

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 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 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 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 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.

Generalized Edema

010 008106 This 33 year old female developed shakiness (nervousness), water retention (generalized edema), falling, blurred vision, fatigue, and loss of appetite on study day 4 and confusion and lack of energy on study day 28. Pregabalin was discontinued on study day 30 for all of these events and all were considered resolved on study day 49. The generalized edema was classified as mild by the investigator. Concomitant medications included lamotrigine.

010 021102 This 28 year old female with a history of partial seizures, weight gain, cholecystectomy, and pleurisy withdrew for generalized edema. On study day 52 she developed shortness of breath, and edema of both feet. On day 65 she developed generalized edema. Weight had increased from 98kg on day -28 to 111kg on day 64 and 122kg on day 127. She took her last dose of pregabalin on study day 127. The dyspnea was resolved on study day 147 but the edema was continuing at follow up. On day 206, her weight had dropped to 114kg. Concomitant medications included clobazam, topiramate, and carbamazepine.
034 083003 This 30 year old female with a history of partial seizures, right posterior cerebral hemisphere cyst, ovarian cancer, headaches, withdrew from the study for generalized edema. The edema was first noted six days prior to starting study medication and the investigator rated the intensity as mild. Study medication was stopped on day 34 and the edema was reported as resolved on day 55. Concomitant medications included Maalox, paracetamol, oral contraceptives, phenytoin, and carbamazepine.

Hallucinations

009 011006 (See SAEs above, Cholestatic jaundice)
034 008008 This 55 year old female with seizures and history of an astrocytoma, craniotomy, radiation, chemotherapy, brain biopsies, right ankle edema, and endometriosis experienced hallucinations, dizziness, and nausea on study day 1. Pregabalin was stopped and the hallucinations and dizziness resolved on study day 2. The nausea resolved on day 3. She entered the open label study and developed hypokinesia and abnormal gait and pregabalin was again discontinued. Concomitant medications included phenytoin and lamotrigine.
034 063002 This 50 year old male with partial seizures, depression, anxiety, nightmares and insomnia withdrew from the study on day 12 for hallucinations. The hallucinations began on study day 2 and were described as a possible visual hallucination following a seizure. He also experienced vivid dreams. His wife found him in the bathroom looking for bugs and turning the light on and off. No auditory hallucinations were reported. Three days after stopping pregabalin, the hallucinations resolved. Concurrent medications included phenytoin, sertraline, lorazepam, and panadeine CO (paracetamol/codeine).

CK increased

009 005002 This 29 year old female with partial seizures s/p left frontal lobectomy, discontinued for elevated CK and other AEs. Her baseline CK was elevated at 478U/L. On study day 13, while taking pregabalin 600mg/d TID, she had a CK 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 CK 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 CKs ranged from a low of 240U/L and a high of 436U/L.
009 014012 This 40 year old male with partial seizures discontinued pregabalin treatment for elevated CK results during an open label study. This subject participated in the preceding double blind study but CK was not tested either at baseline or during placebo treatment. On open label study day 28, his CK (first available) was 611 U/L. His CK remained elevated throughout treatment and the highest recorded value was 1378 U/L on study day 507. Concomitant medications were topiramate and carbamazepine.

Allergic reaction

035 070101 This 41 year old female experienced an allergic reaction on study day 1. The event was not described in the narrative and the investigator rated the intensity as severe. When questioned about the event Pfizer listed the following symptoms: dizziness, swollen eyes, thick tongue, and chest pain. These symptoms began 7 hours after the subject's first dose of pregabalin. She subsequently developed tiredness and said she was unable to walk without assistance. Her symptoms improved within several hours but she continued to feel tired. The subject took no additional pregabalin doses. The subject was seen on study day 3 (two days after her only pregabalin dose) and she continued to feel tired and as if her chest was bruised but her exam that day was unremarkable (Information from 3/19/04 submission). The only concomitant medication was phenytoin.

Cholestatic Jaundice

009 011006 (see above 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.

LFT abnormal

009 033005 (See above SAEs)

Maculopapular rash

011 037001 (See above SAEs)

Pancreatitis

034 036006 (See above 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 in 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, phenytoin, and lamotrigine.

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.

Ventricular tachycardia

034 004004 (See above SAEs)

Discontinuations for AEs, Epilepsy Trials, Safety Update

In the safety update, Pfizer noted two new subjects who discontinued from epilepsy trials for AEs (Safety Update, p.64). The AEs leading to discontinuation of these two subjects were dizziness, somnolence, and convulsion.

Discontinuation for Adverse Events GAD Trials

GAD Controlled Trials

Pfizer reported that 12.0% (138/1149) of pregabalin-treated subjects and 9.9% (48/484) of placebo-treated subjects discontinued from GAD controlled trials for adverse events (Table 21, Summary of Safety, p.52).[9] The risk of discontinuations due to adverse events at the highest pregabalin dose, 600 mg/day, was approximately two times higher than in the placebo group. At lower doses ranging from 150 mg/day to 450 mg/day, the risk of discontinuations due to adverse events in pregabalin-treated patients was similar to placebo without a consistent dose-response relationship. In the following table, I summarize the events leading to discontinuation of at least 1% of pregabalin GAD subjects and occurring at least twice as frequently when compared to placebo.

FDA Table 12. Adverse Events Leading to Discontinuation of at least 1% of Subjects in the Pregabalin Group and at least Twice as Frequently as the Placebo Group, GAD Controlled Trials

Event	Placebo (n=484)	150 mg/d (n=210)	200 mg/d (n=78)	300 mg/d (n=91)	400 mg/d (n=186)	450 mg/d (n=178)	600 mg/d* (n=406)	All PGB (n=1149)
Overall	48 (9.9%)	13 (6.2%)	7 (9.0%)	3 (3.3%)	18 (9.7%)	19 (10.7%)	78 (19.2%)	138 (12.0%)
Somnolence	6 (1.2%)	1 (0.5%)	2 (2.6%)	0 (0%)	6 (3.2%)	5 (2.8%)	32 (7.9%)	46 (4.0%)
Dizziness	3 (0.6%)	0 (0%)	1 (1.3%)	0 (0%)	3 (1.6%)	7 (3.9%)	18 (4.4%)	29 (2.5%)
Thinking Abnormal	1 (0.2%)	0 (0%)	1 (1.3%)	0 (0%)	3 (1.6%)	3 (1.7%)	6 (1.5%)	13 (1.1%)
Incoordination	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	1 (0.6%)	8 (2.0%)	11 (1.0%)

From Appendix GAD.064 and GAD 065 (Summary of Safety, pp.14314-14333).
*Combines BID and TID dosing regimens

GAD Combined Controlled and Uncontrolled Trials

Pfizer reported that 309/1962 (15.7%) of pregabalin-treated subjects in combined controlled and uncontrolled GAD studies discontinued for adverse events (Appendix GAD.066, Summary of Safety, p.14339). In the table below I identify ~~the~~ adverse events that led to discontinuation of at least 1% of pregabalin-treated subjects in GAD trials.

[9] These rates are based on information reported in the Adverse Event case report form page. Pfizer reported that different rates were obtained when the data was procured from the Patient Status case report form page. Per the Patient Status case report form pages, 11.3% (130/1149) of pregabalin-treated subjects and 9.3% (45/484) of placebo-treated subjects discontinued from GAD controlled trials for adverse events (Table 122, Summary of Safety, p. 216).

FDA Table 13. Adverse Events Leading to Discontinuation of at least 1% of Pregabalin Subjects in the GAD Combined Controlled and Uncontrolled Trials

Adverse event leading to discontinuation	Frequency (n=1962) [no.(%)]
Overall	**309 (15.7%)**
Somnolence	80 (4.1%)
Dizziness	55 (2.8%)
Thinking abnormal	27 (1.4%)
Headache	20 (1.0%)

From Pfizer Appendix GAD.067 (Summary of Safety, pp 14340-14344).

No subjects discontinued from GAD trials for acute hepatic failure, acute renal failure, rhabdomyolysis, blood dyscrasias, toxic epidermal necrolysis, or Stevens Johnson syndrome. Four subjects discontinued for rash, four for SGPT increased, three for syncope, two for generalized edema, two for liver function tests abnormal, and one each for amylase increased, carcinoma, cardiomyopathy, CK increased, face edema, hormone level altered, neoplasm, ovarian cancer, SGOT increased, tachycardia, thrombosis, and urticaria. I summarize those events below.

Rash

021_004026 This 48 year old female developed rash on study day 13 of treatment with pregabalin 600 mg/day. The rash was not described; the investigator considered it to be moderate and related to study medication. Pregabalin was discontinued on study day 14. She was treated for the rash with diphenhydramine on days 14-16 and with loratidine on day 21. The patient was considered recovered on study day 16. Concomitant medications taken within 30 days of rash onset were Estratest (esterified estrogens and methyltestosterone), alendronate, medroxyprogesterone, zolpidem, mometasone, and multivitamin, calcium, and vitamin C supplements.

083_304085 This 64 year old male developed a rash on day 8 of open-label treatment with pregabalin 300 mg/day after receiving placebo in the previous double-blind study. The rash was described as a small rash on the patient's torso, arms, and chest. Study medication was discontinued on day 52 due to the rash and the patient was considered to be recovered from the rash on day 60. The patient was receiving no concomitant medications at the time of rash onset. The investigator classified the rash as mild in intensity.

083_306004 This 24 year old female developed a rash on day 18 of treatment with pregabalin 600 mg/day. The investigator described the rash as being located on the patient's neck, face, and right arm. The rash was not otherwise described. Pregabalin was discontinued on study day 20. The patient was treated with diphenhydramine on study days 20-26. The rash reportedly resolved on study day 24. Concomitant medications at the time of rash onset were paracetamol and mutivitamins. The investigator classified the rash as moderate in intensity.

087_055007 This 43 year old female with a history of seborrheic eczema capitis developed a rash on study day 62 of open-label treatment with pregabalin 400 mg/day. The patient had received venlafaxine in the previous double-blind study. The investigator described the rash as "allergic erythema arms and legs." The patient was treated for the rash with "ureumzalf" cream, sulconazole cream, and sodium chloride creme hydrophyle. Pregabalin was discontinued on study day 139 and the patient recovered on study day 158. The patient also experienced the adverse event of edema on study days 89 through 102. Concomitant medications at the time of rash onset were coal tar, betamethasone, levomenthol, miconazole, and alprazolam.

Urticaria

087_059009 This 75 year old male with a history of atrial fibrillation and "cardiac decompensation" developed urticaria on study day 97 of open-label treatment with pregabalin 400 mg/day. Including 56

days of exposure to pregabalin 400 mg/day in the preceding double-blind study, total exposure to pregabalin at the time of urticaria onset was 153 days. Concomitant medications were digoxin, ibuprofen, acetaminophen, acenocoumarol, and zolpidem. Pregabalin was discontinued on study day 97, the day of urticaria onset. The patient was treated for the urticaria with desloratidine, prednisolone, and clemastine. The patient had not recovered from the urticaria, which the investigator considered to be moderate in intensity, at the time of withdrawal from the study.

Face Edema

087_065008 This 72 year old female with a history of hysterectomy and nephrolithiasis developed face edema (verbatim term: swollen eyes) on study day 3 of double-blind treatment with pregabalin during the titration phase. Assigned to the 600 mg/day dose, she had received 150 mg/day of pregabalin for two days followed by one 300 mg dose prior to developing face edema. She also developed headaches, muscle aches, and tremor on study day 3. Pregabalin was discontinued on study day 4 due to face edema and other adverse events. The face edema, which the investigator considered to be of moderate intensity, resolved on study day 6. Concomitant medications were conjugated estrogens, medrogestone, atorvastatin, Vaseretic (enalapril and hydrochlorothiazide; the patient had been taking this medication since 1988), and Moduretic (amiloride and hydrochlorothiazide). The latter two medications were for "edema prophylaxis" per the patient profile.

Abnormal liver function tests

085_408022 This 18 year old female with a history of exercise-induced asthma, left kidney removal, and migraine headaches developed elevated SGPT (ALT) on day 43 of double-blind study 85. SGOT was also mildly elevated. She received pregabalin at 400 mg/day for 49 days in this study and continued to receive pregabalin in open-label study 84 at doses ranging from 100 to 300 mg/day. The patient's transaminases returned to the normal range on open-label study day 8 while the patient was still receiving pregabalin. Pregabalin was discontinued on day 9 of study 84 due to the elevated SGPT. The patient's only concomitant medication was paracetamol 1000 mg prn for migraine headaches. The following table chronicles the patient's transaminases measured during the course of the studies (total bilirubin and alkaline phosphatase were normal throughout the studies):

Study Day	SGPT (ALT) [ref. range: 9-29]; U/L	SGOT (AST) [ref. range: 12-31]; U/L
-7 (study 85)	16	18
42 (study 85)	68	36
49 (study 85)	67	40
8 (study 84)	27	23
9 (study 84)	Pregabalin discontinued	

088_504004 This 29 year old male with a history of eczema and allergies to pollen, eggplants, and avocados developed an increase in his SGPT (ALT) on study day 35 of open-label treatment with pregabalin at 450 mg/day[10]. His baseline SGPT was slightly above the reference range. His SGPT decreased with each subsequent measurement while still on pregabalin, although it remained above the reference normal range and above his baseline when last measured on study day 49. Pregabalin was discontinued on study day 49; the patient was considered to be recovered from the SGPT increase on day 49 as well. There are no laboratory values measured after study day 49. The patient was not receiving any concomitant medications. The patient also experienced conjunctivitis (study days 4 through 10), leg cramps (study days 8 through 9) and weight gain (study days -17 through 67) during the course of the study and experienced a rise and fall in creatine kinase (not noted by the sponsor), although the CK remained just within the normal range. The following table chronicles the patient's transaminases and CK as measured during the course of the studies; total bilirubin and alkaline phosphatase remained normal throughout the studies:

[10] This patient and the two subsequent patients were in study 088, a randomized withdrawal design relapse prevention study; therefore the open label portion preceded the randomized phase.

Study Day	SGPT (ALT) [ref. range: 10-45]; U/L	SGOT (AST) [ref. range:12-31]; U/L	Creatine kinase (ref. range: 52-336); U/L
-10	52	27	131
35	145	42	181
39	109	39	321
42	104	33	226
49	68	23	184
49	Pregabalin discontinued		

088_507025 This 27 year old female with migraine headaches and a history of ovarian cysts, a total hysterectomy, hip fracture, and partial amputation of her left index finger, developed an increased SGPT (ALT) on study day 49 of open-label treatment with pregabalin at 450 mg/day. SGPT remained increased on study day 51. Pregabalin was discontinued on study day 55. Concurrent adverse events included weight gain of 1.4 kg from study days 14 through 55 and moderate abdominal pain on study days 9 through 20. The patient underwent an ultrasound on study day 13 to further investigate the abdominal pain, the results of which are not reported. Concomitant medications included conjugated estrogens and vitamins B12, B6, and E. The patient was lost to follow-up after withdrawal from the study and there are no laboratory values reported after study day 51. The following table chronicles the patient's transaminases measured during the course of the study:

Study Day	SGPT (ALT) [ref. range: 9-29]; U/L	SGOT (AST) [ref. range: 12-31]; U/L
-9	27	25
49	63	50
51	65	52
55	Pregabalin discontinued	

088_515016 This 21 year old male with mildly elevated AST and ALT at study inception developed SGOT and SGPT increases above his baseline on study day 14 of open-label treatment with pregabalin 450 mg/day. Pregabalin was discontinued due to the SGOT and SGPT increases on study day 19. By study day 33, both SGOT and SGPT levels had decreased to below the patient's baseline values, although SGOT was still above the normal range. The patient was considered to have recovered on study day 33. The patient was taking no concomitant medications at the time of the transaminase elevations. The patient received ibuprofen from study days -8 through -6. Although not noted by the sponsor, the patient's creatine kinase also increased concurrently with the SGOT and SGPT increases. The following table chronicles the patient's transaminases and creatine kinase measured during the course of the study:

Study Day	SGPT (ALT) [ref. range:10-45]; U/L	SGOT (AST) [ref. range:12-31]; U/L	Creatine kinase [ref. range: 52-336]; U/L
-8	86	39	164
14	219	118	492
19	Pregabalin discontinued		
33	68	30	192

088_510092 This 20 year old female with recurrent lower back and neck pain, muscle aches, and headaches developed "liver function tests abnormal" on day 50 of open-label treatment with pregabalin 450 mg/day. Study medication was discontinued on study day 57. The patient also had concurrent elevations in creatine kinase, although this elevation is not reported in the patient profile or the case report form as an adverse event. Elevated at 1144 seven days prior to the start of the study, CK increased to 2513 on study day 50 and decreased somewhat but remained elevated when last reported on study day 71. Concomitant medications included naproxen (5 to 6 tablets prn, per patient profile) and ibuprofen (1200 mg prn, per patient profile). The following table chronicles the patient's SGOT, SGPT, and CK values as measured during the course of the studies:

Study day	SGPT (ALT) [ref. range: 10-45]; U/L	SGOT (AST) [ref. range:12-31]; U/L	Creatine kinase (ref. range: 52-336) ; U/L
-7	42	53	1144
50	158	123	2513
57	149	74	941
57	Pregabalin discontinued		
71	83	55	1278

085_410003 This 27 year old female with a history of asthma, allergies and mildly elevated baseline transaminases developed SGOT and SGPT increases (preferred term: "liver function tests abnormal") above her baseline during double-blind study 85. She received pregabalin 450 mg/day for 48 days in this study. SGPT and SGOT increases above baseline were evident on study day 42, the first day during which the patient had laboratory measurements while receiving pregabalin. During a 23 day interval off pregabalin, the patient's transaminases decreased and then increased again on the first day of open-label pregabalin treatment in study 84. SGPT increased substantially higher than SGOT. The patient received pregabalin 200 mg/day for three days in study 84 prior to discontinuation of pregabalin due to persistently elevated liver function tests. Following pregabalin discontinuation, the patient's transaminases decreased. On study day 7, the last day for which laboratory measurements are available, SGOT had returned to near normal and to close to the patient's measured value prior to receiving pregabalin. SGPT remained elevated above the reference range but had also returned to the patient's baseline value. Concomitant medications were salbutamol, fexofenadine, budesonide, and oral contraceptives. The patient received Dayquil (acetaminophen/dextromethorphan/pseudoephedrine) from eight to four days prior to beginning pregabalin treatment in study 85. The following table chronicles the patient's transaminases measured during the course of the studies:

Study Day	Date	SGPT (ALT) [ref. range: 9-29); U/L	SGOT (AST) [ref. range: 12-31); U/L
-8 (study 85)	12/9/99	99	35
-2 (study 85)	12/15/99	41	21
1 (study 85)	12/17/99	Double-blind pregabalin started	
42 (study 85)	1/27/00	111	74
48 (study 85)	2/2/00	Double-blind pregabalin taper completed	
50 (study 85)	2/4/00	84	33
1 (study 84)	2/25/00	Open-label pregabalin started	
1 (study 84)	2/25/00	185	130
3 (study 84)	2/28/00	Pregabalin discontinued	
7 (study 84)	3/2/00	104	38

Amylase increased

088_509009 This 69 year old male developed elevated serum amylase on day 51 of study 88 during the double-blind phase. In that study, he received pregabalin 450 mg/day for 58 days followed by placebo for 10 days in the double-blind phase. He then entered open-label study 84, during which he received pregabalin at doses ranging from 100 to 400 mg/day. Pregabalin was discontinued on day 46 of study 84 due to the increased amylase. There were no concomitant medications. The patient also experienced nausea beginning on 3/10 (study 88 day 60). There is no reference to the development of clinical pancreatitis. White blood cell count remained within the normal range during the course of the studies. The following table documents the patient's amylase values measured over the course of the studies:

Study day	Date	Amylase (ref. range: 35-115); U/L
-6	1/5/00	145
51	3/1/00	204
57	3/7/00	204
57	3/7/00	Open-label pregabalin ended, patient assigned to double-blind placebo

63	3/13/00	185
67	3/17/00	194
1*	3/18/00	Open-label pregabalin started
5*	3/22/00	221
18*	4/5/00	177
46*	5/2/00	Pregabalin discontinued
53*	5/9/00	179

*study 84. All other study days refer to study 88.

CK increased

083_301019 This 33 year old female with a history of headache and backache developed elevated CK on study day 29 while receiving pregabalin at 450 mg/day during the taper phase. She had been randomly assigned to 600 mg/day pregabalin and had completed 28 days of treatment at that dosage prior to beginning the taper. The patient's CK at baseline as measured on study day -7 had been 198 U/L (reference range: 38-176 U/L). CK increased to 4925 U/L on study day 28. Pregabalin was discontinued due to this AE on study day 30. On study day 35, CK had decreased to 249 and to 178 U/L by study day 42. CK levels continued to fluctuate thereafter; CK was 339 U/L on study day 49, 509 U/L on study day 56, and 169 U/L on study day 70. The patient had the concurrent adverse event of "liver function tests abnormal." Her AST and ALT, which were 13 and 29 at baseline, increased to 40 and 109, respectively, on study day 28. By study day 35, they had decreased to 27 and 35, respectively; on study day 42, they were 18 and 29, respectively. They remained in that range on subsequent study days. Concomitant medications included acetylsalicylic acid, ibuprofen, medroxyprogesterone, oxymetazoline, and loratidine.

Edema

026_004026 This 45 year old female with a history of alcohol abuse developed generalized edema (verbatim term: swollen body) accompanied by loss of appetite, sedation, and legs burning on study day 31 of treatment with pregabalin, 25 days after titrating to a dose of 600 mg/day and one day after tapering to 500 mg/day. The investigator considered the "swollen body" moderate in severity. The patient's weight, which was 59.5 kg on study day -7, increased to 62.7 kg by study day 30. There are no subsequent weight measurements. Urinalysis performed on study day 30 demonstrated no proteinuria. Study medication was discontinued on study day 31 due to generalized edema and the other adverse events. The patient was considered recovered on study day 35. There were no concomitant medications.

088_509024 This 65 year old female with a history of osteoporosis and GERD developed generalized edema (verbatim term: fluid retention) on study day 23 of open-label treatment with pregabalin at 450 mg/day. She also experienced a concurrent adverse event of weight gain; her weight increased from 70.5 kg on study day -7 to 72.7 kg on study day 40. Pregabalin was discontinued on study day 34 for the generalized edema and weight gain as well as decreased libido (coded to the preferred term impotence). Urine protein as measured in the baseline urinalysis on study day -23 was 4 mg/dL (reference range: 1-14 mg/dL) and increased to 7 mg/dL on study day 40. Serum protein at baseline was 6.7 g/dL (reference range: 6.3-7.9 g/dL) and 6.5 g/dL on study day 40. The patient was considered to be recovered from the generalized edema on study day 52. Concomitant medications included raloxifene, various vitamins and supplements (multivitamins, calcium, ascorbic acid, vitamin B, selenium, chromium, vitamin K, magnesium, and carotenoid complex), buspirone, and celecoxib.

088_516009 This 41 year old female with a history of hypothyroidism and migraine headaches developed edema on day 51 of open-label treatment with pregabalin at 450 mg/day after experiencing peripheral edema, for which she was treated with hydrochlorothiazide, from days 23 through 50. Urine protein as measured in the baseline urinalysis on study day -8 was 1 mg/dL (reference range: 1-14 mg/dL) and was unchanged at 1 mg/dL on study day 49. Pregabalin was discontinued due to the edema, which the investigator considered to be severe, on study day 51. The patient recovered on study day 58. Concomitant medications included levothyroxine, rabeprazole, and Excedrin Migraine (acetylsalicylic acid, acetaminophen, and caffeine).

Syncope

087_003009 This 61 year old female assigned to pregabalin 600 mg/day had an adverse event coded to the preferred term syncope from the verbatim term "faint" on study day 1 after receiving pregabalin 150 mg/day during titration. Study medication was discontinued on the same day. The event, which was considered to be mild in intensity, was not otherwise described. The only concomitant medication was diazepam.
088_502052 This 40 year old female with a history of panic disorder, obsessive compulsive disorder, GERD, headaches, myopia, and left eye retinal changes experienced two episodes of syncope beginning on study day 123 of study 88 while receiving double-blind pregabalin 450 mg/day. Pregabalin was discontinued on study day 123 due to the syncope as well as worsened headaches. The patient was considered recovered from the syncope on study day 130. The two syncopal events were not otherwise described. Concomitant medications at the time of syncope onset were acetaminophen, naproxen, and etodolac. Sumatriptan was started on study day 123 for the patient's headaches.
088_502059 This 27 year old female with a history of endometriosis, headaches, and vulvar vestibulitis developed syncope and lightheadedness on study day 3 of open-label pregabalin at 300 mg/day. The day prior, the patient had experienced an adverse event of "spacey feeling." Study medication was discontinued on study day 3 for the syncope and lightheadedness, and the patient was considered to be recovered on the same day. Concomitant medications were Excedrin (acetaminophen and caffeine) and oral contraceptives.

Tachycardia

085_410017 This 56 year old male with a history of skin cancer developed tachycardia of an unspecified nature on day 10 of open-label treatment with pregabalin 300 mg/day. He had received pregabalin 400 mg/day in the previous double-blind study and had accrued 59 days of exposure to pregabalin prior to tachycardia onset. Pregabalin was discontinued due to tachycardia as well as ataxia (verbatim term: balance trouble) on study day 15. The tachycardia resolved on study day 15. The patient's heart rate and EKG findings at any time during the period of tachycardia are not recorded on the patient profile. There were no concomitant medications.

Cardiomyopathy

025_004021 This 39 year old male diagnosed with cardiomyopathy during treatment with pregabalin is discussed in the SAE section.

Thrombosis

083_306077 This 56 year old female with a history of obesity and headaches was hospitalized for left leg thrombosis on study day 27 of open-label treatment with pregabalin. She had been receiving pregabalin 300 mg/day for 20 days prior to the diagnosis of thrombosis. She had received placebo for 34 days in the previous double-blind study 83. Pregabalin was discontinued on study day 27, and the patient was considered recovered from her thrombosis on study day 33. Concomitant medications were medroxyprogesterone actetate/estrogens conjugated, acetylsalicylic acid/caffeine/paracetamol, fexofenadine, and celecoxib. Concurrently, the patient experienced the adverse event of cholelithiasis, which was diagnosed on study day 23 and considered resolved on study day 56.

Carcinoma

087_055009 This patient diagnosed with an unspecified adenocarcinoma, which was also a serious adverse event, is described elsewhere

Neoplasm

087_079017 This 54 year old female diagnosed with an angioleiomyoma of her right kidney on study day 292 of open-label pregabalin is discussed in greater detail elsewhere. This adverse event was also an SAE.

Ovarian cancer

088_516022 This 64 year old female diagnosed with ovarian cancer during treatment with open-label pregabalin is discussed elsewhere

Discontinuations for Adverse Events, Safety Update

In their Safety Update, Pfizer reported that there were no additional withdrawals due to adverse events in either the controlled or the uncontrolled GAD studies after the original NDA cutoff date.

4.6.4 Adverse Events in the Integrated Safety Database

Adverse Events Controlled Trials

Pfizer reported that 79.3% (4369/5508) of pregabalin-treated patients experienced adverse events during the controlled trials included in the NDA integrated safety database compared with 64.7% (1542/2384) of placebo-treated patients. The following table summarizes the adverse events experienced by at least 2% of pregabalin-treated patients that occurred statistically significantly more frequently in the overall group of patients treated with pregabalin compared with placebo-treated patients (p=.05).

FDA Table 14. Adverse Events Occurring in =2% of Pregabalin-Treated Patients by Decreasing Frequency; Controlled Trials in NDA Integrated Safety Database (All Indications)

Preferred Term	Placebo (n=2384); % (no.)	Pregabalin 150 mg/d (n=1164); % (no.)	Pregabalin 200 mg/d (n=208); % (no.)	Pregabalin 300 mg/d (n=1224); % (no.)	Pregabalin 400 mg/d (n=360); % (no.)	Pregabalin 450 mg/d (n=501); % (no.)	Pregabalin 600 mg/d (n=1802); % (no.)	Pregabalin; all doses and regimens (n=5508); % (no.)
Dizziness	8.7% (208)	15.4% (179)	30.3% (63)	30.4% (372)	33.1% (119)	40.5% (203)	35.9% (647)	29.2% (1606)
Somnolence	7.7% (183)	13.1% (152)	29.3% (61)	20.6% (252)	24.7% (89)	28.7% (144)	28.2% (508)	22.2% (1225)
Dry Mouth	3.4% (82)	5.4% (63)	15.9% (33)	6.8% (83)	11.7% (42)	14.0% (70)	11.0% (198)	9.1% (499)
Asthenia	5.2% (124)	6.0% (70)	8.7% (18)	5.6% (68)	9.4% (34)	6.2% (31)	9.2% (165)	7.2% (397)
Amblyopia	2.1% (49)	4.2% (49)	4.8% (10)	5.6% (68)	5.8% (21)	7.2% (36)	8.9% (161)	6.4% (351)
Peripheral edema	1.8% (42)	4.8% (56)	1.9% (4)	8.9% (109)	1.9% (7)	5.0% (25)	7.3% (131)	6.1% (336)
Weight gain	0.8% (19)	3.5% (41)	2.4% (5)	5.1% (63)	5.3% (19)	6.6% (33)	8.2% (148)	5.6% (311)
Thinking abnormal	1.6% (38)	2.3% (27)	6.7% (14)	2.9% (35)	10.6% (38)	7.0% (35)	8.2% (147)	5.4% (300)
Constipation	2.2% (53)	3.4% (39)	3.4% (7)	4.3% (53)	7.5% (27)	6.0% (30)	5.6% (101)	4.8% (262)
Ataxia	1.0% (24)	2.0% (23)	3.4% (7)	3.6% (44)	2.5% (9)	4.0% (20)	8.2% (148)	4.7% (260)
Accidental injury	2.9% (69)	3.1% (36)	1.9% (4)	3.7% (45)	2.2% (8)	3.8% (19)	5.6% (101)	4.2% (233)
Incoordination	0.7% (17)	1.0% (12)	5.3% (11)	2.5% (31)	7.5% (27)	8.0% (40)	5.3% (95)	4.0% (221)
Euphoria	0.5% (11)	0.8% (9)	5.8% (12)	4.4% (54)	6.1% (22)	9.8% (49)	3.2% (57)	3.7% (205)

Amnesia	1.0% (24)	1.5% (18)	1.9% (4)	2.2% (27)	2.5% (9)	3.0% (15)	4.4% (79)	2.8% (156)
Confusion	0.5% (13)	1.7% (20)	1.4% (3)	2.5% (30)	2.5% (9)	4.2% (21)	3.7% (67)	2.7% (151)
Increased appetite	0.8% (20)	1.5% (17)	2.9% (6)	1.8% (22)	2.8% (10)	3.6% (18)	3.0% (54)	2.3% (128)
Flatulence	1.2% (29)	1.8% (21)	3.8% (8)	1.6% (19)	1.7% (6)	3.8% (19)	2.7% (48)	2.3% (127)
Tremor	1.3% (31)	1.1% (13)	1.4% (3)	1.5% (18)	1.9% (7)	0.8% (4)	4.3% (77)	2.3% (127)
Diplopia	0.5% (11)	1.5% (17)	0.5% (1)	2.0% (24)	0.6% (2)	1.4% (7)	3.2% (58)	2.0% (111)

From Pfizer Table 7 (Summary of Safety, p. 28).

Dizziness and somnolence were the two most common adverse events in pregabalin-treated patients, occurring in 29.2% and 22.3% of pregabalin-treated patients, respectively. Risks for these events in pregabalin-treated patients relative to placebo-treated patients were 3.4 for dizziness and 2.9 for somnolence. Adverse events that occurred in at least 5% of pregabalin-treated patients and had a statistically significantly higher incidence in pregabalin-treated patients than in placebo-treated patients were dry mouth, asthenia, amblyopia, peripheral edema, weight gain, and thinking abnormal.

AEs by Dosing Regimen

In many of the safety presentations that stratify by dose, the dose is presented in mg/day but these categories are not necessarily based on a single dosing regimen. In some cases the dose was administered as BID or TID regimens. Pfizer pooled the different regimens for given doses in summary presentations after concluding that pregabalin exposure parameters were similar with bid and tid administration based on their pharmacokinetic analyses (page 25, Summary of Clinical Safety). Pfizer did present data for bid and tid regimens separately in the appendix tables. To look for differences in AE risks for different dosing regimens, I reviewed an AE table (Appendix ALL.13) where dose in mg/day was presented also stratified by the regimen (BID, TID). The following table includes some of the more commonly occurring AEs as well as AEs that appeared to have consistent differences in risk when comparing the BID and TID regimens (Ex. risk among BID higher than TID). There were few instances where there were consistent differences between the AEs risks for BID and TID regimens, and in those cases the magnitude of the differences tended to be small. This analysis supports Pfizer's decision to present data by dose in mg/day but not to further stratify by dosing regimen.

FDA Table 15. Comparison of selected AE risks by dose and dosing regimen, NDA integrated controlled trials database

AE	PBO N=2384	150 BID n=357	150 TID n=807	300 BID n=460	300 TID n=764	600 BID n=551	600 TID n=1251
Face edema	0.4% (9)	1.7% (6)	0.4% (3)	1.1% (5)	0.5% (4)	2.9% (16)	0.7% (9)
Gen edema	0.1% (2)	0.6% (2)	0.5% (4)	1.1% (5)	1% (8)	0.7% (4)	0.9% (11)
Peripheral edema	1.8% (42)	9.2% (33)	2.9% (23)	11.1% (51)	7.6% (58)	8.2% (45)	6.9% (86)
Syncope	0.2% (5)	0.6% (2)	0.2% (2)	0.9% (4)	0.3% (2)	0.5% (3)	0.2% (2)
Hypertension	1.1% (27)	1.4% (5)	0.7% (6)	0.7% (3)	0.4% (3)	1.5% (8)	0.8% (10)
Dry mouth	3.4% (82)	3.4% (12)	6.3% (51)	4.8% (22)	8% (61)	9.1% (50)	11.8% (148)
Nausea	7% (167)	2.2% (8)	6.1% (49)	2.2% (10)	5.9% (45)	5.4% (30)	7% (87)
Dyspepsia	2.7% (65)	0.6% (2)	2.2% (18)	0.9% (4)	2.1% (16)	0.7% (4)	2% (25)

Dizziness	8.7% (208)	15.7% (56)	15.2% (123)	26.1% (120)	33% (252)	34.7% (191)	36.5% (456)
Somnolence	7.7% (183)	11.5% (41)	13.8% (111)	12% (55)	25.8% (197)	22.9% (126)	30.5% (382)
Think abnl.	1.6% (38)	2.5% (9)	2.2% (18)	2.6% (12)	3% (23)	6.7% (37)	8.8% (110)
Ataxia	1% (24)	3.6% (13)	1.2% (10)	5.7% (26)	2.4% (18)	7.6% (42)	8.5% (106)
Incoordin.	0.7% (17)	1.7% (6)	0.7% (6)	1.3% (6)	3.3% (25)	4.4% (24)	5.7% (71)
Euphoria	0.5% (11)	0.3% (1)	1% (8)	1.3% (6)	6.3% (48)	0.9% (5)	4.2% (52)
Amblyopia	2.1% (49)	2.2% (8)	5.1% (41)	3.7% (17)	6.7% (51)	7.4% (41)	9.6% (120)
Diplopia	0.5% (11)	2% (7)	1.2% (10)	2.2% (10)	1.8% (14)	4.4% (24)	2.7% (34)

Summary of Safety, Appendix ALL.13

Pfizer noted that because titration schedule, study duration, and patient population varied across indications, the relationship between adverse events and dose is difficult to interpret for the controlled trials in the integrated safety database as a whole.[11] Despite these limitations, the sponsor does make observations regarding dose-response relationships for the two most common adverse events. Although still statistically significantly more frequent than in the placebo group, dizziness and somnolence were substantially less frequent in the 150 mg/day dose group than in all higher dose groups. At doses =200 mg/day, however, dizziness and somnolence demonstrated no clear dose-response relationship. In all dose groups studied, dizziness and somnolence occurred significantly more frequently than in the placebo group.

Many of the other adverse events in the table above also demonstrated a pattern of no clearly linear dose-response relationship at doses =200 mg/day. Amnesia and amblyopia, in contrast, did appear to demonstrate a dose-response relationship. Weight gain and ataxia also demonstrated a dose-response relationship that was slightly less consistent. Tremor and accidental injury had substantially higher incidences in the 600 mg/day dose group than all other dose groups. Only in this dose group did tremor and accidental injury occur statistically significantly more frequently than in the placebo group.

In addition to presenting adverse event incidences according to assigned pregabalin dose groups, Pfizer presented the incidences of adverse events by dose at onset of the event.[12] When analyzed in this manner, the incidence distributions of many adverse events, including dizziness and somnolence, shifted to dose ranges lower than the randomized dose. The majority of patients who experienced dizziness and somnolence had the onset of the relevant event at pregabalin doses ranging from 150-449 mg/day. Many of the other common adverse events demonstrated a similar bell-shaped distribution curve,

[11] The frequency of adverse events for events occurring in at least 2% of pregabalin-treated patients by dose groups is presented in Table 7 (Summary Safety, p.28). The frequency of all adverse events by dose groups is presented in Appendix ALL.025 (Summary Safety, pp. 2354-2405).

[12] These data are presented in Table 14 (Summary of Safety, p.35) and Appendix ALL.038 (Summary of Safety pp. 2988-3014).

reflecting that the majority of patients experienced adverse event onset at doses between 150 and 449 mg/day, with fewer having the onset of the event at doses <150 mg/day or =450 mg/day. Incidences of onset at doses ranging from 1-149 mg/day were <15% for all adverse events that occurred in at least 4% of pregabalin-treated patients.

Notably, several adverse events had relatively high incidences of onset at doses of at least 600 mg/day—25.4% (89/351) of patients who experienced amblyopia had its onset at doses =600 mg/day; 31.8% (107/336) of patients who experienced peripheral edema had its onset at doses =600 mg/day; 27.9% (73/262) of patients who experienced constipation had its onset at doses =600 mg/day; 37.9% (118/311) of patients who experienced weight gain had its onset at doses =600 mg/day; 27.3% (82/300) of patients who experienced thinking abnormal had its onset at doses =600 mg/day; 41.2% (107/260) of patients who experienced ataxia had its onset at doses =600 mg/day; and 37.8% (88/233) of patients who experienced accidental injury had its onset at doses =600 mg/day.

These data demonstrate that adverse events frequently began prior to a patient reaching his or her assigned pregabalin dose, which exposes a central difficulty of assessing dose-response relationships for adverse events associated with pregabalin.

Adverse Events by Intensity

In the NDA controlled studies, 8.0% (192/2384) of placebo-treated patients and 11.0% (608/5508) of pregabalin-treated patients had at least one severe adverse event.[13] Somnolence and dizziness were the most frequently reported severe adverse events. Severe somnolence was experienced by 2.1% (115/5508) of pregabalin-treated patients and 0.2% (4/2384) of placebo-treated patients. Severe dizziness was experienced by 2.0% (108/5508) of pregabalin-treated patients and 0.3% (7/2384) of placebo-treated patients. Other severe adverse events that occurred more frequently among pregabalin-treated patients than placebo-treated patients and in at least 15 pregabalin-treated patients were severe asthenia (which occurred in 0.6% [32/5508] of pregabalin-treated patients and 0.3% [6/2384] of placebo-treated patients), severe accidental injury (which occurred in 0.4% [22/5508] of pregabalin-treated patients and 0.0% [1/2384] of placebo-treated patients), severe thinking abnormal (which occurred in 0.4% [22/5508] of pregabalin-treated patients and 0.3% [6/2384] of placebo-treated patients), severe ataxia (which occurred in 0.3% [18/5508] of pregabalin-treated patients and 0.1% [2/2384] of placebo-treated patients), and severe dry mouth (which occurred in 0.3% [15/5508] of pregabalin-treated patients and 0.2% [4/2384] of placebo-treated patients).

Time to Onset and Duration of Adverse Events

Pfizer presents the median time to onset of selected adverse events occurring in all NDA controlled trials by dose group in Table 13 (Summary of Safety, p.34). Dizziness and somnolence had a median time to onset of one to two days in all dose groups. Median

[13] Pfizer provides a tabulation by dose of adverse events in controlled studies judged by investigators to be severe in Table 11 (Summary of Safety, p.32) and Appendix ALL.032 (page 2583, Summary of Clinical Safety).

time to onset for these events in the placebo group was three days for both events. Weight gain and peripheral edema had much longer median times to onset, ranging from five to 21 days for weight gain and 13 to 37 days for peripheral edema. Median time to onset of weight gain for the 0.8% (19/2384) of patients who experienced this adverse event in the placebo group was 16 days, whereas median time to onset of peripheral edema for the 1.8% (42/2384) of patients who experienced this adverse event in the placebo group was 24 days. There was no clear relationship between increasing dose and decreasing median time to adverse event onset for any of the adverse events listed in Table 13.

Pfizer presents the duration of adverse events for double-blind completers of the NDA controlled studies in Appendix ALL.044 (Summary of Safety, pp. 3090-3116). They note that since the duration of the controlled studies varied by indication, data regarding adverse event duration in which all controlled studies are pooled are difficult to interpret. Moreover, these analyses represent adverse event duration only in those patients who were able to tolerate the adverse event enough to remain on pregabalin. Patients with more severe adverse events may have been more likely to discontinue; such discontinuations complicate any interpretation of adverse event duration.

To further examine duration for the two most frequent adverse events, Pfizer presents flowcharts delineating the course of patients who experienced dizziness and somnolence in Figures 1 and 2 and Appendices ALL.046-ALL.048 (Summary of Safety pp. 36-37 and 3131-3146). Of the 5507 patients treated with pregabalin, 29% (1606/5507) experienced the adverse event of dizziness. 14% (223/1606) of these patients ultimately withdrew due to dizziness and 1383 (86%) did not withdraw from the study due to this adverse event. 69% (950/1383) of these patients who did not withdraw had resolution of dizziness prior to their last dose of pregabalin. In contrast, 9% (208/2384) of patients treated with placebo experienced the adverse event of dizziness. 7% (14/208) of these patients ultimately withdrew and 93% (194/208) did not withdraw due to dizziness. 67% (130/194) of these patients who did not withdraw had resolution of their dizziness prior to their last dose of pregabalin.

22% (1225/5508) of pregabalin-treated patients experienced somnolence. 16% (191/1225) of these patients ultimately withdrew due to somnolence, while 84% (1034/1225) continued in the study despite somnolence. 54% (560/1034) of these patients who continued in the study had resolution of their somnolence prior to the last dose of pregabalin, a smaller percentage of patients than had dizziness resolution prior to the last dose of pregabalin. In contrast, 8% (183/2384) of placebo-treated patients experienced somnolence as an adverse event. 4% (7/183) of these patients withdrew due to somnolence while 96% (176/183) continued in the study despite somnolence. 51% of these patients (89/176) had resolution of their somnolence prior to the last dose of pregabalin.

For both dizziness and somnolence, the percentage of patients who did not have resolution of the adverse event was greatest in the highest pregabalin dose group (600 mg/day). The following table summarizes the percentage of pregabalin- and placebo-

patients who experienced dizziness or somnolence and did not have resolution of the adverse event prior to their last dose of pregabalin:

FDA Table 16. Percentage of Patients by Dose Group without Resolution of Dizziness or Somnolence; NDA Controlled Studies (All Indications)

Adverse Event	Placebo	Pregabalin dose group (mg/day)							
		50	75	150	200	300	400	450	600
Dizziness	33% (64/194)	38% (3/8)	20% (3/15)	32% (51/157)	16% (10/61)	29% (93/326)	28% (31/109)	24% (43/181)	38% (199/526)
Somnolence	49% (87/176)	29% (2/7)	20% (2/10)	45% (64/141)	40% (21/53)	40% (87/215)	47% (38/81)	40% (51/126)	52% (209/401)

From Pfizer Appendix ALL.45 (Summary of Safety, pp. 3117-3125) and Appendix ALL.47 (Summary of Safety, pp. 3132-3140).

Adverse Events by Age

Pfizer presents adverse events by gender, menopausal status, and race for each indication individually, although not for all studies pooled. They present adverse events by age for all controlled studies pooled as well as each indication individually. Age distribution varied considerably across indications. The majority of patients =65 in the safety database were from the neuropathic pain trials. Of the 718 pregabalin-treated patients aged 65-74 in controlled trials, 528 (73.5%) were participants in neuropathic pain trials. Of the 487 pregabalin-treated patients aged =75 in controlled trials, 452 (92.8%) were participants in neuropathic pain trials. Adverse event data by age for all controlled studies are summarized in Table 26 (Summary of Safety, p. 70) and Appendix ALL.123 (Summary of Safety pp. 7215-7266). I calculated excess and relative risks by age for selected common adverse events of interest in the controlled study population. The following table summarizes Pfizer's data and my risk calculations:

FDA Table 17. Relative Risks for Adverse Events of Interest by Age; Controlled Trials in Integrated Safety Database (All Indications)[14]

Adverse Event Age group	Placebo	Pregabalin	Excess risk	Relative risk
Dizziness				
All patients	8.7%	29.2%	20.5%	3.4

[14] Events in table are arranged in order of decreasing frequency in the overall population of pregabalin-treated patients. The table includes all events that occurred in at least 5.0% of pregabalin-treated patients and significantly more frequently than in placebo-treated patients. In addition, the table includes ataxia, accidental injury, amnesia, and confusion, as these were common adverse events of clinical interest that occurred at least twice as frequently in pregabalin-treated patients as in placebo-treated patients. In one case in which there were no events in the placebo group I counted one event to allow for a relative risk calculation. The result is an underestimation of the relative risk for pregabalin in this case. This case is identified by an asterisk in the table.

	(208/2384)	(1606/5508)		
<65[15]	8.9% (160/1787)	29.0% (1246/4303)	20.1%	3.3
65-74	7.1% (26/367)	31.9% (229/718)	24.8%	4.5
=75	9.6% (22/230)	26.9% (131/487)	17.3%	2.8
Somnolence				
All patients	7.7% (183/2384)	22.2% (1225/5508)	14.5%	2.9
<65	8.7% (156/1787)	23.4% (1008/4303)	14.7%	2.7
65-74	4.4% (16/367)	18.5% (133/718)	14.1%	4.2
=75	4.8% (11/230)	17.2% (84/487)	12.4%	3.6
Dry mouth				
All patients	3.4% (82/2384)	9.1% (499/5508)	5.7%	2.7
<65	3.9% (69/1787)	9.3% (401/4303)	5.4%	2.4
65-74	2.2% (8/367)	8.4% (60/718)	6.2%	3.8
=75	2.2% (8/230)	7.8% (38/487)	5.6%	3.5
Amblyopia				
All patients	2.1% (49/2384)	6.4% (351/5508)	4.3%	3.0
<65	2.1% (38/1787)	6.2% (267/4303)	4.1%	2.9
65-74	1.1% (4/367)	7.1% (51/718)	6.0%	6.4
=75	3.0% (7/230)	6.8% (33/487)	3.8%	2.3
Peripheral edema				
All patients	1.8% (42/2384)	6.1% (336/5508)	4.3%	3.4
<65	1.3% (23/1787)	4.3% (186/4303)	3.0%	3.3
65-74	3.3% (12/367)	12.1% (87/718)	8.8%	3.7
=75	3.0% (7/230)	12.9% (63/487)	9.9%	4.3
Weight gain				
All patients	0.8% (19/2384)	5.6% (311/5508)	4.8%	7.0
<65	0.9% (16/1787)	6.1% (263/4303)	5.2%	6.8
65-74	0.5% (2/367)	4.2% (30/718)	3.7%	8.4
=75	0.4% (1/230)	3.7% (18/487)	3.3%	9.2
Thinking abnormal				
All patients	1.6% (38/2384)	5.4% (300/5508)	3.8%	3.4
<65	1.8% (33/1787)	6.3% (273/4303)	4.5%	3.5
65-74	0.3% (1/367)	2.8% (20/718)	2.5%	9.3
=75	1.7% (4/230)	1.4% (7/487)	n/a	0.8
Ataxia				
All patients	1.0% (24/2384)	4.7% (260/5508)	3.7%	4.7
<65	1.0% (18/1787)	4.6% (200/4303)	3.6%	4.6

[15] This age group includes six placebo-treated patients younger than 18 and 14 pregabalin-treated patients younger than 18. These patients are from the epilepsy controlled trials.

65-74	0.5% (2/367)	4.9% (35/718)	5.4%	9.8
=75	1.7% (4/230)	5.1% (25/487)	3.4%	3.0
Accidental injury				
All patients	2.9% (69/2384)	4.2% (233/5508)	1.3%	1.4
<65	3.2% (58/1787)	4.1% (177/4303)	0.9%	1.3
65-74	1.6% (6/367)	3.9% (28/718)	2.3%	2.4
=75	2.2% (5/230)	5.7% (28/487)	3.5%	2.6
Amnesia				
All patients	1.0% (24/2384)	2.8% (156/5508)	1.8%	2.8
<65	1.3% (23/1787)	2.5% (135/4303)	1.2%	1.9
65-74	0.3% (1/367)	1.9% (14/718)	1.6%	6.3
=75	.4% (1/230)*	1.4% (7/487)	1.0%	3.5
Confusion				
All patients	0.5% (13/2384)	2.7% (151/5508)	2.2%	5.4
<65	0.4% (8/1787)	2.5% (108/4303)	2.1%	6.2
65-74	0.8% (3/367)	3.3% (24/718)	2.5%	4.1
=75	0.9% (2/230)	3.9% (19/487)	3.0%	4.3

From Pfizer Appendix ALL.123, Summary of Safety, pp. 7215-7266.

The relative risks associated with pregabalin treatment compared to placebo in the 65-74 year age group were higher than the risks associated with pregabalin treatment compared to placebo for all patients irrespective of age for all of the adverse events listed in the table above except confusion. The relative risks for confusion associated with pregabalin in the 65-74 year age group and the oldest age group were lower than the relative risks associated with pregabalin in the overall group and those patients younger than 65. For peripheral edema, weight gain, and accidental injury, a pattern was evident in which relative risks associated with pregabalin compared to placebo increased with increasing age. In contrast, for dizziness, somnolence, dry mouth, thinking abnormal, ataxia, and amnesia, the relative risk associated with pregabalin in the oldest age group was lower than for patients in the 65-74 year age group.

For many adverse events listed above, the effect modification by age was modest. For amblyopia, thinking abnormal, ataxia, and amnesia, the effect modification by age was more striking. For these adverse events, the relative risk associated with pregabalin in patients aged 65-74 was at least twice the relative risk observed for the overall population of pregabalin-treated patients. There was only one instance in which patients in an age category had a lower risk of an adverse event than was observed in placebo-treated patients in that age group; pregabalin-treated patients older than 74 had a risk of thinking abnormal that was slightly lower than the risk observed in placebo-treated patients older than 74. This observation was based on few events, however, and may not be a strong signal for effect modification for this event in this age group.

Adverse Events, Safety Update; Controlled Trials

In their four month safety update, Pfizer provided updated information regarding adverse events in controlled trials. In the placebo-treated group, there were 65 new patients at

risk and 29 new adverse events. In the pregabalin-treated group, there were 273 new patients at risk and 195 new adverse events. Neither the overall risk of adverse events in the pregabalin- and placebo-treated groups nor the risk of the most common adverse events was substantially altered by the incorporation of updated adverse event information. In the appendix, I have included a table summarizing the risk of adverse events occurring in =2% of pregabalin-treated patients, comparing the risks before and after the incorporation of updated data.

Dizziness and somnolence remained the most frequent adverse events by a large margin; the relative risk associated with pregabalin was 3.4 for dizziness and 2.9 for somnolence. Other events with pregabalin-associated relative risks =2 were constipation (relative risk associated with pregabalin=2.0); dry mouth (relative risk associated with pregabalin=2.5); amnesia (relative risk associated with pregabalin=2.8); increased appetite (relative risk associated with pregabalin=2.9); amblyopia (relative risk associated with pregabalin=3.1); thinking abnormal (relative risk associated with pregabalin=3.3); peripheral edema (relative risk associated with pregabalin=3.4); confusion (relative risk associated with pregabalin=4.5); ataxia (relative risk associated with pregabalin=4.6); diplopia (relative risk associated with pregabalin=5.0); incoordination (relative risk associated with pregabalin=5.6); weight gain (relative risk associated with pregabalin=6.7); and euphoria (relative risk associated with pregabalin=9.0).

I reviewed the preferred terms for all adverse events experienced by pregabalin-treated patients in controlled trials through the Safety Update to identify the risks for less frequent but potentially important adverse events. All adverse events are presented by dose and body system in Appendix ALL.023 (Summary of Safety pp. 2236-2290) for the NDA and in Appendix ALL.10 (Safety Update, pp. 165-194) for the Safety Update. I identified the following adverse events of interest in pregabalin-treated patients:

FDA Table 18. Events of Interest in Pregabalin- and Placebo-Treated Patients through the Safety Update; Controlled Studies (All Indications)

Preferred Term	Placebo (n=2449); % ,(no.)	Pregabalin; all doses and regimens (n=5781); % ,(no.)
Generalized edema	0.1% (2)	0.7% (39)
Edema	0.3% (8)	1.1% (64)
AV block	0.0% (1)	0.0% (2)
AV block first degree	0.0% (1)	0.2% (10)
AV block second degree	0% (0)	0.0% (2)
Heart block	0% (0)	0.0% (1)
Ventricular tachycardia	0% (0)	0.0% (1)
Pancreatitis	0.0% (1)	0.0% (2)
Cholelithiasis	0.0% (1)	0.1% (3)
Cholecystitis	0% (0)	0.1% (5)
Thrombocytopenic purpura	0% (0)	0.0% (1)
Purpura	0% (0)	0.0% (1)

Coagulation disorder	0% (0)	0.0% (2)
Myopathy[16]	0% (0)	0.0% (2)
Acute kidney failure	0% (0)	0.0% (1)
Hepatorenal syndrome	0% (0)	0.0% (1)
Suicide attempt	0% (0)	0.1% (3)

From Pfizer Appendix ALL.10 (Safety Update, pp. 165-194,).

There were no adverse events coded as liver failure, aplastic anemia, Stevens Johnson syndrome, or toxic epidermal necrolysis.

Adverse Events Combined Controlled and Uncontrolled Trials

In the combined controlled and uncontrolled studies in the NDA integrated safety database, 89% (7711/8666) of patients treated with pregabalin had adverse events. Dizziness and somnolence were the two most frequently occurring adverse events, as they were in the controlled studies. Dizziness occurred in 33.5% (2902/8666) of patients and somnolence occurred in 26.8% (2325/8666) of patients. They each occurred substantially more frequently than any other adverse event. The third most frequently occurring adverse event, infection, occurred in 16.0% of patients. The following table summarizes the adverse events that occurred in at least 3% of patients:

FDA Table 19. Adverse Events Occurring in =3% of Pregabalin-Treated Patients by Decreasing Frequency; Controlled and Uncontrolled Trials in NDA Integrated Safety Database (All Indications)

Adverse event Preferred Term	% (no.) N=8666	Adverse event Preferred Term	% (no.) N=8666
Dizziness	33.5% (2902)	Amnesia	5.1% (442)
Somnolence	26.8% (2325)	Euphoria	4.9% (423)
Infection	16.0% (1385)	Back pain	4.8% (419)
Headache	15.8% (1368)	Nervousness	4.6% (401)
Weight gain	12.2% (1059)	Rash	4.6% (396)
Accidental injury	11.6% (1003)	Depression	4.6% (395)
Asthenia	11.2% (973)	Pharyngitis	4.1% (354)
Peripheral edema	9.9% (860)	Sinusitis	4.0% (349)
Nausea	9.5% (824)	Confusion	4.0% (344)
Pain	9.4% (812)	Tremor	4.0% (344)
Dry mouth	9.3% (806)	Abdominal pain	4.0% (343)
Amblyopia	8.9% (773)	Dyspepsia	3.8% (325)
Thinking abnormal	8.3% (716)	Diplopia	3.5% (305)
Flu syndrome	6.9% (601)	Urinary tract infection	3.5% (303)

[16] Myopathy was the preferred term to which rhabdomyolysis was coded. Rhabdomyolysis is the only verbatim term listed for myopathy in the coding dictionary found in Appendix ALL.010 (Summary of Safety, p. 767).

Ataxia	6.7% (577)	Vomiting	3.4% (293)
Constipation	6.3% (544)	Rhinitis	3.3% (283)
Diarrhea	5.9% (510)	Flatulence	3.2% (277)
Insomnia	5.8% (501)	Increased appetite	3.2% (272)
Incoordination	5.6% (482)	Chest pain	3.1% (270)

From Pfizer Table 9 (Summary of Safety, p. 30) and Appendix ALL.029 (Summary of Safety, pp. 2511-2540).

Adverse Events Combined Controlled and Uncontrolled Trials; Safety Update

In all controlled and uncontrolled studies combined, there were 1617 patients at risk for new events; the majority of these patients were from neuropathic pain trials.[17] Pfizer summarizes updated adverse event information by body system in Appendix ALL.12 (Safety Update, pp. 223-255) and by decreasing frequency in Appendix ALL.13 (Safety Update, pp. 256-287). No substantial changes resulted from the incorporation of data from the safety update. In the appendix, I have included a table summarizing adverse events occurring in at least 3% of pregabalin-treated patients, comparing frequencies of adverse events in the original NDA with frequencies of adverse events incorporating data from the safety update.

I reviewed the preferred terms for all adverse events in the controlled and uncontrolled trials through the Safety Update to identify less frequent adverse events of potential interest. All adverse events are presented by body system in Appendix ALL.028 (Summary of Safety pp. 2480-2510) for the NDA and in Appendix ALL.12 (pages 223-255, Safety Update) for the Safety Update. I identified the following adverse events of interest in pregabalin-treated patients:

FDA Table 20. Events of Interest in Pregabalin-Treated Patients through the Safety Update; Controlled and Uncontrolled Studies (All Indications)

Preferred Term	Pregabalin; all doses and regimens (n=9278); % ,(no.)
Generalized edema	1.1% (102)
Edema	1.6% (147)
AV block	0.1% (5)
AV block complete	0.0% (1)
AV block first degree	0.2% (15)
AV block second degree	0.0% (4)
Heart block	0.0% (2)
Ventricular tachycardia	0.0% (2)

[17] Of the 1617 patients with the potential to contribute new adverse event data, 958 were from neuropathic pain trials (597 from diabetic neuropathy trials and 361 from postherpetic neuralgia trials), 344 from epilepsy trials, 14 from GAD trials, 21 from "other" chronic pain trials, and 280 from "other" psychiatry trials. See Table 1 (Safety Update, p. 11) for a complete description of the number of pregabalin- and placebo-treated patients from each indication contributing data to the original NDA and the safety update.

QT interval prolonged	0.0% (4)
Pancreatitis	0.1% (8)
Necrotizing pancreatitis	0.0% (1)
Cholelithiasis	0.3% (26)
Cholecystitis	0.2% (19)
Thrombocytopenic purpura	0.0% (2)
Purpura	0.0% (3)
Coagulation disorder	0.0% (2)
Myopathy[18]	0.0% (4)
Liver damage	0.0% (1)
Acute kidney failure	0.1% (9)
Kidney failure	0.0% (3)
Hepatorenal syndrome	0.0% (1)
Suicide attempt	0.1% (12)
Erythema nodusum	0.0% (1)
Stevens Johnson syndrome	0.0% (1)

From Pfizer Appendix ALL.12 (Safety Update, pp. 223-255).

The hepatorenal syndrome AE was not reported as an SAE and did not lead to discontinuation. Given the potential significance of such an event, we requested a narrative from Pfizer. That information is summarized below.

155-003004 This 54 year old male with neuropathy and diabetes mellitus who was hospitalized on study day 45 (post treatment day 7) for gangrenous cholecystitis. The narrative reported that during surgery (cholecystectomy) he was found to suffer from cholelithiasis and cirrhosis. The narrative also states that the subject developed hepatorenal syndrome and hematemesis and he was diagnosed with reflux esophagitis during the hospitalization. The narrative reported that the subject was recovered on study day 63 (post treatment day 25). Concomitant medications included aspirin, insulin, metformin, and ramipril.

Epilepsy Adverse Events

Controlled Trials

Pfizer reported that 84% (637/758) of pregabalin subjects and 70.1% (206/294) of placebo subjects experienced one or more treatment emergent AEs during NDA epilepsy controlled trials (Appendix Epilepsy Table .21). No new epilepsy controlled trials were included in the Safety Update. Overall treatment emergent AE risks exhibited dose response (see below). In the following table, I summarize the treatment emergent AEs reported for at least 2% of pregabalin epilepsy subjects and at least twice as frequently for any of the pregabalin dose groups compared to placebo.

[18] Myopathy was the preferred term to which rhabdomyolysis was coded. Rhabdomyolysis is the only verbatim term listed for myopathy in the coding dictionary found in Appendix ALL.010 (Summary of Safety p. 767).

FDA Table 21. Treatment Emergent Adverse Events Occurring in at least 2% of Subjects in the Pregabalin Group and at least twice as frequently for any of the pregabalin dose groups compared to placebo, Epilepsy Controlled Trials

Adverse Event	PBO	50mg/d BID	150mg/d BID	150mg/d TID	300mg/d BID	600mg/d BID	600mg/d TID	All PGB
	N=294	N=88	N=86	N=99	N=90	N=192	N=203	N=785
Overall	70.1% (206)	67% (59)	70.9% (61)	75.8% (75)	84.4% (76)	94.3% (181)	91.1% (185)	84% (637)
Dizziness	10.5% (31)	9.1% (8)	16.3% (14)	19.2% (19)	31.1% (28)	43.2% (83)	33% (67)	28.9% (219)
Somnolence	10.9% (32)	10.2% (9)	17.4% (15)	6.1% (6)	17.8% (16)	29.7% (57)	27.1% (55)	20.8% (158)
Ataxia	4.1% (12)	3.4% (3)	10.5% (9)	2% (2)	10% (9)	15.6% (30)	23.2% (47)	13.2% (100)
Weight gain	1.4% (4)	1.1% (1)	2.3% (2)	7.1% (7)	6.7% (6)	16.7% (32)	15.3% (31)	10.4% (79)
Accidental Injury	5.4% (16)	14.8% (13)	5.8% (5)	8.1% (8)	11.1% (10)	12% (23)	7.9% (16)	9.9% (75)
Amblyopia	4.4% (13)	3.4% (3)	3.5% (3)	7.1% (7)	7.8% (7)	10.4% (20)	13.8% (28)	9% (68)
Diplopia	3.7% (11)	3.4% (3)	4.7% (4)	6.1% (6)	6.7% (6)	9.9% (19)	13.8% (28)	8.4% (64)
Tremor	3.7% (11)	3.4% (3)	3.5% (3)	3% (3)	6.7% (6)	10.9% (21)	10.3% (21)	7.5% (57)
Thinking abnormal	2% (6)	3.4% (3)	7% (6)	1% (1)	7.8% (7)	7.3% (14)	10.8% (22)	7% (53)
Amnesia	2.4% (7)	2.3% (2)	3.5% (3)	3% (3)	2.2% (2)	5.7% (11)	5.9% (12)	4.4% (33)
Peripheral edema	2% (6)	1.1% (1)	3.5% (3)	3% (3)	3.3% (3)	5.2% (10)	5.9% (12)	4.2% (32)
Speech disorder	0.7% 2	0% (0)	2.3% (2)	0% (0)	2.2% (2)	8.3% (16)	5.9% (12)	4.2% (32)
Dry Mouth	1.4% (4)	2.3% (2)	1.2% (1)	1% (1)	2.2% (2)	7.8% (15)	4.9% (10)	4.1% (31)
Incoordination	1% (3)	2.3% (2)	2.3% (2)	0% (0)	3.3% (3)	6.3% (12)	5.9% (12)	4.1% (31)

Increased appetite	1% (3)	1.1% (1)	2.3% (2)	1% (1)	3.3% (3)	8.9% (17)	3.4% (7)	4.1% (31)
Constipation	2% (6)	2.3% (2)	0% (0)	1% (1)	1.1% (1)	7.3% (14)	5.9% (12)	4% (30)
Abnormal vision	0.7% (2)	2.3% (2)	3.5% (3)	2% (2)	1.1% (1)	4.7% (9)	4.9% (10)	3.6% (27)
Abnormal gait	0.3% (1)	1.1% (1)	1.2% (1)	0% (0)	3.3% (3)	6.3% (12)	4.4% (9)	3.4% (26)
Twitching	0.7% (2)	0% (0)	0% (0)	0% (0)	4.4% (4)	5.7% (11)	4.9% (10)	3.3% (25)
Confusion	1.7% (5)	0% (0)	2.3% (2)	0% (0)	2.2% (2)	5.2% (10)	4.9% (10)	3.2% (24)
Visual field defect	1.7% (5)	1.1% (1)	7% (6)	0% (0)	6.7% (6)	2.6% (5)	1% (2)	2.6% (20)
Nervousness	0.7% (2)	0% (0)	2.3% (2)	3% (3)	1.1% (1)	4.7% (9)	2% (4)	2.5% (19)
Nystagmus	1.7% (5)	2.3% (2)	0% (0)	1% (1)	4.4% (4)	3.1% (6)	3% (6)	2.5% (19)
Vomiting	2% (6)	0% (0)	1.2% (1)	4% (4)	1.1% (1)	4.2% (8)	2% (4)	2.4% (18)
Paresthesia	1% (3)	2.3% (2)	1.2% (1)	2% (2)	0% (0)	3.1% (6)	2.5% (5)	2.1% (16)
Myoclonus	0.3% (1)	0% (0)	1.2% (1)	0% (0)	0% (0)	3.6% (7)	3.4% (7)	2% (15)

From Summary of Safety, Appendix Epilepsy.21 and .23

Adverse Events by Intensity

Pfizer further characterized the treatment emergent AEs from the epilepsy controlled trials in terms of investigator recorded intensity. Pfizer noted that 9.2% (70/758) of pregabalin subjects with AEs had an event that was considered severe compared to 5.1% (15/294) of placebo subjects. Pregabalin subjects were more likely to have one of the following AEs classified as severe compared to placebo subjects: dizziness (pregabalin 2%, n=15, placebo 0); somnolence (pregabalin 2%, n=15, placebo 0); ataxia (pregabalin 1.6%, n=12, placebo 0); headache (pregabalin 1.1%, n=8, placebo 0.7%, n=2); and accidental injury (pregabalin 0.7%, n=7, placebo 0) (Summary of Safety, p.184).

Adverse Events by Time to Onset

Pfizer provided a table summarizing the median time to onset for commonly occurring adverse events in the combined epilepsy trial database. That table is reproduced below.

Pfizer Table 100. Median Time to Onset[a] Common Adverse Events Controlled Epilepsy Studies (009, 011, 034)

Adverse Event Preferred Term	Placebo N = 294			Pregabalin 150 mg/day N = 185			Pregabalin 300 mg/day N = 90			Pregabalin 600 mg/day N = 395		
	n (%)		Days	n (%)		Days	n (%)		Days	n (%)		Days
Somnolence	32	(10.9)	13	21	(11.4)	1	16	(17.8)	2	112	(28.4)	2
Dizziness	31	(10.5)	7	33	(17.8)	3	28	(31.1)	0	150	(38.0)	3
Asthenia	24	(8.2)	7	20	(10.8)	5	11	(12.2)	0	49	(12.4)	3
Thinking Abnormal	6	(2.0)	14	7	(3.8)	20	7	(7.8)	1	36	(9.1)	4
Ataxia	12	(4.1)	22	11	(5.9)	6	9	(10.0)	1	77	(19.5)	5
Diplopia	11	(3.7)	31	10	(5.4)	7	6	(6.7)	1	47	(11.9)	5
Amblyopia[b]	13	(4.4)	43	10	(5.4)	3	7	(7.8)	2	48	(12.2)	6
Tremor	11	(3.7)	23	6	(3.2)	42	6	(6.7)	11	42	(10.6)	6
Weight Gain	4	(1.4)	19	9	(4.9)	0	6	(6.7)	14	63	(15.9)	13
Headache	34	(11.6)	13	14	(7.6)	8	5	(5.6)	7	44	(11.1)	13
Accidental Injury	16	(5.4)	26	13	(7.0)	20	10	(11.1)	26	39	(9.9)	35
Infection	15	(5.1)	20	14	(7.6)	22	5	(5.6)	33	19	(4.8)	40

[a] In days from beginning of double-blind study medication, sorted by increasing median time to onset in the 600 mg/day group; median among patients who had the adverse event.
[b] Amblyopia was reported by the investigators mainly as blurred/blurry vision.

The above table illustrates that for many of the AEs that were more common among pregabalin treated subjects compared to placebo treated subjects, the median time to onset was much shorter in the pregabalin group compared to the placebo group. The dose classification portrayed above is unreliable since two of the included studies, 009 and 011, included a one week period where subjects were titrated to their randomized dose and for many of the events above, the median time to onset is less than one week.

Adverse Events by Duration

Pfizer provided a summary of the median duration of selected AEs by pregabalin dose groups for subjects who completed their trials (Summary of Safety, Table 101, p.187).