CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-724

MEDICAL REVIEW

MEMORANDUM

DATE: June 10, 2005

FROM: Division Director

TO: File, NDA 21-724

SUBJECT: Action Memo for NDA 21-724, for the use of LYRICA (pregabalin) in the treatment of partial seizures in adults

NDA 21-724, for the use of LYRICA (pregabalin) in the treatment of partial seizures in adults, was submitted by C.P. Pharmaceuticals International C.V. (c/o Pfizer) on 10/30/03. It was the subject of an Approvable letter dated 8/31/04 relating to the epilepsy claim (it was subsequently approved for the indications post-herpetic neuralgia and painful diabetic neuropathy in 12/04). In that 8/31/04 Approvable letter, we asked the sponsor to further analyze blood pressure changes in patients with and without dizziness, to explore the relationship between dyspnea and edema, and further characterize the nature of the previously seen PR interval prolongation in various sub-sets of patients. In addition, we asked the sponsor to agree to perform, in Phase 4, 1) studies to assess sperm function in humans (based on animal findings), 2) studies in animals to further assess ocular lesions seen in earlier animal studies, and 3) studies in humans to assess ophthalmologic function, based on concerns raised in those earlier animal studies.

The sponsor responded to the 8/31/04 Approvable letter with a submission dated 4/11/05. This re-submission has been reviewed by Dr. Gerard Boehm, safety reviewer, Dr. Olivia Easley, medical reviewer, DRUDP, and Dr. Thomas Broadbent, chemist.

The review team recommends that the application be approved. Dr. Boehm has found that there are no meaningful relationships between decreases in blood pressure and dizziness, or between edema and dyspnea. He also found that the data do not suggest that patients with baseline PR prolongation or taking PR prolonging drugs at baseline are at particular risk for further PR prolongation, but that the number of patients in these categories are too small to provide a definitive answer.

The sponsor has agreed to commit to perform the requested Phase 4 studies, and we have agreed with them on product labeling. In addition, they have agreed to test the first 3 commercial lots of pregabalin for ——— ——————and to set a specification for this impurity of NMT ———

For the reasons given above, I will issue the attached Approval letter, with the attached agreed upon product labeling.

One other issue needs to be mentioned.

The product is in the process of being scheduled under the Controlled Substances Act (it will likely receive designation as Schedule V). Until it has been officially scheduled, the sponsor has agreed to not market the product. The product has, therefore, not been marketed despite its earlier approval for the two pain indications, and will remain unmarketed until scheduling is complete.

Russell Katz, M.D.

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/s/

Russell Katz
6/10/05 01:19:07 PM
MEDICAL OFFICER

Review of Clinical Data

NDA:	21-724
Drug Name:	Generic Name: Pregabalin Trade Name: Lyrica
Sponsor:	Pfizer
Material Reviewed:	Response to Approvable letter 3/11/05, 4/11/05; Responses to Reviewer questions 3/31/05, 4/19/05, 5/5/05; Proposed labeling 3/18/05
Reviewer:	Gerard Boehm, MD, MPH
Date Completed:	6/6/05

Executive Summary

The HFD-120 approvable letter for pregabalin dated 8/31/04 included requests for additional safety analyses and a safety update. Pfizer submitted their response on 3/11/05. After agreeing to file the response, I discovered difficulties in locating narratives referenced in the safety update that greatly impeded the review. The Division informed Pfizer of these difficulties and Pfizer re-submitted the response on 4/11/05. This resubmission included electronic links that facilitated location of narratives.

Pfizer's submitted safety analyses examining the association between blood pressure and dizziness and examining the association between edema and dyspnea provided some reassuring results and did not support the need for labeling changes. There did not appear to be evidence of increased risk of hypotension among pregabalin subjects experiencing dizziness. An analysis of dyspnea AEs in patients who also experienced edema did not suggest that these subjects were experiencing concerning outcomes, discontinuing treatment, or requiring additional treatment.

Pfizer's analyses of PR changes in patients with baseline PR prolongation or patients who were taking other PR prolonging agents was less helpful and questions remain about appropriate labeling. The PR analysis in patients with baseline PR prolongation and in patients who were taking other PR prolonging agents did not suggest increased risk for pregabalin patients. However, both analyses included fairly small sample sizes. In addition, the analysis of the effect of pregabalin on the PR interval in patients taking other PR prolonging drugs included a number of patients who were taking lamotrigine, a drug with questionable ability to prolong the PR interval. I recommend that the

[redacted] using other PR prolonging agents but I admit that this concern is hypothetical and not based on data from the development program.

Pfizer's Periodic Safety Update, that included post marketing safety data from Europe, and Safety Update 3 from the development program did not suggest any changes in the current understanding of pregabalin's safety profile.

The pregabalin approvable letter requested three phase IV studies and Pfizer responded to these requests. The Division requested a human male reproductive function study to further explore concerning animal findings. Pfizer had already performed a human study of reproductive function but our consultant in HFD-580 felt that study was not powered to adequately assess all relevant parameters. Pfizer rejected the Division's request to perform another human study and provided an argument for their position. HFD-580 reviewed this information and again concluded that the previous human study was inadequate but that the decision to require another study should be based on the risk benefit assessment. Given the previous study's inability to address our concerns it seems appropriate to require an additional study to address the lingering questions. Pfizer has already agreed to conduct a Phase IV human study of ophthalmologic function. Pfizer

disagreed with a request for conducting additional animal studies to further characterize ocular lesions seen in rats.

Materials Used in This Review

This memo reviews Pfizer's response to the pregabalin approvable letter sent from HFD-120 on 8/31/04. This response included safety analyses requested by the Division, a Periodic Safety Update Report submitted to the EMEA, a four month safety update, a response to a request for a Phase IV human male reproductive function study, an acknowledgement of the agreement for a phase IV ophthalmologic study in humans, a response to the request for a phase IV study of ocular lesions in animals, and proposed labeling. After agreeing to file the original response, I discovered difficulties in locating narratives referenced in the safety update that greatly impeded the review. There were instances where specific events were identified in SU3 but the narratives for these events had been provided in previous submissions. Pfizer did not identify the location of these narratives making it necessary to search for narratives across four submissions (NDA, SU1, SU2, and SU3). The Division informed Pfizer of these difficulties and Pfizer re-submitted the response on 4/11/05. This resubmission included electronic links that facilitated location of narratives. During the course of the review Pfizer also provided responses to reviewer questions.

Response Topics

Peripheral Edema and Dyspnea Adverse Events

As part of their original NDA submission, Pfizer examined the potential association between peripheral edema and selected cardiorespiratory adverse events, vital signs, and laboratory values in controlled studies. They did not observe any clinically significant differences in changes in blood pressure, heart rate, or respiratory rate in subjects with peripheral edema compared with the overall controlled study population. They did, however, observe that pregabalin-treated subjects who experienced peripheral edema were more likely to report the adverse events hypertension and dyspnea compared with pregabalin-treated patients who did not experience peripheral edema (see FDA Table 84, page 165, NDA Safety Review).

To further examine the potential relationship between edema and dyspnea in pregabalin-treated subjects, the Division requested that Pfizer provide narrative summaries and a tabular listing for all pregabalin- and placebo-treated subjects in controlled studies who experienced adverse events coded to both the preferred term dyspnea and one of the edema-related preferred terms—peripheral edema, edema, or generalized edema. The Division requested that the listing include the dates on which the subjects experienced the adverse events of edema and dyspnea.

In controlled studies, 1.0% (54/5508) of pregabalin-treated subjects and 0.8% (19/2384) of placebo-treated subjects experienced dyspnea. 7.8% (430/5508) of pregabalin-treated subjects and 2.1% (51/2384) of placebo-treated subjects experienced edema. The majority of these adverse events were coded to the preferred term peripheral edema.

In their March 11, 2005 response to our query, Pfizer reported that 14 pregabalin-treated subjects (14/5508; 0.3%) experienced both edema and dyspnea in controlled studies. No placebo-treated subjects (0/2384) experienced both dyspnea and edema. 25.9% (14/54) of pregabalin-treated subjects who experienced dyspnea also experienced edema, whereas 3.3% (14/430) of pregabalin-treated subjects who experienced edema also experienced dyspnea.

According to Pfizer's tabular listing, there was some degree of temporal overlap between edema and dyspnea for all 14 pregabalin-treated subjects who experienced both adverse events. In 13 of the cases, the onset of edema occurred prior to the onset of the dyspnea.

Five of the subjects who experienced both edema and dyspnea were being treated with pregabalin for painful diabetic peripheral neuropathy; three were being treated for pain due to postherpetic neuralgia; two were being treated for epilepsy; two were being treated for osteoarthritis pain; one was being treated for fibromyalgia; and one was being treated for generalized anxiety disorder.

Among the 14 patients who reported edema and dyspnea, the majority of edema-related adverse events were coded to the preferred term peripheral edema (n=11). The investigators' (i.e., verbatim) terms used to describe the 11 events that were coded to this preferred term included leg swelling, pitting edema, pedal edema, foot edema, ankle swelling, ankle edema, and puffy fingers. Three events described by the investigators as fluid retention or generalized edema were coded to the preferred term generalized edema. One event was described as and coded to the preferred term edema. Some subjects experienced more than one edema-related adverse event.

Events coded to the preferred term dyspnea were most commonly described by the investigators as shortness of breath or dyspnea. In two cases, the events were described as shortness of breath on exertion or breathlessness on exertion

Review of the narratives revealed that five of the pregabalin-treated subjects who experienced both dyspnea and edema had a history of coronary artery disease; four had a history of edema; ten had a history of hypertension; two had a history of congestive heart failure; and four were receiving concomitant thiazolidinedione therapy. Four subjects had no cardiac history with the exception of pericarditis in one case. Three subjects had relevant pulmonary history. One (subject 105_529011) had a history of smoking and shortness of breath. Another (029_025009) had a history of pneumonia. One subject (149_430007) had a history of asthma. One subject (196_655011) appears to have had an upper respiratory tract infection prior to the onset of shortness of breath. This subject, who had the onset of peripheral edema on study day 8, had a cold on study days 22—29,

clear nasal discharge on study day 54 to the end of the study, and shortness of breath on study day 55 through the end of the study.

None of the narratives described a diagnostic work-up having been done to investigate either the dyspnea or edema. Twelve of the subjects with both dyspnea and edema adverse events completed their trial, one discontinued for edema and one discontinued for a CVA. For seven subjects, both the dyspnea and edema were continuing at the end of the study. For two subjects, both edema and dyspnea resolved prior to the end of the study. For two subjects, the dyspnea but not the edema resolved prior to the end of the study and for three subjects the edema but not the dyspnea resolved prior to the end of the study.

Discussion

In controlled trials, edema AEs occurred more frequently among pregabalin treated subjects compared to placebo treated subjects while dyspnea AEs occurred at comparable frequencies in the two treatment groups. The concurrent reporting of both dyspnea and edema was observed in 0.3% of pregabalin subjects but did not occur for placebo subjects. The reason for further exploring these concurrent events is to determine if dyspnea signals a particularly concerning outcome for edema related to pregabalin exposure.

Since edema and dyspnea are common symptoms and can occur together in disorders, for example in the setting of volume overload, it is not surprising to observe instances where they are reported together for a given subject or that the frequency of concurrent reporting exceeds that expected if these were independent events. Among pregabalin subjects who developed edema, 3.3% (14/430) also developed dyspnea. If one assumes this is the background risk of dyspnea in patients with edema, then one would have expected less than two placebo patients with edema to also have dyspnea (3.3% x 51=1.7) and there were none, not an unusual finding. Furthermore if one assumes that pregabalin increases the risk for edema, leading also to increased dyspnea then it seems one would also expect notably higher risks for dyspnea in pregabalin subjects compared to placebo but the risks for dyspnea were comparable.

Examination of the narratives for pregabalin patients with concurrent dyspnea and edema did not clarify the relationship between these events. The narratives did not support a single unifying diagnosis (ex. CHF) in these patients but the narratives were of limited value because they did not document evaluations of the events (for example was dyspnea a cardiac symptom, a respiratory symptom related to anxiety etc.). In some of the cases, the subjects had a history of edema, congestive heart failure, or COPD that predated the study and could have contributed to these events; without additional documentation/evaluation, this is speculation. The narratives did not suggest any unusual common factors among the subjects experiencing both edema and dyspnea.

The outcomes in patients who experienced concurrent reporting of edema and dyspnea events did not seem concerning. Only one of the fourteen pregabalin subjects who experienced both edema and dyspnea discontinued from a trial for these events (edema). For half of the pregabalin subjects with concurrent edema and dyspnea, one or both of

these adverse events resolved with continued pregabalin treatment complicating the assessment of relationship to drug particularly given the small number of events.

Taken together the results of the requested analyses do not strongly signal that pregabalin induced edema led to increased risk of dyspnea or diagnoses suggestive of congestive heart failure. The analyses are limited by the number of subjects included in the studies and have limited ability to describe small risk increases.

Blood Pressure/Dizziness

In the pregabalin approvable letter, the Division requested that Pfizer provide analyses that compare blood pressure changes in patients with an AE of dizziness to those without an AE of dizziness. The purpose of this request was to look for evidence of a relationship between dizziness AEs and hypotension. The Division requested mean and mean maximum BP change from baseline for subjects with and without AEs of dizziness, stratified by treatment assignment. In addition, the Division requested comparisons of BP outliers for subjects with and without AEs of dizziness, stratified by treatment assignment (SBP if <90 and decrease from baseline of >=30mm Hg; DBP if <50 and decrease from baseline of >=20 mm Hg).

Pfizer provided their response in the 3/11/05 submission. After reviewing the submission, I recognized that while we were interested in an analysis that used the lowest BP, Pfizer's submission provided comparisons using subjects' highest recorded on treatment BP. We requested an additional analysis that used the lowest on treatment BP for comparison and Pfizer provided that information in a 3/31/05 submission.

Results
Mean Change Analyses
Pfizer provided a table summarizing the results of the BP mean change from baseline to termination stratified by dizziness. I summarize information from that table below.

Mean BP Change from Baseline to Termination for Subjects With and Without Dizziness

	Patients with AE of Dizziness				Patients with No AE of Dizziness			
	Placebo (N=208)		PGB (N=1606)		Placebo (N=2176)		PGB (N=3902)	
	N	Mean	N	Mean	N	Mean	N	Mean
SBP (Supine)	85	-2.5	694	-4.3	1068	-2.8	1947	-4.3
DBP (Supine)	85	-0.2	694	-2.5	1068	-1.3	1947	-2.3
SBP(Standing)	94	-2.8	749	-3.7	1186	-2.8	2096	-3.9
DBP(Standing)	94	-1.6	748[a]	-2.5	1186	-1.6	2096	-2.6
SBP (Sitting)	117	2.1	893	-1.9	1058	-0.4	1855	-1.7
DBP(Sitting)	117	0.3	893	-0.9	1058	0.1	1855	-1.1

DBP=diastolic blood pressure; SBP=systolic blood pressure
[a] Patient 132_103009 had standing SBP assessed at baseline but not standing DBP.

In the following table I summarize the mean change compared to placebo for patients with and without dizziness.

Pregabalin BP Mean Change from Baseline Compared to Placebo for Subjects with and without Dizziness AEs

	Patients with AE of Dizziness	Patients with no AE of Dizziness
	PGB mean change-PBO mean change	PGB mean change-PBO mean change
SBP (supine)	-1.8	-1.5
DBP (supine)	-2.3	-1.0
SBP(standing)	-0.9	-1.1
DBP (standing)	-0.9	-1.0
SBP (sitting)	-4	-1.3
DBP (sitting)	-1.2	-1.0

The next table provides the mean change for minimum BP compared to baseline for subjects with and without dizziness.

Mean change for Minimum BP Compared to Baseline for Subjects With and Without Dizziness

	Patients with AE of Dizziness				Patients with No AE of Dizziness			
	Placebo (N=208)		PGB (N=1606)		Placebo (N=2176)		PGB (N=3902)	
	N	Mean	N	Mean	N	Mean	N	Mean
SBP (Supine)	85	-8.4	694	-10.4	1068	-9.0	1947	-10.8
DBP (Supine)	85	-4.4	694	-6.2	1068	-5.1	1947	-6.5
SBP(Standing)	94	-9.5	749	-10.1	1186	-9.4	2096	-10.8
DBP(Standing)	94	-6.1	748[a]	-6.2	1186	-5.7	2096	-6.7
SBP (Sitting)	117	-7.1	893	-8.3	1058	-8.1	1855	-8.8
DBP(Sitting)	117	-5.8	893	-6.0	1058	-5.8	1855	-6.4

In the following table I summarize the mean change for minimum BP compared to placebo for patients with and without dizziness.

Pregabalin BP Mean Change for Minimum BP to Baseline Compared to Placebo for Subjects with and without Dizziness AEs

	Patients with AE of Dizziness	Patients with no AE of Dizziness
	PGB mean change-PBO mean change	PGB mean change-PBO mean change
SBP (supine)	-2.0	-1.8
DBP (supine)	-1.8	-1.4
SBP(standing)	-0.6	-1.4
DBP (standing)	-0.1	-1.0
SBP (sitting)	-1.2	-0.7
DBP (sitting)	-0.2	-0.6

Outlier Analyses
Pfizer provided the requested low BP outlier analysis that examined the risks in subjects with and without dizziness AEs. I provide those results in the following table.

Low BP Outliers for Subjects With and Without dizziness AEs

	Patients with AE of Dizziness				Patients with No AE of Dizziness			
	Placebo (N=208)		PGB (N=1606)		Placebo (N=2176)		PGB (N=3902)	
	N	Mean	N	Mean	N	Mean	N	Mean
SBP (Supine)	85	0% (0)	694	0.7% (5)	1068	0.2% (2)	1947	0.1% (1)
DBP (Supine)	85	0% (0)	694	0.4% (3)	1068	0.1% (1)	1947	0.4% (8)
SBP(Standing)	94	0% (0)	749	0.4% (3)	1186	0% (0)	2096	0.2% (5)
DBP(Standing)	94	0% (0)	748[a]	0.4% (3)	1186	0.1% (1)	2096	0.1% (3)
SBP (Sitting)	117	0.9% (1)	893	0.1% (1)	1058	0.1% (1)	1855	0.2% (4)
DBP(Sitting)	117	0.9% (1)	893	0.3% (3)	1058	0.2% (2)	1855	0.1% (1)

DBP=diastolic blood pressure; SBP=systolic blood pressure
Clinically important decreases defined as follows: SBP if <90 and decrease from baseline of >=30 mm Hg; DBP if <50 and decrease from baseline of >=20 mm Hg
a Patient 132_103009 had standing SBP assessed at baseline but not standing DBP.

In the following table I summarize the relative risks for low BP outliers for patients with and without dizziness.

Relative Risks for Low BP Outlier Analyses for Subjects with and without Dizziness AEs

	Patients with AE of Dizziness	Patients with no AE of Dizziness
	RR (PGB risk/ PBO Risk)	RR (PGB risk/ PBO Risk)
SBP (supine)	- (0.7%/0%)	0.5 (0.1%/0.2%)
DBP (supine)	- (0.4%/0%)	4 (0.4%/0.1%)
SBP(standing)	- (0.4%/0%)	- (0.2%/0)
DBP (standing)	- (0.4%/0%)	1.0 (0.1%/0.1%)
SBP (sitting)	0.1 (0.1%/0.9%)	2.0 (0.2% /0.1%)
DBP (sitting)	0.3 (0.3%/0.9%)	0.5 (0.1%/0.2%)

The above analysis is limited in ability to assess relative risk differences due to the small number of subjects meeting outlier criteria.

Discussion
The analyses provided by Pfizer do not support an association between low blood pressure and dizziness AEs. The mean change from baseline and the lowest BP changes from baseline compared to placebo were similar for subjects who experienced dizziness AEs and those who did not. The outlier analyses were of limited value due to the small number of subjects who met the low BP outlier criteria.

PR Interval Analyses

In their NDA submission, Pfizer provided analyses that demonstrated that pregabalin results in PR interval prolongation. Pfizer characterized the pregabalin related mean

increase in the PR interval as 3-6msec compared to placebo and there appeared to be a dose response. The risk of PR interval increased outliers was generally higher among pregabalin subjects compared to placebo subjects but a linear dose response relationship was not clearly present in these analyses. Despite these findings, there did not appear to be an increased risk of adverse events of AV block among pregabalin subjects compared to placebo subjects, based on a small number of such events in randomized, placebo-controlled, development program studies.

Although the mean PR interval prolongation in the overall pregabalin population was mild, Pfizer did not explore the effect in subpopulations that might be at increased risk of PR interval prolongation. In the approvable letter, the Division requested stratified analyses of PR interval data for two populations that might be at increased risk, those with PR interval prolongation at baseline, and those taking concomitant medications that are known to prolong the PR interval. Specifically, the Division requested analyses of the mean maximum changes in PR interval that stratified subjects by their baseline PR interval (<=.2sec vs. >.2sec). In addition, the Division requested an analysis that examined mean maximal change in PR interval that stratified subjects by use of concomitant medications known to prolong the PR interval.

Pfizer provided the requested analyses in their response to the approvable letter. Pfizer's response consisted of tables that provided the requested analyses for individual study groupings as well as summary tables of the results.

Below, I provide the summary table of the results of the mean maximum change in PR interval by baseline PR interval and indication.

Table 1. Mean Maximum Change (msec) in PR Interval Stratified by Baseline PR Interval

Indication	Baseline PR Interval		Placebo	150mg/ day	300mg/ day	600mg/ day	All PGB
All Pain	≤200 msec	N	724	288	358	446	1394
		Mean(SD)	3.0(14.2)	5.8(13.1)	5.8(13.9)	6.9(13.6)	6.1(13.6)
	>200 msec	N	49	24	27	38	109
		Mean(SD)	1.5(15.8)	-0.9(13.3)	-12(33.3)	2.1(15.9)	-1.5(23.4)
Epilepsy	≤200 msec	N	182	80	77	276	511
		Mean(SD)	3.8(14.0)	7.9(13.0)	4.3(11.8)	6.9(13.5)	6.4(12.9)
	>200 msec	N	8	2	2	16	22
		Mean(SD)	-3.3(7.6)	-4.0(0.0)	12(11.3)	-0.6(12.4)	0.8(11.6)
GAD	≤200 msec	N	242	156	66	213	658
		Mean(SD)	-0.1(13.5)	0.0(12.7)	0.8(15.7)	4.0(13.3)	2.5(13.2)
	>200 msec	N	8	8	2	2	18
		Mean(SD)	-12(10.8)	-5.4(10.8)	-12(0.0)	2.0(2.8)	-4.2(11.4)

All Pain=Studies 014, 029, 030, 032, 040, 104, 105, 127, 131; Epilepsy=Studies 007, 009, 034; GAD=Studies 021, 025, 026, 083, 085. Note that All PGB includes doses not presented in table, such as 50, 75, 400 and 450 mg/day. The pooled studies were fixed dose with some of the studies using a short (around 1 week) titration.

In the following table, I summarize the changes relative to placebo for the studies analyzed by Pfizer.

Changes in PR Interval Relative to Placebo Stratified by Baseline PR Interval and Indication for Pregabalin Studies

Indication	Baseline PR Interval	All PGB (n)	Placebo (n)	PGB-PBO
Epilepsy	<=200msec	6.4 (511)	3.8 (182)	2.6
	>200msec	0.8 (22)	-3.3 (8)	4.1
GAD	<=200msec	2.5 (242)	-0.1 (658)	2.6
	>200msec	-4.2 (18)	-12 (8)	7.8
New Psychiatry*	<=200msec	4.5 (630)	1.5 (213)	3
	>200msec	2.5 (15)	-17 (6)	19.5
Psychiatry	<=200msec	2.7 (384)	0.7 (198)	2.0
	>200msec	-3.1 (12)	-2.0 (3)	-1.1
Pooled Pain	<=200msec	6.1 (1394)	3 (724)	3.1
	>200msec	-1.5 (109)	1.5 (49)	-3

From Response to the approvable Letter, Question 3, ECG tables pP.1-18
The above table does not include results from studies 82 and 88 since there were very few subjects with PR>200msec at baseline in these studies
*The studies in the Psychiatry group were 017, 021, 022, 025, 026. The studies in the New Psychiatry group were 080, 083, 085, 092, and 094. Both the New Psychiatry and the Psychiatry groups included similar indications such as GAD, social phobia, and [redacted] but the New Psychiatry group studies were completed after the studies in the Psychiatry group and were analyzed separately.

These stratified outlier analyses resulted in cells with small numbers of subjects. The pooled pain studies indication was the only subgroup with more than 10 subjects in each of the cells.

In the pooled pain studies and the psychiatry studies pregabalin subjects with baseline PR>200msec had an absolute mean maximum decrease in PR as well as a decrease relative to placebo. In the GAD studies, the pregabalin subjects with baseline PR>200msec experienced a mean maximum decline in PR that was less than the decline observed in the corresponding placebo group. In the Epilepsy and New Psychiatry studies, subjects with PR>200msec at baseline and exposed to pregabalin experienced mean maximum increases in PR interval while the corresponding placebo groups experienced decreases.

The above analysis does not strongly support that subjects with PR interval prolongation at baseline are at increased risk for greater PR prolongation with exposure to pregabalin but the analysis was limited by small number of subjects with PR interval prolongation at baseline. Although the PR mean maximum changes relative to placebo were greater in some cases for subjects with PR>200msec at baseline compared to subjects with PR<=200msec at baseline, this was based on greater declines in the placebo group and decreases or small increases in the pregabalin treated group.

Pfizer also performed the requested analyses examining if patients on concomitant medications known to prolong the PR interval were at greater risk of PR interval prolongation with pregabalin. Pfizer provided a listing of medications associated with PR prolongation as an appendix to their response. The listing included beta blockers, calcium channel blockers, antihypertensive combination products, and other agents that included antiarrhythmics (amiodarone, flecanide, quinidine, procainamide, propafenone, and dofetalide), triptans (naritriptan, sumatriptan), atazanavir, amiloride, digoxin, lamotrigine, and mefloquine. After classifying subjects by the use of one or more of the included PR prolonging drugs, Pfizer calculated the mean maximum PR interval changes. I provide Pfizer's summary table of results below.

Table 2. Mean Maximum Change (msec) in PR Interval Stratified by Presence or Absence of Concomitant Medications Associated with Prolonged PR Interval

Indication	Con-comitant Med		Placebo	150mg/ day	300mg/ day	600mg/ day	All PGB
All Pain	No	N Mean(SD)	627 3.0(13.7)	260 5.5(13.1)	323 4.3(15.2)	413 6.3(14.0)	1266 5.4(14.3)
	Yes	N Mean(SD)	146 2.8(16.7)	52 4.5(13.7)	62 5.9(22.3)	71 7.5(13.2)	237 6.2(16.2)
Epilepsy	No	N Mean(SD)	130 3.0(13.5)	62 0.0(12.7)	61 3.7(11.4)	213 6.6(13.2)	392 6.4(12.6)
	Yes	N Mean(SD)	60 4.6(14.6)	20 3.2(12.9)	18 7.1(12.7)	79 6.4(14.3)	141 5.6(13.4)
GAD	No	N Mean(SD)	248 -0.5(13.6)	162 -0.3(12.7)	66 0.3(15.8)	213 4.0(13.3)	666 2.3(13.3)
	Yes	N Mean(SD)	2 0.0(5.7)	2 4.0(5.7)	2 2.0(2.8)	2 4.0(5.7)	10 2.4(4.7)

In the following table, I summarize the changes relative to placebo for the studies analyzed by Pfizer.

Changes in PR Interval Relative to Placebo Stratified by Presence or Absence of Concomitant Medications Associated with Prolonged PR Interval

Indication	Concomitant Medication	All PGB (n)	Placebo (n)	PGB-PBO
Epilepsy	No	6.4 (392)	3.0 (130)	3.4
	Yes	5.6 (141)	4.6 (60)	1.0
GAD	No	2.3 (666)	-0.5 (248)	2.8
	Yes	2.4 (10)	0.0 (2)	2.4
New Psychiatry*	No	4.5 (634)	0.8 (216)	3.7
	Yes	4.7 (11)	13.3 (3)	-8.6
Psychiatry	No	2.5 (390)	0.5 (196)	2.0
	Yes	5.3 (6)	8.0 (5)	-2.7
Pooled Pain	No	5.4 (1266)	3.0 (627)	2.4
	Yes	6.2 (237)	2.8 (146)	3.4

From Response to the approvable Letter, Question 3, ECG tables pP.1-18
The above table does not include results from studies 82 and 88 since there were very few subjects with taking one of the PR prolonging medications in these studies
*The studies in the Psychiatry group were 017, 021, 022, 025, 026. The studies in the New Psychiatry group were 080, 083, 085, 092, and 094. Both the New Psychiatry and the Psychiatry groups included similar indications such as GAD, social phobia, and acute mania but the New Psychiatry group studies were completed after the studies in the Psychiatry group and were analyzed separately.

With the exception of the Pooled Pain studies, the pregabalin subjects taking concomitant medications associated with PR prolongation had smaller mean maximum increases in PR relative to placebo than did the pregabalin subjects who did not take a concomitant medication associated with PR prolongation.

I was aware of the PR prolonging effect of many of the drugs on Pfizer's list but there were several drugs that they included that I did not recognize as PR interval prolonging agents. Using the PDR, PubMed, and the American Hospital Formulary I examined information about PR interval prolongation for atazanavir, amiloride, naratriptan, sumatriptan, lamotrigine and mefloquine.

Atazanavir, a protease inhibitor, has a Warning for PR prolongation in labeling. The labeling does not provide an estimate of the mean PR prolonging effect, but reports that in clinical trials, first degree AV block was observed in 5.9% of atazanavir treated patients (n=920) 5.2% of lopinavir/ritonavir treated patients (n=252), 10.4% of nelfinavir treated patients (n=48) and 3% of efivirenz treated patients (n=329). The label describes the risk for first degree heart block in another trial and also states that there have been rare reports of second degree AV block and no reports of third degree AV block. The label describes results from a PK study that found increased levels of diltiazem when given concomitantly with atazanavir and an additive effect on the PR interval.

Amiloride, a potassium sparing a diuretic, has a warning statement that describes the risk of hyperkalemia. The warning statement also describes the ECG findings associated with hyperkalemia, including prolongation of the PR interval. There did not appear to be any other language related to PR prolongation in the amiloride label.

Naratriptan and Sumatriptan are $5HT_1$ agonists approved for the treatment of migraine headaches. In the naratriptan label, PR prolongation is mentioned only in the post marketing reports section. In the sumatriptan label (injection), prolongation of the PR interval was mentioned in the Adverse Events section under the sub section titled of Other Events Observed in Association with the Administration of IMITREX Injection.

In the lamotrigine product labeling PR interval prolongation is mentioned as an effect of the 2-N-methyl metabolite in dogs, and that this finding is not expected in humans since only trace amounts of this metabolite are found in human urine. In a 2/1/05 ODS consult on lamotrigine, the reviewer identified a total of 5 spontaneous reports related to heart block during the 10 years of post marketing experience. Although ODS recommended adding heart block to the adverse events section of the lamotrigine label, they wrote in their conclusion section that they did not feel that a signal for heart block existed at that time.

Labeling notes that mefloquine is a myocardial depressant and produces 50% of the increase in PR interval reported with quinine. The labeling also reports first degree AV block among the ECG alterations reported during use of mefloquine.

There appeared to be little evidence supporting the inclusion of lamotrigine, naratriptan, sumatriptan, or amiloride among drugs that prolong the PR interval. Inclusion of these drugs in the analysis could result in diminish the ability to detect an effect, if present. I requested tables identifying the number of patients taking each of the drugs identified by Pfizer as prolonging the PR interval to determine whether a substantial number of subjects were taking one of the included drugs that did not appear to prolong the PR interval.

For the epilepsy studies, 123 of the 141 pregabalin subjects identified as taking a PR prolonging agent were taking lamotrigine and 4 were taking sumatriptan. Of the 10 pregabalin subjects identified as taking a PR prolonging drug in the anxiety studies, 2 were taking sumatriptan. Of the 237 pregabalin subjects identified as taking a PR prolonging drug in the pooled pain studies, the majority were taking recognized PR prolonging drugs with only 1 taking lamotrigine, and 14 taking sumatriptan.

Discussion
To further assess the risks of pregabalin related PR prolongation, the Division requested ECG data analyses in subgroups of subjects with PR interval prolongation at baseline and subjects taking other PR prolonging medications. Neither the analysis of patients with PR interval prolongation at baseline nor the analysis of pregabalin subjects using other PR prolonging drugs supported an interaction that would result in increased risk.

The analysis of pregabalin subjects using other PR prolonging drugs was limited by the inclusion of drugs with questionable ability to prolong PR interval and both analyses were limited by small sample sizes. In the epilepsy studies a majority of subjects included as taking a PR prolonging drug were taking lamotrigine, a drug with little evidence of PR prolonging ability. Including lamotrigine as a PR prolonging agent, results in misclassification which would decrease the ability to detect an effect if present. Unfortunately, in most indication subgroups there are very few patients taking a PR prolonging agent or with PR prolongation at baseline. Given the limitations of the analyses, I would recommend including language that cautions about use in patients with PR interval prolongation at baseline and in patients taking other PR prolonging drugs but I admit that this is based on hypothetical concerns rather than affirmative findings of increased risk in the safety data.

Pregabalin PSUR

Pfizer submitted a Periodic Safety Update Report (PSUR) to the EMEA that described the pregabalin-related safety data collected from 7/7/04 through 1/6/05. Pregabalin was approved by the EMEA on 7/6/04 and was launched first in the United Kingdom on

7/19/04 (PSUR p.31). Pfizer submitted this PSUR to the Division as part of their response to the Approvable letter.

The adverse events captured in the PSUR are from several sources. Pfizer explained that these events came from spontaneous reports, cases reported from health authorities, cases reported in the medical literature, and cases reported from ongoing clinical studies and marketing programs (PSUR p.3).

Pfizer provided a line listing of all cases included in the PSUR. For cases involving patient death and cases from clinical trials, Pfizer provided individual case reviews. In addition, Pfizer provided summaries of adverse events related to weight increase, eye events, somnolence, edema, euphoria, psychosis, ataxia, drug interaction, overdose, and decreased therapeutic response. Pfizer also examined adverse events reported in children and the elderly. I present the information below using a different order than that used in the PSUR. I used an order that matches more closely the format of Division reviews. All page numbers cited below refer to the PDF document page numbers.

Results

Exposure

During the period covered by this safety report, Pfizer estimated that [redacted] patients had been exposed to pregabalin in the post-marketing setting. In addition, Pfizer reported that 464 subjects had been exposed to pregabalin in ongoing clinical trials (PSUR, p.3).

Adverse Events in the PSUR from Clinical Trials

Pfizer provided the following table summarizing events identified from clinical trials that were ongoing during the reporting period and where the investigator reported the event was possibly due to pregabalin. I provide information from that table below.

Case# Age/Gender Sponsor	Study Indication	Event(s)	Pfizer's Comment
200406440 83/F Pfizer	Post herpetic neuralgia	Disorientation Drug withdrawal syndrome Somnolence	Events occurred after three days of not receiving pregabalin because patient ran out of drug. Symptoms improved approximately one week after restart of pregabalin. Per the reference safety document, if pregabalin has to be discontinued, either in neuropathic pain or epilepsy, it is recommended that this should be done gradually over a minimum of one week.
2004089261 71/F Pfizer	Spinal cord injury	Depressed level of consciousness	Patient on multiple medications (12). Difficult to determine most likely suspect drug on review.
2004097436 28/M Pfizer	Partial seizures	Hallucinations, mixed	Patient on multiple concomitant medications (carbamazepine, enalapril, tiagabine) which have been associated with hallucinations.
2004108406 67/F Pfizer	Generalized anxiety disorder	Anxiety	Most likely manifestation of underlying generalized anxiety disorder, on review.
2004112428	Neuropathic pain	Pulmonary	Based on the information provided, it could

54/F Pfizer		embolism, Thrombosis	not be determined if the events were related to use of pregabalin.
2004120131 63/M Pfizer	Neuropathic pain Neuropathy peripheral	Hypertension	Most likely manifestation of underlying arterial hypertension, on review.

From p.10, PSUR

Adverse Events Identified from the Medical Literature
Pfizer reported that no pregabalin adverse event cases were identified from the medical literature.

General Overview of All Adverse Events
This safety report included 302 cases describing 816 events in patients prescribed pregabalin. Most of the cases were reported from the United Kingdom (135) and Germany (120). Pfizer summarized demographic data for the cases. Of the 251 cases that reported sex, 171 patients were female (68%). For the 181 cases that reported age, the age range was 9-90 years with a mean age of 60 years (PSUR, p.13).

Adverse Events with an Outcome of Death
Pfizer identified 4 reports with an outcome of death (PSUR, p.9). Two of the cases did not identify the specific cause of death but one report mentioned overdose, and the other report noted renal function abnormal. Pfizer provided the following summaries for the remaining 2 deaths:

Case 2004072632 described a 49-year-old female who experienced clinically diagnosed erythema exsudativum multiforme while receiving pregabalin, nitrofurantoin and topiramate. All three drugs were discontinued due to the event. The patient died primarily due to underlying neurological history (condition after encephalitis) and pneumonia. The reporting physician stated that there was no causal relationship with pregabalin or erythema exsudativum multiforme and the fatal outcome.
Case 2004088687 described an 82-year-old female in poor health who died due to acute pre-renal failure, pseudomembranous colitis, paralytic ileus and peritonitis six days after pregabalin had been discontinued due to myoclonus. The reporting physician stated there was no relationship between pregabalin and the events leading to death.

Serious Cases
Among the 302 total cases, there were 126 cases reporting 428 serious adverse events. Pfizer identified Nervous system disorders, General disorders and administration site conditions, and Psychiatric disorders as the most common SOCs for the serious adverse events. The most common serious adverse event preferred terms were dizziness (32), nausea (23), fatigue (23), headache (22), and circulatory collapse (22). (PSUR, p.18)

Most Frequently Reported Adverse Events
Pfizer provided a table with the events for the most frequently reported System Organ Classes (table not shown). In addition, Pfizer provided a table with the AEs reported in at least >=2% of all cases and/or serious cases (PSUR, p.15). I reproduce that table below.

Summary Tabulation of Adverse Events Reported in >= 2% of All Cases and/or Serious Cases During the Current Reporting Period (07 July 2004 through 06 January 2005)

System Organ Class	**All Cases**	**Serious Cases**
Preferred Term	# (% All Cases)	# (% Serious Cases)

Eye disorders		
Diplopia*	7 (2.3%)	3 (2.4%)
Vision blurred*	7 (2.3%)	5 (4.0%)
Visual disturbance*	6 (2.0%)	2 (1.6%)
Gastrointestinal disorders		
Diarrhoea	8 (2.6%)	2 (1.6%)
Dry mouth*	7 (2.3%)	4 (3.2%)
Nausea**	41 (13.6%)	23 (18.3%)
Vomiting*	8 (2.6%)	2 (1.6%)
General disorders and administration site conditions		
Asthenia*	4 (1.3%)	4 (3.2%)
Drug ineffective	9 (3.0%)	2 (1.6%)
Drug interaction	10 (3.3%)	3 (2.4%)
Fatigue*	29 (9.6%)	23 (18.3%)
Feeling abnormal	11 (3.6%)	3 (2.4%)
Feeling drunk*	4 (1.3%)	3 (2.4%)
Pain	6 (2.0%)	1 (0.8%)
Pain exacerbated*	5 (1.7%)	4 (3.2%)
Injury, poisoning and procedural complications		
Fall*	5 (1.7%)	5 (4.0%)
Nervous system disorders		
Ataxia*	9 (3.0%)	7 (5.6%)
Balance disorder	5 (1.7%)	3 (2.4%)
Convulsion	4 (1.3%)	3 (2.4%)
Coordination abnormal*	6 (2.0%)	3 (2.4%)
Dizziness*	52 (17.2%)	32 (25.4%)
Dysarthria*	9 (3.0%)	8 (6.3%)
Headache**	28 (9.3%)	22 (17.5%)
Memory impairment*	6 (2.0%)	5 (4.0%)
Paresthesia*	6 (2.0%)	1 (0.8%)
Somnolence*	20 (6.6%)	11 (8.7%)
Speech disorder*	7 (2.3%)	6 (4.8%)
Syncope*	4 (1.3%)	3 (2.4%)
Tremor*	12 (4.0%)	7 (5.6%)
Psychiatric disorders		
Agitation*	4 (1.3%)	3 (2.4%)
Confusional state*	17 (5.6%)	14 (11.1%)
Depression*	7 (2.3%)	5 (4.0%)
Hallucination*	4 (1.3%)	3 (2.4%)
Insomnia*	7 (2.3%)	2 (1.6%)
Psychotic disorder	9 (3.0%)	3 (2.4%)
Suicidal ideation	3 (1.0%)	3 (2.4%)
Renal and urinary disorders		
Urinary retention	6 (2.0%)	1 (0.8%)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea*	7 (2.3%)	1 (0.8%)
Skin and subcutaneous tissue disorders		
Pruritus	7 (2.3%)	1 (0.8%)
Vascular disorders		
Circulatory collapse**	23 (7.6%)	22 (17.5%)
Total Number of Cases	**302**	**126**

Summaries of Selected Adverse Events

Pfizer provided brief summaries for the following adverse events: nausea, headache, and myocardial infarction cases. These summaries did not provide useful new information about these events (PSUR pp.16-18).

Suicide attempt/Suicidal ideation
Pfizer noted that there were four serious cases with preferred terms of suicide attempt (n=2) and/or suicidal ideation (n=3). I summarize the information for these cases as presented by Pfizer below (PSUR, p.17).

2004117398 A 58 year old female receiving gabapentin and pregabalin for unknown indications developed severe depression with suicidal tendency requiring medical emergency procedures (not detailed).
2004089574 A 49 year old female treated with pregabalin for an unknown indication experienced a sudden and specific urge to commit suicide (drive car into wall) seven days after starting pregabalin. Pregabalin was continued and the outcome was unknown.
2004099599 A 61 year old female ingested 30 pregabalin capsules in a suicide attempt. She had a prior hospitalization years prior for a paranoid episode. A concomitant medication was simvastatin.
2004100914 A 48 year old female treated with pregabalin for pain experienced profound suicidal ideation three days after starting pregabalin. Pregabalin was stopped and the patient recovered.

Weight Increased Adverse Events
Pfizer received five reports of weight increased during the reporting period. In all five cases the amount of weight gain was not specified and in two cases the weight gain was reported as occurring on the day pregabalin was initiated (PSUR, p.6).

Eye Adverse Events
Pfizer reported 27 eye adverse event cases. Fourteen events were classified as serious. The preferred terms for the eye adverse events were: diplopia (7), vision blurred (7), visual disturbance (6), eye pain (5), accommodation disorder (2), eye redness (2), astigmatism, dry eye, eye irritation, eyelid margin crusting, eyelid oedema, eye swelling, presbyopia, and visual acuity reduced (one each). None of the events appeared to describe visual field defects. Pfizer identified factors that complicated the assessment of these events including insufficient information, concomitant medications, and concurrent disorders (PSUR pp.18-20).

Somnolence Adverse Events
Pfizer identified 20 somnolence adverse events. Eleven of these events were classified as serious. Pfizer identified factors that complicated the assessment of these events including insufficient information, concomitant medications, and concurrent disorders (PSUR, p.20).

Edema Adverse Events
Pfizer identified 10 edema adverse events under the following preferred terms: edema (4), edema peripheral (3), eyelid edema (1) and generalized edema (1) (PSUR, pp.20-21).

Euphoric Mood Disorder Adverse Events
Pfizer identified 14 cases reporting an adverse event of euphoric mood or feeling abnormal. Five of these events were classified as serious. Pfizer felt that 12 of the cases

had insufficient information to allow a meaningful assessment. Pfizer felt the remaining two cases were confounded by concomitant morphine use (PSUR, p.21).

Psychotic Disorder Adverse Events
Pfizer identified nine psychotic disorder events during the reporting period. Three of these cases were classified as serious. Pfizer felt there was insufficient information to assess six cases. For the three remaining cases, one involved a patient with a history of hospitalization for a paranoid episode who attempted suicide by ingesting 30 pregabalin capsules. The reporting physician described this event as a parasuicidal gesture in association with an affective unsteady depression (included above with suicide attempt cases, 2004099599). In a second case, a patient required hospitalization for a psychotic reaction that resolved with continued pregabalin and haloperidol. The third case was a 75 year old female who experienced a psychotic event with an acute confusional state that began one week after starting pregabalin and resolved seven days after stopping pregabalin. Pfizer identified concomitant amitriptyline use as a possible confounder in this case (PSUR pp.21-22).

Gait Disturbance/Fall/Ataxia/Balance Disorder Adverse Events
Pfizer identified 22 cases with preferred terms of gait disturbance (5), fall (5), ataxia (9), and balance disorder (5). Fifteen cases were classified as serious. Pfizer identified insufficient information, concomitant medications, and concurrent disorders as factors complicating the assessment of these events (PSUR pp. 22-23).

Drug Interaction Adverse Events
Pfizer identified 10 cases with a preferred term of interaction. Three events were classified as serious. Pfizer noted that one event of increased sedation followed treatment with ethanol and oxycodone. Two events were nausea that followed treatment with pregabalin and morphine. The remaining interaction events included speech disorder and gait disturbance (tilidine/naloxone), muscle cramp (atorvastatin and levodopa/benserazide), seizure (phenytoin), coma (dihydrocodeine), PT prolonged (phenprocoumon), and circulatory collapse (metoprolol/ramipril). There were few details provided for these events (PSUR, pp. 23-24).

Overdose
Pfizer reported three cases of pregabalin overdose (patients ingested pregabalin doses exceeding the maximum recommend dose of 600mg). Two of the cases reported no associated adverse events. In the remaining case, a 61 year old female who ingested 30 pregabalin capsules in a suicide attempt (see above, psychotic disorder) experienced agitation, confusion, and aggressiveness. She was treated with tranquilizers (not specified) and was psychotic the following day (PSUR pp. 24-25).

Decreased Therapeutic Response
Pfizer received nine cases with the preferred term drug ineffective. Patients mentioned in these reports were being treated with pregabalin for pain related indications (3 reports did not include indication) (PSUR p.25).

Abuse/Misuse Reports
Pfizer received no reports of pregabalin abuse or misuse (PSUR p.26).

Pregnancy/Lactation
Pfizer received no reports of pregabalin use during pregnancy or lactation (PSUR p.26).

Adverse Events in Children, the Elderly
Pfizer received two cases of adverse events in children. A nine year old male treated with pregabalin, phenytoin and other unspecified medications experienced decreased phenytoin levels. A sixteen year old female treated with pregabalin for neuropathic pain experienced dry mouth associated with mouth ulceration, poor concentration and memory, and depression. Pregabalin was stopped and the patient was recovering (PSUR pp 26-27).

Pfizer received 81 cases of adverse events in elderly patients (age >=65 years or patient described as elderly by the reporter). Forty-two cases were classified as serious and two were deaths. The most commonly reported preferred terms for elderly patients were confusional state (11), somnolence (10), and tremor (7) (PSUR pp 26-27).

Pfizer reported that the following events had a higher proportionate reporting rate (>3:1 ratio) in the elderly compared to the non-elderly: tremor, confusional state, asthenia, fall, balance disorder, dysgeusia, disorientation, and hallucination (PSUR pp 26-27).

Pfizer Conclusions
Pfizer conclude that their first PSUR identified no new safety information that would alter the risk/benefit assessment of pregabalin. They felt no changes were required for the pregabalin core data sheet. They acknowledged the need to continue to follow reports of the following events: weight increase, nausea, suicide, eye disorder, euphoric mood, and gait disturbance/fall/ataxia/balance disorder.

FDA Review of Listings
I reviewed the line listing of events to identify potential adverse events of concern with pregabalin. The listings included limited information about the adverse events. I identified the following potentially important events myelosupression (1), coagulopathy (1), pancytopenia (1), platelet count decreased (1), oral mucosal blistering/lip blistering (1), tongue ulceration (1), hallucination (4), psychotic disorder (9), suicide attempt (2), suicidal ideation (3), agitation (4), self injurious behavior (1), aggression (2), paranoia, polymyalgia (1), muscle cramp (5), myalgia (1), muscle spasms (3), blisters (1), liver function test abnormal/blood bilirubin increased (1), respiratory depression (1), vasculitis (1), and hypertensive crisis (1).

Discussion
Pfizer's PSUR describing reports received from 7/7/04 through 1/6/05 did not suggest meaningful changes in pregabalin's safety profile. The PSUR covered a relatively short period of time and the estimated post marketing exposure was comparable to the exposure in the development program. The events reported in the PSUR were generally

similar to the events observed in the development program. The information provided for individual cases in the PSUR was limited.

Pregabalin Safety Updates 2 and 3

As part of the response to the Approvable letter for pregabalin, Pfizer submitted the third safety update (SU3). The first pregabalin safety update was submitted in February 2004 and those data were included in the HFD-120 safety review for the NDA. The second pregabalin safety update was submitted to HFD-170 on November 1, 2004 to support the peripheral neuropathy and post herpetic neuralgia indications. SU2 had a cutoff date of April 30, 2004. HFD-170 read SU2 to determine if there were changes in the safety profile of pregabalin but did not write a formal review of that submission (personal communication M. Kashoki). The SU3 cutoff date is January 12, 2005 (p.3).

In this document I will review safety information from SU2 and SU3. For the parts of this review that focus on the cumulative experience such as exposure and adverse event risks, I will rely on the cumulative data presented in SU3 which includes data from the NDA through SU3. For individual events of potential concern including deaths, SAEs, and discontinuations for AEs, I will review the presentations in both SU2 and SU3. I will identify and summarize newly reported cases related to previously identified potential safety signals (ex., myopathy, thrombocytopenia) as well as cases of potentially important events (ex. hepatic failure, serious skin reactions, etc.)

Source of New Safety Data in SU3
SU3 includes data from four recently completed controlled trials and two open-label extensions. The following are the new studies in SU3:

108-pain with irritable bowel syndrome
112-epilepsy
114-OL extension for 112
125-spinal cord injury/neuropathic pain
202-OL extension for 125
167-epilepsy sleep study

Through the cutoff date of SU3, Pfizer submitted data from 65 trials from their phase II/III development program. This total includes 37 controlled trials. The following table summarizes the studies included in SU3 (p.4).

Table 2. Studies Included in the Pregabalin Third Safety Update (SU3)

Study Grouping	Studies Included in Grouping
37 Controlled Studies Combined	**13** Neuropathic Pain: 014, 029, 030, 040, 045, **125**, 127, 131, 132, 149, 155, 173, 196 **6** Add-on Epilepsy: 009, 011, 034, **112**, 157, **167** **5** Other Chronic Pain: 031, 032, 104, 105, **108** **6** Generalized Anxiety Disorder: 021, 025, 026, 083, 085, 087 **7** Other Psychiatry: 017, 022, 080, 081/153[a], 092[b], 094[b], 091
65 Controlled +	Controlled (Double Blind)

Uncontrolled Extension Studies Combined	**15** Neuropathic Pain: 014, 029, 030, 040, 045, **125**, 127, 131, 132, 149, 155, 173, 060[c], 160[c], 196 **8** Epilepsy: 007[c], 009, 011, 034, **112**, 145[c], 157, **167** **5** Other Chronic Pain: 031, 032, 104, 105, **108** **8** Generalized Anxiety Disorder: 021, 025, 026, 083, 085, 087, 088[c], 181[c] **9** Other Psychiatry: 017, 022, 080, 081/153[a], 082[c], 092, 094, 093/192[a,c], 91
	Uncontrolled (Open Label) **12** Pain: 015, 033, 061, 074, 134, 165, 166, 174, 183, 197, 198, **202** **6** Epilepsy: 008, 010, 012, 035, **114**, 164 **2** Psychiatry: 084, 100

Study numbers for studies included since SU2 are **bolded** (ie, these studies provide new patients in SU3).
[a] Twin studies summarized in 1 research report and therefore 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 37 controlled studies because of differences in study design or indication, or because they were terminated early with minimal enrollment.

In addition to above, Pfizer reported that they completed a Phase I study in 30 healthy Korean volunteers (no deaths, SAEs, or discontinuations for AEs for this trial).

Exposure
Since SU2, Pfizer reported an additional 1605 subjects exposed to pregabalin in completed controlled and uncontrolled phase II/III studies. The total number of subjects exposed in completed controlled and uncontrolled phase II/III studies in the integrated safety database is 10367. Pfizer reported that subjects were exposed to pregabalin for a total of 9210 person years in phase II/III studies in the integrated safety database, an increase of 1146 person years from SU2 (pp.5-6).

In completed phase II/III controlled trials, Pfizer reported an additional 245 pregabalin exposed subjects in SU3 for a total of 6469 subjects. Pfizer also reported that an additional 229 subjects were exposed to placebo for a total of 2839 subjects. Pfizer did not update the person time exposure for the controlled trials in SU3 (pp.5-6).

As an appendix to this review I include a table that summarizes the number of subjects exposed by indication for the pregabalin phase II/III studies included in the integrated safety database.

Safety databases from which adverse event data is drawn
In their SU presentations of adverse events, Pfizer has presented data from two databases. Data presented from the integrated safety database comes from Pfizer's Oracle Clinical Study Database and includes safety data from completed pregabalin phase II/III clinical trials that were entered by the cutoff date. Pfizer possess additional pregabalin safety data. Data from completed clinical trials not entered into the Oracle Clinical Study Database by the cutoff date, data from ongoing pregabalin clinical studies and data from other sources are included in a separate database, ARISg. Pfizer made limited

presentations of ARISg safety data. While some adverse events presented in SU3 may be identified as new to the Oracle database, they may have been included in previous submissions, particularly narratives for AEs, because they were previously identified from the ARISg database.
Review of Adverse Events

Deaths
SU2
Through SU2, there were 76 deaths in the Oracle Clinical Study Database. SU2 identified eight new deaths entered into the Oracle Clinical Study Database by the cutoff date (SU2, p.20). Information for six of these deaths was reported in previous submissions from the ARISg database, and two of the deaths were not previously identified. Six additional new deaths were reported from the ARISg database. These six deaths were from studies included in the integrated safety database but had not been entered into the Oracle database by the SU2 cutoff date. Pfizer reported that there were no deaths from ongoing studies during the SU2 period (SU2, p.21).

Below I identify the new deaths from SU2.

SU2 Listing of New Deaths by Database Source

Patient identification	Protocol Number	Days from Last Dose to Death	Preferred Term for Cause of Death
New Deaths from the Oracle Clinical Study Database, Not Previously Identified			
040_067002	1008-74	15	Carcinoma of lung, dyspnea
045_003003	1008-61	4	Cardiomyopathy, sepsis
New Deaths Reported to ARISg but not to the Oracle Clinical Study Database			
149_400002	1008-165		Hepatic neoplasm malignant, portal vein thrombosis
149_400005	1008-165		Gastric cancer/aspiration
149_430008	1008-165		Myocardial ischemia
155_124003	1008-166		Cerebral hemorrhage
197_107007	1008-197		Septic shock
197-132-001	1008-197		Myocardial infarction

Data from SU2 tables 10 and 11, pp.20-21.

These deaths occurred in patients treated for pain related indications and the age range for these subjects was 63-85 years. The reported causes of death did not appear unusual given the age and medical co-morbidities of the subjects who died, although some cases had minimal details and lacked autopsy information. Summaries of information included in the narratives for the above deaths are provided in an appendix to this review.

SU3
Pfizer reports that through SU3, there have been a total of 90 deaths during 9210 person years (9.8/1,000PY) included in their phase II/III integrated safety database of completed double blind studies and their open label extensions (Oracle Clinical Study Database). In the NDA, there were 55 deaths in 6393 person years (8.6/1000PY). In SU3, Pfizer reported 14 new deaths entered into their Oracle Clinical Study Database. Five of these deaths were new since SU2. The remaining 9 deaths were reported in previous

submissions from the ARISg database. In addition to the deaths in the Oracle Safety Database, SU3 includes 4 new deaths from the ARISg database since SU2 that had not been included in the Oracle Safety Database by the SU3 cutoff date (p.7).

I include Pfizer's table that identified the five new deaths in the Oracle Clinical Study Database and the four new deaths in the ARISg database since SU2.

Table 4. New Deaths Included in the SU3 Reporting Interval: Pregabalin-Treated Patients

Patient Identification	Protocol in Which Event Occurred	Indication	Preferred Term for Cause of Death
Integrated Safety Database			
149_354028	1008-165	DPN	Heart failure
132_106006	1008-197	PHN	Intracranial hemorrhage
196_803002	1008-198	PHN	Myocardial infarct
034_017002	1008-035	Epilepsy	Sudden death
112_147001	1008-114	Epilepsy	Death
ARISg database[a]			
010-002001	1008-010	Epilepsy	Lung neoplasm malignant
045_070006	1008-061	PHN	Prostate cancer
149_418005	1008-165	DPN	Lung neoplasm malignant
155_132005	1008-166	NeP	Coronary atheroma Ischemic heart disease

Source: Appendix ALL.8 and the Narrative Overview Table (Appendix ALL.23)
[a] Event was reported to the ARISg database but not the Oracle Clinical database as of the 12 January 2005 cutoff; therefore, this patient is not listed on Appendix ALL.8.

Summaries of information included in the narratives for the above deaths are provided in an appendix to this review.

In addition to the above identified deaths, Pfizer identified 10 pregabalin deaths and 1 blinded treatment death from ongoing studies during the reporting period. Pfizer's appendix ALL.09 is a listing that includes these deaths and provides information about the reported cause of death. Pfizer also provided brief narratives for these deaths. For the blinded treatment assignment subject, the narrative reported that the subject experienced a hypertensive crisis but died from other causes not identified. The reported causes of death for the 10 pregabalin treated subjects were death (no additional information provided, n=2), deterioration of gastric cancer, worsening tumor with metastases, suspected pulmonary embolism, progression of prostate cancer, carcinoma of the rectum, progression of mammary tumor, exacerbation of liver cancer, and coronary artery disease.

Serious AEs

SU2

I examined SU2 Appendix ALL.22 and Listing ALL.27, to identify new SAEs in the integrated safety database that might be concerning. These appendices did not identify new SAEs of CPK increased, myopathy, hepatitis, liver failure, heart block, suicide attempt, aplastic anemia, pancytopenia or Stevens Johnson Syndrome. The following SAEs were reported for the first time in SU2 (not in previous presentations of SAEs in

the integrated safety database): adenoma, infection bacterial, lab test abnormal, duodenal ulcer perforation, perforated stomach ulcer, hypervolemia, agitation, deafness, eye hemorrhage, ptosis, abortion, and hypokinesia. Appendix ALL.22 identified one new SAE of pancreatitis and one new SAE of thrombocytopenia. The SAE of pancreatitis was previously reported in SU1, and the narrative was summarized as part of the NDA review (subject 166-074022, NDA Review p.206).

Listing ALL.27 identified subject 149-401003 as having a new SAE of thrombocytopenia. At the Division's request, Pfizer provided a narrative for this event (4/19/05 submission). The thrombocytopenia event occurred during a hospitalization for pneumonia and COPD exacerbation. The lowest recorded platelet count near the time of this event was 121 x 10^9/L. The event was attributed to quinidine which was continued. A listing of all study hematologic results showed that this subject had his lowest platelet in a subsequent study (97 x 10^9/L). Following this platelet count, the subject had platelet counts that ranged from 105 to 153 x 10^9/L. The only bleeding related AE was an event of mild hemoptysis that was treated with antibiotics and resolved.

Appendix ALL.22 listed one SAE of mesenteric occlusion in the total column but identified no such events through SU1, and no new mesenteric occlusion event in SU2. In response to our request, Pfizer provided this narrative and explained that the event had not been entered into the Oracle database by the cutoff for SU1. This subject did not continue in an extension, and therefore was not among the 1552 subjects identified as new in SU2. Because of these circumstances, the event is included in the total column but does not appear in the columns for SU1 or SU2.

SU3

In SU3, Pfizer provided tables that updated the serious adverse event totals for the controlled and combined controlled and uncontrolled trials. These tables provided columns that identified new SAEs reported in SU3, the total number of AEs from SU2 and the new updated totals after combining data from SU2 and SU3.

Controlled Trials

Pfizer reported that after adding the new controlled trial SAE data from SU3 to the previously available data, the SAE risk for pregabalin subjects was 2.7% (173/6469) compared to 2.1% (60/2839) for placebo subjects. In the following table, I summarize the SAEs that occurred in at least 0.1% of pregabalin subjects and at least twice as frequently compared to placebo using the data through SU3

SAEs that occurred in at least 0.1% of pregabalin subjects and at least twice as frequently compared to placebo, pooled pregabalin controlled trials through SU3

SAE	Pregabalin (n=6469)	Placebo (n=2839)
Accidental injury	0.3% (22)	0.1% (3)
Chest pain	0.2% (10)	0.1% (3)
Dizziness	0.1% (6)	0
Cellulitis	0.1% (5)	0
Confusion	0.1% (5)	0
Cholecystitis	0.1% (4)	0% (1)
Suicide attempt	0.1% (4)	0

Cerebrovascular accident	0.1% (4)	0
Ataxia	0.1% (4)	0% (1)
Urinary tract infection	0.1% (4)	0% (1)

From SU3 table Appendix ALL.10

In the following table I summarize SAE risks for events of interest that did not meet the criteria for inclusion in the above table but are of special interest.

Risks for selected SAEs, pooled pregabalin controlled trials, through SU#3

SAE	Pregabalin (n=6469)	Placebo (n=2839)
Dyspnea	0% (3)	0% (1)
Peripheral edema	0% (3)	0
Myopathy	0% (2)	0
CPK increased	0% (1)	0
Edema	0% (1)	0% (1)
Depression	0% (1)	0.1% (3)
Psychosis	0% (1)	0% (1)
Thrombocytopenia	0% (1)	0
Skin ulcer	0% (1)	0
AV block	0% (1)	0
Pancreatitis	(0)	0% (1)

From SU table Appendix ALL.10

Combined Controlled and Uncontrolled Trials

Through SU3, the SAE risk for the combined controlled and uncontrolled trial data is 10.5% (1084/10367) compared to 9.7% (957/9847) from SU2. I reviewed the new SAEs reported in SU3. Below I list selected risks for SAEs of interest as well as SAEs newly reported in SU3 and not previously reported through SU2.

Risks for selected SAEs, Combined Controlled and Uncontrolled Trials, through SU#3

SAE	Cumulative SU2 (9847)	New SU3 Data (1605)	Cumulative SU3 (10367)
Accidental injury	1.1% (111)	1.4% (23)	1.3% (132)
Congestive heart failure	0.3% (33)	0	0.3% (33)
Overdose	0.2% (15)	0.2% (4)	0.2% (20)
Depression	0.2% (20)	0.1% (2)	0.2% (22)
Confusion	0.1% (14)	0.2% (3)	0.2% (17)
Heart Failure	0.1% (13)	0.1% (2)	0.1% (15)
Suicide attempt	0.1% (11)	0.2% (3)	0.1% (14)
Skin ulcer	0.1% (11)	0.1% (2)	0.1% (13)
Psychosis	0.1% (9)	0.1% (2)	0.1% (11)
Pancreatitis	0.1% (5)	0	0% (5)
LFTs abnormal	0% (3)	0.1% (1)	0% (4)
Hallucinations	0% (2)	0.1% (2)	0% (4)
Intentional Overdose	0% (3)	0.1% (1)	0% (4)
CPK increased	0% (3)	0	0% (3)
Myopathy	0% (2)	0.1% (1)	0% (3)
Thrombocytopenia	0% (2)	0.1% (1)	0% (3)
Necrotizing pancreatitis	0% (1)	0	0% (1)
AV block	0% (1)	0	0% (1)
AV block second degree	0% (1)	0	0% (1)
AV block complete	0% (1)	0	0% (1)
Parathyroid disorder	0	0.1% (1)	0% (1)
Lymphadenopathy	0	0.1% (1)	0% (1)

Lymphangitis	0	0.1% (1)	0% (1)
Uremia	0	0.1% (1)	0% (1)
Peritonitis	0	0.1% (1)	0% (1)
Intentional injury	0	0.1% (1)	0% (1)
Hepatitis	0	0.1% (1)	0% (1)
Aphasia	0	0.1% (1)	0% (1)
Dysautonomia	0	0.1% (1)	0% (1)
Multiple sclerosis	0	0.1% (1)	0% (1)
Sleep disorder	0	0.1% (1)	0% (1)
Emphysema	0	0.1% (1)	0% (1)
Pelvic pain	0	0.1% (1)	0% (1)
Skin disorder	0	0.1% (1)	0% (1)
Papilledema	0	0.1% (1)	0% (1)
Bladder calculus	0	0.1% (1)	0% (1)
Menorrhagia	0	0.1% (1)	0% (1)
Penis disorder	0	0.1% (1)	0% (1)
Drug interaction	0	0.1% (1)	0% (1)

From Appendix ALL.11

Using Appendix ALL.12, I identified the ID numbers for the subjects who experienced selected SAEs included in the above table. I then read and summarized the narratives for these events. The identified SAE of thrombocytopenia (subject 125-001006) was summarized in the NDA review and is not included below.

Suicide Attempt

112-001003 This 50 year old male with partial seizures, hypercholesterolemia and depression attempted suicide on study day 328 by cutting his radial artery with a knife. He called for help and was taken to a hospital by ambulance and survived the attempt. The narrative reported that problems with job "mobbing" led to the suicide attempt. The narrative did not report whether this subject had a history of suicide attempts or self injury. He continued pregabalin. Concomitant medications prior to the suicide attempt were carbamazepine and levetiracetam

112-145004 This 44-year-old white male had a history of partial seizures and depression. Pregabalin was administered orally, daily, from [redacted] a total of 75 days. The subject's last follow-up visit at the site was on [redacted] (Study Day 75), the subject was found dead seated in a chair with some hand written notes at the scene. The cause of death appeared to be possible suicide. There were no reported changes in the subject's financial or social situation. The subject had no history of alcohol or drug abuse and no prior history of suicide attempts. The subject's depression was considered stable at the time of death, and there was no change in the subject's anticonvulsant medications within the two weeks prior to death. The subject was reportedly compliant in taking his study medication, and therefore, it was assumed that he was also compliant in taking his other medications including venlafaxine hydrochloride. On [redacted] an autopsy reported helium anoxia/plastic bag suffocation. Illnesses present at the onset of the event and relevant medical history included mild depression [redacted] present), seizures, headaches, cystic fibrosis, head injury/fractured skull, osteoporosis, chest infections related to cystic fibrosis, horizontal unsustained bilateral nystagmus, and bilateral mild congenital anomaly of optic disc. Concomitant therapy taken within 2 weeks before the onset of the event included carbamazepine, phenytoin sodium, venlafaxine hydrochloride, pancreatin, multivitamins (ergocalciferol, ascorbic acid, folic acid, thiamine hydrochloride, retinol, riboflavin, nicotinamide, panthenol) and Bactrim® (sulfamethoxazole, trimethoprim).

149-430006 This 32-year-old white male subject received pregabalin for the treatment of painful diabetic peripheral neuropathy. The subject was initially enrolled in pregabalin study 1008-149 on [redacted] and was randomized to the 150 mg/day treatment group through [redacted] for a total of 101 days. The subject continued in extension study 1008-165 and received pregabalin orally, daily at a total daily dose

range of 75-600 mg from [redacted] (Study Day 1) through [redacted] and was continued. The total daily dose of pregabalin closest to the onset of the event was 600 mg. On [redacted] (Study Day 642), the subject took an intentional overdose of amitriptyline (dose unknown), collapsed, fell, and developed a hematoma on the clavicle. The subject was hospitalized and the hematoma of the left clavicle was drained. Subsequently, the subject developed a methicillin resistant *Staphylococcus aureus* infection that required 2 weeks of intravenous antibiotic therapy. The subject had a history of voicing or communicating suicidal ideation and attempting suicide and was receiving psychiatric support. In response to the intentional overdose, pregabalin treatment was temporarily interrupted (dates not provided). The subject had not yet recovered from the intentional overdose and the methicillin resistant *Staphylococcus aureus* infection. Illnesses present at the onset of the events and other relevant medical history included diabetes, retinopathy, early renal changes, pilonidal sinus, ischiorectal abscess, hypertension, depression, grand mal seizure, varicose eczema, perianal abscess, urinary retention, and suicidal ideation. Concomitant therapy taken within two weeks before the onset of the intentional overdose included valsartan, insulin humulin, ibuprofen and citalopram hydrobromide.

Hepatitis, LFTs abnormal

149-400002 This 70-year-old white male subject with a history of non alcoholic steatohepatitis (pre-study), received pregabalin for the treatment of painful diabetic peripheral neuropathy. The subject was initially enrolled in study 1008-149 on [redacted] and was randomized to the pregabalin 150 mg/day treatment group through [redacted], for a total of 77 days. The subject continued in extension study 1008-165 and received pregabalin orally twice a day, at a total daily dose range of 150 to 600 mg from [redacted] (Study Day 1), through [redacted], and was continued. The total daily dose of pregabalin closest to the onset carcinoma hepatocellular with portal vein thrombosis was 600 mg and 300 mg, respectively. On [redacted] (Study Day 694), the subject presented to the emergency room with left sided chest soreness that did not respond to nitroglycerine, and epigastric tenderness. Pain responded to oral analgesia. Liver function test results were abnormal including an SGPT of 78 U/L (reference range not provided), SGOT of 122 U/L (reference range not provided), GGTP of 979 U/L (reference range not provided), ALP of 325 U/L reference range: 30-115). Previous liver function tests were within reference range with the exception of alkaline phosphatase, which progressively increased from 104 to 1070 U/L between [redacted] Arrangements were made for the subject to have further outpatient follow-up. On [redacted] (Study Day 731), an upper abdominal ultrasound showed the liver to be grossly abnormal, the spleen enlarged, and the pancreas bulky. A subsequent CT scan on [redacted] (Study Day 732) showed multiple focal lesions in the liver (probable metastatic), abnormal soft tissue masses in the transverse colon (probable neoplastic), and some thickening of the bowel wall with possible neoplastic extension into it. The subject had no known history of smoking, alcohol use, or use of illicit drugs, and no previous history of cancer. Family history of cancer was limited to a brother who had prostate cancer. Work history included employment as an accountant for a company dealing with asbestos. It is unknown if the subject had any exposure to hepatotoxins. The subject had a prior emergency room visit in [redacted] for chest and abdominal pain, nausea and vomiting. At that time, an abdominal CT scan showed thickening of the wall of the ascending colon presumed to be due to fecal matter. A colonoscopy showed normal mucosa up to the caecum, with no abnormalities, and an endoscopy revealed hiatal hernia and duodenal deformity. It is unknown if any polyps were discovered at that time. The subject had not undergone any further colonoscopies or endoscopies since [redacted]. On [redacted] (Study Day 752), the subject was admitted to the hospital for investigation of possible bowel obstruction, and a diagnosis of possible bowel cancer and liver metastasis was made. An abdominal X-ray showed no evidence of bowel obstruction, and a preliminary ultrasound showed no evidence of liver lesions. On [redacted] (Study Day 755), an abdominal and pelvic CT scan revealed widespread metastases in the liver and irregular thickened bowel wall in the ascending colon region. On [redacted] (Study Day 756), a colonoscopy was performed that was negative for colonic malignancy. On [redacted] (Study Day 762), the subject's diagnosis was confirmed as extensive metastatic hepatocellular carcinoma confined to the liver, and portal vein thrombosis (onset date unknown, present on CT scan [redacted]), secondary to hepatocellular carcinoma, and pre-existing non-alcoholic steatohepatitis (onset [redacted]. A liver biopsy was not performed, and the diagnosis was based on imaging results. On [redacted] hemoglobin levels were 12.0 g/dL (reference range: 14-18 g/dL). Low hemoglobin levels were present since baseline and were not considered to be related to the event. In response to these events, no action was taken with study drug, and treatment with pregabalin was continued

unchanged. The subject did not receive any radiation or chemotherapy. On ——— (Study Day 765), the subject was discharged from the hospital with pain medication and palliative care. On ——— (Study Day 791), the subject died. The cause of death was confirmed as hepatocellular carcinoma, per the investigator. No autopsy was performed. Illnesses present at the onset of the event and other relevant medical history included gallbladder removal, acute myocardial infarction, coronary artery bypass, appendectomy, unexplained weight loss (10 kg in the last 6 months), increased indigestion, diabetes, ischemic heart disease, hypertension, and sick sinus syndrome with permanent pacemaker, and non-alcoholic steatohepatitis. Concomitant therapy taken within 2 weeks before the onset of carcinoma hepatocellular, included atorvastatin, rabeprazole sodium, indapamide, paracetamol, isosorbide mononitrate, captopril, acetylsalicylic acid, metformin, insulin, and insulin injection, isophane.

Uremia

029-043019 This 46 year old female had a history of neuropathic pain, diabetes mellitus, and chronic renal insufficiency (creatinine 3.1-3.4mg/dL). On study day 119, she was diagnosed with acute renal failure and treatment included peritoneal dialysis. This event was attributed to progression of diabetes mellitus and poor compliance. On study day 812 she was admitted to a hospital with uremia. Pregabalin was stopped and not restarted. The uremia was considered resolved two days later.

Rhabdomyolysis

105-522001 This 48 year old female had a history of fibromyalgia. On study day 690, she was hospitalized for chest pain and underwent a coronary artery stent placement. On study day 799, she was hospitalized for rhabdomyolysis. Her CK was in the 8,000ug/L range at the time of the event. The event was considered due to treatment with lovastatin, which was stopped. CKs subsequently decreased to 6002 ug/L, 2867ug/L and three days after stopping lovastatin 1531ug/L. Pregabalin was continued during this event. Other concomitant medication taken prior to the rhabdomyolysis event were clopidogrel, topiramate, bupropion, triamterene, aspirin, vicodin, dextropropoxyphene, dyazide, hyoscyamine, chlorpheniramine, diphenhydramine, pseudophedrine, midred, triamcinolone, ketorolac, zolpidem, and levothyroxine.

Psychosis

010-035101 This 56 year old male with partial seizures, ganglioneuroma, s/p right temporal craniotomy, intermittent aggressive behavior (no episodes in the prior 3-4 years), and mental retardation became aggressive, combative, hit people, and threw hot coffee at a nurse because he didn't get the right coffee. He was taken to an ED where he was found to be acutely psychotic and agitated. Pregabalin was continued and the event resolved. Concomitant medications prior to the event were carbamazepine, topiramate, phenytoin, levetiracetam, lorazepam, ranitidine, paracetamol, calcium carbonate, aripiprazole, bisacodyl, and diazepam.

125-002012 This 58 year old female with chronic pain after a spinal cord injury, intermittent UTIs, ileal conduits, developed confusion while being weaned off pregabalin for a mandatory drug holiday. She was admitted to a hospital and had thought disorder and flight of ideas. She had a WBC count of 8.3 and the narrative reported bacteremia with gram negative rods. Pregabalin was permanently stopped and the psychosis resolved. Concomitant medications prior to this event were clonazepam, metoclopramide, omeprazole, ramipril, ascorbic acid, levothyroxine, diazepam, medroxyprogesterone, docusate, and sorbitol.

Pfizer identified subjects with SAEs from ongoing studies in Appendix ALL.9. Below, I identify subjects who experienced SAEs in ongoing trials and were either known to be taking pregabalin or whose treatment assignment remained blinded. The table below does not include events from the table that were identified as occurring pre-randomization.

SAEs from Ongoing studies, SU3

Case#	Sex/Age	Event	Outcome
		Pregabalin treatment	
2004113378	M/83	TIA	Not recovered

2004120131	M/63	Hypertensive derailment	Recovered
2004116351	F/83	Femur neck fracture	Recovered
2004116447	F/71	COPD exacerbation	Not recovered
200418867	M/64	Organic brain syndrome	Unknown
2004112428	F/54	Muscle cramps R calf	Recovered
2004111600	M/42	Stroke	Unknown
2004111582	M/54	Encephalomeningitis	Recovered
2005005733	M/?	Worsening back pain	Unknown
2004102793	F/92	Persisting pain, lack of efficacy	Recovered
2004116260	M/?	Worsening diabetic gangrene	Recovered with sequelae
2005008552	F/74	Exacerbation diabetic foot	Not recovered
2005011443	F/61	R calf muscle cramp	Recovered
		Treatment Assignment Blind not Broken	
2004023221	M/70	Duodenal ulcer	Recovered
2004108406	F/67	Worsening GAD	Recovering
2005011007	F/41	Acute Asthmatic Bronchitis	Recovered
2004103019	F/55	Chest pain	Recovered
2005007735	F/57	Multiple Trauma	Recovered
2005010762	F/76	Staphylococcal Infection	Not recovered
2004106219	F/56	Recurrent acute pancreatitis	Unknown
2004107476	F/66	Gastric bypass surgery	Recovering

Data from SU3, Appendix ALL.9

I read the narratives for the two subjects with SAEs of muscle cramps to look for evidence of myopathy. The narrative for event 2004112428 included no information about the final diagnosis or test results for the muscle cramp symptoms and stated that the subject was hospitalized for dyspnea caused by the events and that the muscle cramps resolved with discontinuation of pregabalin. The narrative for event 2005011443 stated that the subject was admitted for one day for a muscle cramp, provided no information about a diagnosis or test results, and noted that the event resolved with continued pregabalin treatment.

I also read the narrative for the blinded treatment assignment subject with the event recurrent acute pancreatitis. This 56 year old female with fibromyalgia and a history of acute pancreatitis, etiology unspecified, was hospitalized for acute pancreatitis. This subject was taking no known concomitant medications at the time of the event.

Discontinuation for AEs

SU2

I examined SU2 Appendix ALL.38 and Listing ALL.42, to identify new AEs leading to discontinuation in the integrated safety database that might be concerning. There have been no discontinuations for AV block, hepatitis, hepatic failure, angioedema, Stevens Johnson syndrome, or aplastic anemia. There were no new AEs in SU2 that led to discontinuation for pancreatitis, suicide attempt, pancytopenia, CPK increased, myasthenia, or myopathy. Pfizer identified one new discontinuation for each of the following AEs in SU2: thrombocytopenia (157-117003, p.2777), SGPT increased (091-587030, p.2741), myalgia (091-583010, p.2715), and psychosis (157-112018, p.2570, 2769). I summarize those events below.

Thrombocytopenia

157-117003 This 62 year old female with partial seizures, hyperchromic macrocytic anemia, amyloid angiopathy, recurrent intracerebral hemorrhages, osteoporosis, and gastric cancer s/p gastrectomy, developed leucopenia and thrombocytopenia on study day 14. A table that included lab values for this subject reported that the subject had a platelet count of $88x10^9$ on that day with a WBC count of 5.1 $x10^9$ and an ANC of .87 $x10^9$. Study day 17 (still on pregabalin) labs included a platelet count of $190x10^9$ with a WBC count of 7.8 $x10^9$ and an ANC of 2.34 $x10^9$. The narrative noted that study medication was stopped on day 20. She continued in an open label study and had no platelet counts<190 $x10^9$ and no WBC counts<6.5 $x10^9$. Concomitant medications included gabapentin, topiramate, allopurinol, cholecalciferol, potassium, and calcium.

SGPT increased

091-587030 This 33 year old male with anxiety disorder developed an elevated SGPT (63U/L, ULN 22) and uric acid (535umol/L, ULN 416) on study day 205 that led to discontinuation. The narrative noted that the subject recovered from these events 29 days after stopping pregabalin. This subject had no other AEs and was taking no concomitant medications during this study.

Myalgia

091-583010 This 43 year old female with panic disorder and a history of arthritis developed weakness and dizziness on day 1 of pregabalin treatment and muscle aches on day 8. Pregabalin was stopped on day 24, and the narrative reported that all AEs resolved. The narrative included no lab data. Concomitant medication at the time of the event was a hormonal contraceptive.

Psychosis

157-112018 This 39 year old male with partial seizures, a history of encephalitis, and nystagmus developed an acute psychotic disorder on study day 30 of a double blind trial. The subject was described as agitated, very aggressive, and delusional. The subject was restrained and treated with diazepam, levomepromazine, haloperidol, phenytoin, and an electrolyte infusion. The subject recovered on study day 33. This subject had no prior history of psychosis, delusional behavior, or drug abuse. Pregabalin was stopped on the day of the event. The narrative noted that prior to starting pregabalin, this subject was treated with topiramate and lopiremate and experienced "aggressive episodes" that were less severe than this AE. Concomitant medication at the onset of this event was oxcarbazepine.

SU3

In SU3, Pfizer provided tables that updated the discontinuations for adverse event totals for the controlled and combined controlled and uncontrolled trials. These tables provided columns that identified new discontinuations for AEs reported in SU3, the total number of discontinuations for AEs from SU2 and the new updated totals after combining data from SU2 and SU3.

Controlled Trials

Pfizer reported that after adding the new controlled trial discontinuations for AE data from SU3 to the previously available data, the discontinuations for AE risk for pregabalin subjects was 14.1% (915/6469) compared to 6.9% (197/2839) for placebo subjects. These risks were similar to the risks provided in the NDA safety data presentation (pregabalin 13.5%, 741/5508; placebo 6.8% 162/2384).

In the following table, I summarize the AEs that led to discontinuation of at least 0.2% of pregabalin subjects and at least twice as frequently compared to placebo using the data through SU3.

AEs that led to Discontinuation of at least 0.2% of pregabalin subjects and at least twice as frequently compared to placebo, pooled pregabalin controlled trials through SU3

AE	Pregabalin (n=6469)	Placebo (n=2839)
Dizziness	4.2% (274)	0.6% (18)

Somnolence	3.4% (218)	0.4% (10)
Ataxia	1.3% (82)	0.1% (2)
Asthenia	1.1% (69)	0.4% (11)
Confusion	0.9% (58)	0.1% (4)
Thinking abnormal	0.8% (54)	0.2% (6)
Amblyopia	0.8% (51)	0.1% (3)
Incoordination	0.7% (43)	0% (1)
Vertigo	0.6% (39)	0.1% (3)
Peripheral edema	0.5% (35)	0.2% (6)
Diplopia	0.4% (29)	0.1% (3)
Dry mouth	0.4% (25)	0.1% (3)
Nervousness	0.4% (25)	0.2% (6)
Tremor	0.4% (25)	0.1% (4)
Speech disorder	0.4% (24)	0
Abnormal gait	0.3% (20)	0% (1)
Accidental injury	0.3% (19)	0.1% (4)
Euphoria	0.3% (18)	0
Impotence	0.3% (18)	0% (1)
Abnormal vision	0.2% (15)	0
Constipation	0.2% (13)	0.1% (2)
Amnesia	0.2% (14)	0% (1)
Weight gain	0.2% (13)	0% (1)
Pain	0.2% (12)	0.1% (3)
Hallucinations	0.2% (11)	0% (1)
Stupor	0.2% (11)	0
Depersonalization	0.2% (10)	0.1% (2)
Edema	0.2% (11)	0
Depression	0.2% (10)	0.1% (3)
Hypesthesia	0.2% (10)	0
Face edema	0.2% (10)	0.1% (3)

From SU3 table Appendix ALL.15

In the following table I summarize discontinuation for AE risks for events that did not meet the criteria for inclusion in the above table but are of special interest.

Risks for selected Discontinuations due to AEs, pooled pregabalin controlled trials, through SU3

SAE	Pregabalin (n=6469)	Placebo (n=2839)
Dyspnea	0.1% (7)	0.1% (2)
CPK increased	0.1% (5)	0% (1)
Myalgia	0.1% (5)	0
Thrombocytopenia	0.1% (4)	0
Suicide attempt	0% (3)	0
Myopathy	0% (2)	0
Psychosis	0% (1)	0
Skin ulcer	0	0% (1)
Pancreatitis	0	0% (1)
AV block	0	0

From SU3 table Appendix ALL.15

Combined Controlled and Uncontrolled Trials

Through SU3, the discontinuation due to AE risk for the combined controlled and uncontrolled trial data is 19.6% (2036/10367) compared to 19.7% (1936/9847) from SU2.

I reviewed the new AEs leading to discontinuation reported in SU3. Below I list selected risks for AEs leading to discontinuation of interest as well as AEs leading to discontinuation not previously reported through SU2.

Risks for Selected Discontinuations due to AEs, Combined Controlled and Uncontrolled trials, through SU#3

SAE	Cumulative SU2 (9847)	New SU3 Data (1605)	Cumulative SU3 (10367)
Dizziness	4% (397)	0.7% (12)	3.9% (409)
Confusion	0.9% (87)	0.1% (2)	0.9% (89)
Depression	0.5% (45)	0.2% (3)	0.5% (48)
Accidental injury	0.4% (38)	0.2% (3)	0.4% (41)
Hallucinations	0.1% (13)	0.1% (1)	0.1% (14)
CPK increased	0.1% (11)	0	0.1% (11)
SGPT increased	0.1% (10)	0.1% (1)	0.1% (11)
Myasthenia	0.1% (10)	0.1% (1)	0.1% (11)
Congestive heart failure	0.1% (10)	0	0.1% (10)
LFTs abnormal	0.1% (9)	0	0.1% (9)
Myalgia	0.1% (7)	0	0.1% (7)
Heart Failure	0.1% (5)	0.1% (1)	0.1% (6)
Thrombocytopenia	0.1% (5)	0.1% (1)	0.1% (6)
Suicide attempt	0.1% (5)	0.1% (1)	0.1% (6)
SGOT increased	0% (4)	0.1% (1)	0% (5)
Myopathy	0% (2)	0	0% (2)
Psychosis	0% (2)	0	0% (2)
Pancreatitis	0% (2)	0	0% (2)
Grand mal convulsion	0	0.1% (2)	0% (2)
Neurosis	0	0.1% (2)	0% (2)
Pancytopenia	0% (1)	0	0% (1)
Hypervolemia	0	0.1% (1)	0% (1)
Neck pain	0	0.1% (1)	0% (1)
Intentional injury	0	0.1% (1)	0% (1)
Delusions	0	0.1% (1)	0% (1)
Encephalopathy	0	0.1% (1)	0% (1)
Multiple sclerosis	0	0.1% (1)	0% (1)
Skin ulcer	0	0.1% (1)	0% (1)
Scleritis	0	0.1% (1)	0% (1)
Nephrosis	0	0.1% (1)	0% (1)
Photosensitivity reaction	0	0.1% (1)	0% (1)

From SU3 ALL.16

No subjects have discontinued for an AE related to AV block, hepatitis, hepatic failure aplastic anemia or Stevens Johnson syndrome. Subject 112-145004 committed suicide and that event was summarized above with SAEs. Subject 125-002007 discontinued for a skin ulcer that was described as a pressure ulcer secondary to lower leg swelling. Below I summarize additional AEs that led to discontinuation identified from appendix ALL.17.

Photosensitivity Rash

125-005008 This 55 year old male with a history of spinal cord injury discontinued for a photosensitivity rash. The narrative reported that pregabalin was stopped on study day 87 and that the event began on study day 89. The narrative noted that it was not clear why the discontinuation was attributed to this event since study medication had already been stopped. Concomitant medications included celecoxib, aspirin, irbesartan, and atorvastatin.

Intentional overdose

112-148003 This 40 year old male with a history of partial seizures experienced delayed speech and decreased coordination on study day 336, and two days later had a CT that was suspicious for recurrence of oligodendroglioma. An MRI two weeks later demonstrated an intracranial hemorrhage with old and new blood. The subject had not experienced falling, head trauma, hypertension, thrombocytopenia, or coagulopathy prior to this finding. On study day 359, the subject intentionally ingested overdoses of phenytoin, ranitidine, dexamethasone, and pregabalin. He was treated with charcoal and intravenous fluids and was discontinued from the study. The subject recovered from the overdose and underwent a craniotomy and biopsy that documented an anaplastic oligodendroglioma.

Nephrosis

196-006004 This 81 year old female with a history of post herpetic neuralgia, hypothyroidism, angina, hypertension, duodenal ulcer and hypercholesterolemia with normal baseline labs, and no history of renal disease developed nephrotic syndrome. This subject initially enrolled in a pregabalin study on ——— The narrative reported that this subject developed "nephropathy syndrome" in —— but the exact date was unknown and no labs or diagnostic test results were reported. On study day 599 (———), this subject was hospitalized for worsening nephrotic syndrome with progressive lower leg edema. The narrative noted that the subject had proteinuria with a 24 hour urine protein of 8.2 grams, along with a decreased serum albumin and total serum protein. In ——the subject's diuretic was changed from furosemide to Spironol and the narrative reported improvement in edema and proteinuria. The narrative reported that the subject's creatinine potassium and sodium remained within the normal range, and that the subject's TSH was elevated. Pregabalin was stopped due to concern about the potential for water retention. Concomitant medications taken at the time of the hospitalization were furosemide, ticlopidine, levothyroxine, isosorbide dinitrate, propafenone, metildigoxin, hydrochlorothiazide, amiloride, and enalapril.

SGOT increased, SGPT increased

157-132002 This 28 year old male with partial seizures withdrew from an open label pregabalin trial for elevated AST and ALT. The narrative reported that the event began on study day 647 and that pregabalin was stopped on study day 702. The subject had normal transaminases pre-study. In a preceding double blind placebo controlled trial where he received pregabalin, he had elevations in ALT (75U/L) and AST (99U/L) that were not associated with elevated total bilirubin on study day 31 that resolved at the next visit, study day 59. On open label study day 647 his ALT was 111U/L, AST was 63U/L and total bilirubin was 0.6mg/dL. On his next visit on study day 702 his ALT was 38U/L, AST was 27U/L and total bilirubin was 1.2mg/dL. The narrative identified ergenyl chrono (valproate) as the concurrent AED. The subject recovered from the event on study day 721. (LFT values provided as a response to FDA query in a 5/5/05 submission)

Clinical Laboratory Evaluations and Vital Signs

Pfizer provided tables with updated analyses of laboratory results and vital signs. The updated results did not meaningfully differ from the lab and vital sign data previously submitted.

Epilepsy

Source of New Data

In addition to the overall SU3 presentations made by Pfizer, they provided updated safety presentations for just the epilepsy studies. The updated presentations included information from two newly completed controlled trials in epilepsy patients (112 and 167) and data from an open label extension study (114). The newly completed controlled trials included 161 pregabalin (study 112 n=152, study 167 n=9) subjects and 148 placebo (study 112 n=140, study 167 n=8) subjects.

Exposure

Through SU3, Pfizer reports a total of 1,187 subjects exposed to pregabalin and 516 subjects exposed to placebo in epilepsy controlled trials. For combined controlled and

uncontrolled studies Pfizer reported that 2320 subjects have been exposed to pregabalin for 3616 person years through SU3. Through SU3, 366 epilepsy subjects have been exposed to pregabalin for at least 3 years (SU3, p.11).

Deaths

Through SU3 there have been a total of 20 deaths in 2320 (0.9%) epilepsy subjects exposed to pregabalin. The updated mortality rate is not materially changed (5.5/1000PY, 20/3616PY) when compared to the mortality rate calculated in the NDA (5.6/1000PY, 14/2461).

In the NDA there were 14 deaths in epilepsy subjects, all from open label studies. Pfizer identified three additional epilepsy subject deaths that had not been entered into the database at the NDA cutoff date (one occurred >120 days after stopping pregabalin and is not considered further). One new epilepsy subject death was identified in SU1. No new deaths from epilepsy studies were identified in SU2. In SU3, there were three new epilepsy study deaths- one due to lung cancer, one attributed to cardiovascular disease and obesity and one with an unknown cause of death. These deaths are included in Table 4 above and summary information is provided in an appendix to this review.

SAEs

Controlled Epilepsy Trials

Through SU3, the SAE risk among pregabalin treated subjects (4%, 47/1187) was similar to the SAE risk among placebo treated subjects (3.5%, 18/516). Suicide attempt (pregabalin 0.2%, 2/1187, placebo 0), peripheral edema (pregabalin 0.2%, 2/1187, placebo 0), confusion (pregabalin 0.3%, 3/1187, placebo 0), dizziness (pregabalin 0.3%, 3/1187, placebo 0), speech disorder (pregabalin 0.2%, 2/1187, placebo 0) were the SAEs that occurred in more than one pregabalin subject and at least twice as frequently when compared to placebo.

Combined Controlled and Uncontrolled Trials

Through SU3, a total of 324 pregabalin subjects experienced SAEs (14%, 324/2320). This total includes 66 new SAEs that were reported in SU3. There were no new SAEs of myopathy, myalgia, myasthenia, CPK increased, pancreatitis, hepatitis, hepatic failure, aplastic anemia, pancytopenia, thrombocytopenia, or Stevens Johnson syndrome reported in SU3. In the table below, I review SAEs reported in epilepsy studies through SU3. I list selected risks for SAEs of interest as well as SAEs newly reported in SU3 and not previously reported through SU2.

Risks for selected SAEs, Combined Controlled and Uncontrolled Epilepsy Trials, through SU#3

SAE	Cumulative SU2 (1938)	New SU3 Data (813)	Cumulative SU3 (2320)
Accidental injury	3.1% (60)	4.4 (36)	3.1% (73)
Overdose	0.5% (10)	0.4% (3)	0.6% (14)
Depression	0.6% (11)	0.2% (2)	0.6% (13)
Psychosis	0.5% (9)	0.1% (1)	0.4% (10)
Confusion	0.4% (8)	0.1% (1)	0.4% (9)
Suicide attempt	0.3% (5)	0.2% (2)	0.3% (7)
Peripheral edema	0.2% (3)	0.1% (1)	0.2% (4)

Grand mal convulsion	0	0.5% (4)	0.2% (4)
Intentional Overdose	0.2% (3)	0.1% (1)	0.2% (4)
CPK increased	0.2% (3)	0	0.1% (3)
Hallucinations	0.1% (1)	0.2% (2)	0.1% (3)
LFTs abnormal	0.1% (2)	0	0.1% (2)
Accidental Overdose	0	0.2% (2)	0.1% (2)
Congestive heart failure	0.1% (1)	0	0% (1)
Pancreatitis	0.1% (1)	0	0% (1)
Stevens Johnson Syndrome	0.1% (1)	0	0% (1)
Constipation	0	0.1% (1)	0% (1)
Parathyroid disorder	0	0.1% (1)	0% (1)
Intentional injury	0	0.1% (1)	0% (1)
Aphasia	0	0.1% (1)	0% (1)
Encephalopathy	0	0.1% (1)	0% (1)
Multiple Sclerosis	0	0.1% (1)	0% (1)
Papilledema	0	0.1% (1)	0% (1)
Menorrhagia	0	0.1% (1)	0% (1)
Penis disorder	0	0.1% (1)	0% (1)
Urinary incontinence	0	0.1% (1)	0% (1)
Death	0	0.1% (1)	0% (1)

From Appendix Epilepsy.7

Discontinuation for AEs

Controlled Epilepsy Trials

Through SU3, the discontinuation due to AE risk among pregabalin treated subjects (17%, 202/1187) was higher than the discontinuation due to AE risk among placebo treated subjects (6.4%, 33/516). These risks were minimally changed from the discontinuation for AE risks for epilepsy controlled trials that were provided in the NDA safety presentation (pregabalin 15.3% 116/758; placebo 6.1%, 18/294).The following table identifies AEs that led to discontinuation of at least 0.5% of pregabalin subjects, and at least twice as frequently compared to placebo.

AEs that led to Discontinuation of at least 0.5% of pregabalin subjects and at least twice as frequently compared to placebo, epilepsy controlled trials through SU3

AE	Pregabalin (n=1187)	Placebo (n=516)
Dizziness	6.1% (72)	0.6% (3)
Ataxia	4% (48)	0.4% (2)
Somnolence	3.2% (38)	0.4% (2)
Asthenia	2% (24)	0.6% (3)
Diplopia	1.7% (20)	0.6% (3)
Amblyopia	1.5% (18)	0
Thinking abnormal	1.3% (16)	0
Nausea	1.2% (14)	0.4% (2)
Tremor	1.2% (14)	0.2% (1)
Vertigo	1.2% (14)	0.2% (1)
Accidental injury	0.7% (8)	0
Headache	1.1% (13)	0.2% (1)
Confusion	1% (12)	0.2% (1)
Speech disorder	0.8% (9)	0
Incoordination	0.7% (8)	0
Dry mouth	0.7% (8)	0.2% (1)
Abnormal gait	0.6% (7)	0
Abnormal vision	0.6% (7)	0

Weight gain	0.5% (6)	0
Vomiting	0.5% (6)	0.2% (1)

From SU3 Appendix ALL.10

The risks for AEs leading to discontinuation for events of interest that did not meet the criteria for inclusion in the above table include the following: suicide attempt (pregabalin 0.2%, 2/1187, placebo 0), thrombocytopenia (pregabalin 0.1%, 1/1187, placebo 0), CPK increased (pregabalin 0.1%, 1/1187, placebo 0), myalgia (pregabalin 0.1%, 1/1187, placebo 0), peripheral edema (pregabalin 0.3%, 4/1187, placebo 0), edema (pregabalin 0.1%, 1/1187, placebo 0), psychosis (pregabalin 0.1%, 1/1187, placebo 0). No subjects discontinued from an epilepsy controlled trial for pancreatitis, AV block, or skin ulcer.

Combine Controlled and Uncontrolled Trials

The discontinuation due to AE risk for the combined controlled and uncontrolled epilepsy trials was the same in SU2 and SU3 (19% each). There were no new discontinuations for AEs of myopathy, myalgia, myasthenia, CPK increased, pancreatitis, hepatitis, hepatic failure, aplastic anemia, pancytopenia, thrombocytopenia, or Stevens Johnson syndrome reported in SU3. In the table below, I review discontinuations for AEs reported in epilepsy studies through SU3. I list selected risks for discontinuations for AEs of interest as well as SAEs newly reported in SU3 and not previously reported through SU2.

Risks for selected SAEs, Combined Controlled and Uncontrolled Epilepsy Trials, through SU3

SAE	Cumulative SU2 (1938)	New SU3 Data (813)	Cumulative SU3 (2320)
Confusion	1.0% (19)	0.1% (1)	0.9% (20)
Peripheral edema	0.8% (16)	0.1% (1)	0.7% (17)
Accidental injury	0.6% (12)	0.2% (2)	0.6% (14)
Depression	0.5% (10)	0.4% (3)	0.6% (13)
Constipation	0.4% (7)	0	0.3% (7)
Hallucinations	0.2% (3)	0.1% (1)	0.2% (4)
Intentional Overdose	0.1% (2)	0.1% (1)	0.1% (3)
Suicide attempt	0.1% (2)	0.1% (1)	0.1% (3)
CPK increased	0.1% (2)	0	0.1% (2)
Overdose	0.1% (2)	0% (0)	0.1% (2)
Psychosis	0.1% (2)	0	0.1% (2)
Grand mal convulsion	0	0.2% (2)	0.1% (2)
Edema	0.1% (1)	0	0% (1)
Pancreatitis	0.1% (0)	0	0% (1)
LFTs abnormal	0.1% (0)	0	0% (1)
Deep thrombophlebitis	0	0.1% (1)	0% (1)
SGOT increase	0	0.1% (1)	0% (1)
SGPT increased	0	0.1% (1)	0% (1)
Intentional injury	0	0.1% (1)	0% (1)
Pulmonary embolus	0	0.1% (1)	0% (1)
Viral infection	0	0.1% (1)	0% (1)
Face edema	0	0.1% (1)	0% (1)
Delusions	0	0.1% (1)	0% (1)
Encephalopathy	0	0.1% (1)	0% (1)
Multiple Sclerosis	0	0.1% (1)	0% (1)
Neurosis	0	0.1% (1)	0% (1)
Tinnitus	0	0.1% (1)	0% (1)
Scleritis	0	0.1% (1)	0% (1)

Abnormal ejaculation	0	0.1% (1)	0% (1)
Congestive heart failure	0	0	0

From Appendix Epilepsy.11

Clinical Laboratory Evaluations and Vital Signs

Pfizer reported no change in pregabalin's laboratory or vital sign profile based on the data included in SU3.

Discussion

The information submitted in the safety updates does not appear to suggest changes in the safety profile for pregabalin. The mortality risks calculated based on the new data are not materially different compared to the risks from the NDA. The new deaths reported in the safety update did not appear to be due to unusual causes although there were deaths with few details and without identified causes. The SAE risk and discontinuation due to AE risk were not substantially different from the risks described in the NDA safety presentation. There were no newly identified safety update SAEs or discontinuations due to AEs of hepatic failure, pancreatitis, Stevens Johnson syndrome, or pancytopenia that were treatment emergent.

Pfizer reported additional cases of adverse events that were identified in the NDA as potentially related to pregabalin. The safety updates included additional cases SAEs and discontinuations due to AEs of accidental injury, ataxia, somnolence, confusion and dizziness. The newly identified case of rhabdomyolysis appears more likely due to statin therapy than pregabalin. The newly identified thrombocytopenia adverse events in the safety updates seem similar to the thrombocytopenia events described in the NDA.

Along with the events mentioned above, Pfizer reported new psychiatric related SAEs and discontinuation due to AEs. The safety updates included new suicide attempt, suicide ideation, and overdose events. The Division is investigating these events as part of a larger effort exploring suicidal ideation with all antiepileptic drugs. The safety updates also included new psychosis and hallucinations events. Psychosis and hallucinations were reported in the NDA and epilepsy patients appeared to be at higher risk for these events. In the NDA, all nine of the psychosis AEs were reported from open label epilepsy studies and six of the nine occurred in the postictal period. One of the psychosis events reported in the safety updates occurred in a pain study patient, the first in a non epilepsy study pregabalin patient. In the NDA controlled trials, hallucinations occurred more frequently among pregabalin treated subjects than placebo patients in epilepsy (pregabalin 0.4%, 3/758; placebo 0) and pain studies (pregabalin 0.4% 7/1831; placebo 0). In the combined controlled and uncontrolled trial database, hallucinations were reported by 0.6% (52/8666) of pregabalin patients and were reported most frequently in epilepsy patients (1.5%, 24/1613) followed by pain patients (0.5%, 13/2524) and GAD patients (0.2%, 3/1962).

Review of HFD-580 Consult Regarding Human Male Reproductive Function

Background

During the development program, concerns arose regarding the effect of pregabalin on male reproductive function. Pregabalin had adverse effects on reproductive parameters in male animal studies. Pfizer conducted a study in humans to further explore the significance of these animal findings. A consult review by HFD-580 concluded that Pfizer's study in humans did not provide assurance of no effect of pregabalin on human sperm. Therefore, HFD-580 recommended that an additional human trial be performed to assess male reproductive function. HFD-580 felt this study could be performed as a phase IV commitment. Pfizer disagreed with HFD-580's position that an additional study is needed and provided the basis for their disagreement in the response to the approvable letter. The Division asked HFD-580 to review and comment on Pfizer's submission.

HFD-580 reviewer, Dr. Easley, identified the three points made by Pfizer in their response that argues against the need for another human male reproductive function study.

- Pfizer's first point provided their interpretation of results from the animal studies including a lack of effect on testicular spermatogenesis and lack of findings in mouse and monkey studies, conclusions which are disputed by our pharmacology/toxicology reviewer, Dr. Fisher. Pfizer also pointed to negative findings from the completed human study but Dr. Easley responded that Pfizer did not provide outlier results in their report and that the study was not powered to detect a significant change in sperm concentration.
- Pfizer's second point rejects a possible FSH mediated mechanism for sperm effects based on results in the preclinical and human studies. Dr. Easley commented that the significance of the decreased FSH and reduction in motility without a correlation with computer aided sperm analysis of motility was not clear.
- Pfizer's third point was that the completed human study considered multiple sperm parameters and therefore was the most sensitive assessment of human male reproductive function. Dr. Easley agreed that multiple sperm parameters offer the most sensitive assessment of human male reproductive function but that the completed study was not powered to detect a significant change in sperm concentration or morphology. In addition, Dr. Easley felt that the study design limited conclusions that could be made about sperm motility.

Dr. Easley concluded that data from rats and mice identified potential adverse effects of pregabalin on the testes and that monkey data were conflicting. Dr. Easley felt that the completed human study did not raise any specific concerns but that the study was not able to allay the concerns identified in mouse, rat, and monkey studies. Dr. Easley felt that the likelihood of pregabalin having an impact on sperm parameters is low but acknowledged that insufficient data were provided to assess pregabalin's effect on sperm concentration. Dr. Easley commented that the decision on whether to require an additional human trial should be based on the risk benefit assessment. If the Division decides to require a study, Dr. Easley noted that the study design recommendations from HFD-580 were included in their 4/30/04 consult.

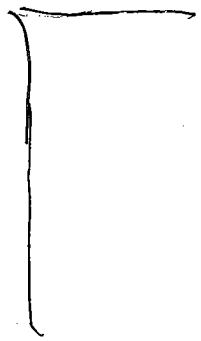
Discussion

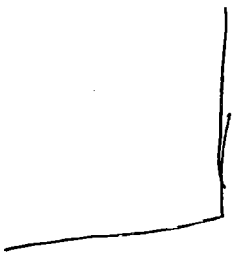
Our consultants in HFD-580 remain convinced that the completed study was not capable of ruling out a pregabalin effect on human male reproductive function. Although they felt that the likelihood of pregabalin an impact on sperm parameters is low, they maintain that the previously conducted study was not appropriately designed to assess sperm concentration or morphology. HFD-580 ultimately left the decision about requiring another human study up to the Division and suggested considering a risk benefit assessment.

Given the lingering questions it seems appropriate to require that Pfizer perform another human male reproductive study. The study would not be overly complex or burdensome for Pfizer. In addition, these issues are potentially relevant for the younger male patients who would be treated with pregabalin, particularly in the epilepsy population.

Pregabalin safety labeling review

Pfizer provided the division with an annotated labeling proposal in a 3/18/2005 submission. This review will focus on the labeling changes related to human safety, particularly for the epilepsy indication. In the following sections the edits (language struck, added blue lettered language) represent changes compared to the labeling in the HFD-120 approvable letter from 8/31/04. Many of these changes have been agreed to and were included in the labeling in the approval letter sent by HFD-170 on 12/30/04.





10 Page(s) Withheld

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

X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 2

Appendix

Table 3. Overview of Source and Number of Subjects Who Received Study Medication – Phase 2/3 Integrated Clinical Safety Database

	Placebo SU2 Data	Placebo New Data	Placebo SU3 Data	All PGB SU2 Data	All PGB New Data	All PGB SU3 Data
All Controlled Studies	2610	229	2839	6224	245	6469
Neuropathic Pain	922	67	989	2104	70	2174
Diabetic Neuropathy	507	0	507	1180	0	1180
Postherpetic Neuralgia	415	0	415	924	0	924
Spinal Cord Injury	0	67	67	0	70	70
Epilepsy (Adjunctive Therapy in Partial Seizures)	367	149	516	1026	161	1187
Generalized Anxiety Disorder	484	0	484	1149	0	1149
Other[a]	837	13	850	1945	14	1959
Other Chronic Pain	416	13	429	1068	14	1082
Other Psychiatry	421	0	421	877	0	877
All Controlled and Uncontrolled Studies	--	--	--	9847	1605	10367
Neuropathic Pain	--	--	--	2864	696	2987
Diabetic Neuropathy				1650	402	1650
Postherpetic Neuralgia				1214	171	1214
Spinal Cord Injury				0	123	123
Epilepsy (Adjunctive Therapy in Partial Seizures)[b]	-	--	--	1938	813	2320
Generalized Anxiety Disorder[c]	--	--	--	1962	0	1962
Other[a]	--	--	--	3083	96	3098
Other Chronic Pain	--	--	--	1364	32	1378
Other Neuropathic Pain	--	--	--	28	0	28
Other Psychiatry[d]	--	--	--	1691	64	1692

[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 OL extension (Study 008).

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

[d] Includes the following long-term, placebo-controlled, relapse prevention/sustained efficacy studies: Study 082 (social anxiety disorder [SAD]) and Study 093/192 (panic disorder).

Sponsor's Summary of New Deaths in SU2

040-067002 This 67 year old male with diabetes mellitus, peripheral neuropathy, 21 year history of smoking (quit 15 years ago), peripheral vascular disease and hypertension developed a cough with hemoptysis on study day 1047. A chest x-ray showed shadowing, a bronchoscopy with biopsy was negative for malignancy but a CT scan showed a 6 cm peripheral mass postero-laterally in the right upper lobe with a large hilar mass invading the mediastinum. He was subsequently diagnosed with adenocarcinoma. Approximately one month later he was hospitalized with increasing shortness of breath and was transferred to hospice care. He died and the reported cause of death was lung adenocarcinoma.

040-003003 This 70 year old male with post herpetic neuraligia, myocardial infarction, bowel cancer, TURP, and squamous cell skin cancer was hospitalized on study day 1450 with altered consciousness, fever, abdominal pain, and distension. He was diagnosed with sepsis and renal failure. An echo documented severe global LV dysfunction and severe RV hypokinesis. An abdominal MRI documented possible colonic pseudo-obstruction. Pregabalin was stopped, and the subject died on post therapy day 4. The reported cause of death was sepsis and severe cardiomyopathy. No autopsy was performed. Concomitant medications prior to this event were digoxin, furosemide, simvastatin, amitriptyline, baclofen, and acetaminophen.

149-400002 This 70-year-old white male subject with a history of diabetes mellitus, gallbladder removal, acute myocardial infarction, coronary artery bypass, appendectomy, unexplained weight loss (10 kg 6 months), increased indigestion, ischemic heart disease, hypertension, sick sinus syndrome with permanent pacemaker, and non-alcoholic steatohepatitis (pre-study), received pregabalin for the treatment of painful diabetic peripheral neuropathy. On Study Day 694, the subject presented to the emergency room with left sided chest soreness that did not respond to nitroglycerine, and epigastric tenderness. Pain responded to oral analgesia. Liver function test results were abnormal including an SGPT of 78 U/L (reference range not provided), SGOT of 122 U/L (reference range not provided), GGTP of 979 U/L (reference range not provided), ALP of 325 U/L reference range: 30-115). Previous liver function tests were within reference range with the exception of alkaline phosphatase, which progressively increased from 104 to 1070 U/L. On Study Day 731, an upper abdominal ultrasound showed the liver to be grossly abnormal, the spleen enlarged, and the pancreas bulky. A subsequent CT scan on Study Day 732 showed multiple focal lesions in the liver (probable metastatic), abnormal soft tissue masses in the transverse colon (probable neoplastic), and some thickening of the bowel wall with possible neoplastic extension into it. The subject had no known history of smoking, alcohol use, or use of illicit drugs, and no previous history of cancer. Family history of cancer was limited to a brother who had prostate cancer. Work history included employment as an accountant for a company dealing with asbestos. It is unknown if the subject had any exposure to hepatotoxins. The subject had a prior emergency room visit in [redacted], for chest and abdominal pain, nausea and vomiting. At that time, an abdominal CT scan showed thickening of the wall of the ascending colon presumed to be due to fecal matter. A colonoscopy showed normal mucosa up to the caecum, with no abnormalities, and an endoscopy revealed hiatal hernia and duodenal deformity. It is unknown if any polyps were discovered at that time. The subject had not undergone any further colonoscopies or endoscopies since 1998. On Study Day 752, the subject was admitted to the hospital for investigation of possible bowel obstruction, and a diagnosis of possible bowel cancer and liver metastasis was made. An abdominal X-ray showed no evidence of bowel obstruction, and a preliminary ultrasound showed no evidence of liver lesions. On Study Day 755, an abdominal and pelvic CT scan revealed widespread metastases in the liver and irregular thickened bowel wall in the ascending colon region. On Study Day 756, a colonoscopy was performed that was negative for colonic malignancy. On Study Day 762, the subject's diagnosis was confirmed as extensive metastatic hepatocellular carcinoma confined to the liver, and portal vein thrombosis (onset date unknown, present on CT scan [redacted], secondary to hepatocellular carcinoma, and pre-existing non-alcoholic steatohepatitis. A liver biopsy was not performed, and the diagnosis was based on imaging results. On [redacted], hemoglobin levels were 12.0 g/dL (reference range: 14-18 g/dL). Low hemoglobin levels were present since baseline and were not considered to be related to the event. In response to these events, no action was taken with study drug, and treatment with pregabalin was continued unchanged. The subject did not receive any radiation or chemotherapy. On Study Day 765, the subject was discharged from the hospital with pain medication and palliative care. On Study Day 791, the subject died. The cause of death was confirmed as hepatocellular carcinoma, per the

investigator. No autopsy was performed. Concomitant medications taken within two weeks before the onset of carcinoma hepatocellular, included atorvastatin, rabeprazole sodium, indapamide, paracetamol, isosorbide mononitrate, captopril, acetylsalicylic acid, metformin, insulin, and insulin injection, isophane.

149-400005 This 63 year old male with a history of bowel cancer s/p resection, smoking, hypertension, diabetes mellitus, peripheral neuropathy was admitted to a hospital after collapsing at home on study day 642. He was found to be anemic (Hgb 6.9g/dL) with melena and anorexia. On study day 645 an abdominal CT was negative for recurrent malignancy. The subject was discharged and scheduled for outpatient follow up gastroscopy to rule out an ulcer. In the interim, a study visit (study day 649) check documented postural drop in blood pressure and he was advised to return to the hospital but apparently decided not to follow that advice. On study day 656 he was hospitalized for additional tests and an endoscopy revealed a fungating gastric ulcer with mild stricture of the GE junction, an old clot, and a necrotic base with evidence of active bleeding. Biopsy revealed large undifferentiated malignant tumor. He underwent a laparotomy that showed the lesser omentum was grossly involved with nodules on the lesser curve. The tumor was proximal to the stomach and posteriorly fixed to the pancreas and left gastric artery. His post operative course was complicated by volume overload and continued anemia. He received chemotherapy on study day 679 and died on study day 695. The reported cause of death was aspiration following a two day history of decreased consciousness due to presumed advanced gastric carcinoma (pathology indicated a high grade neuroendocrine carcinoma). An autopsy was not performed.

149-430008 This 76 year old male with a history of myocardial infarction, ischemic heart disease, mild heart failure, hypercholesterolemia, hypertension, diabetes mellitus and peripheral neuropathy, presented to his physician with shortness of breath and edema and was prescribed bumetanide. Approximately one month later (study day 503), during a study visit he was noted to have raised internal jugular pressure and was diagnosed with mild heart failure. On study day 504, his bumetanide dose was increased. On study day 541, he died while at his daughter's house and details leading up to the event were unknown. The death certificate listed ischemic heart disease as the primary cause of death and no autopsy was performed. Concomitant medications prior to death were insulin, metformin, amitriptyline, simvastatin, nitrates, candesartan, aspirin, and bumetanide.

155-124003 This 76 year old male with post herpetic neuralgia, diabetes mellitus, atrial fibrillation, hypertension, coronary artery disease, COPD, gout, and Quincke's edema died on study day 505 while on vacation in Vietnam. The reported cause of death was cerebral hemorrhage and the autopsy results were pending. Concomitant medications prior to death were metformin, glimepiride, magnesium aspartate hydrochloride, phenprocoumon, furosemide, metolazone, adenoprostat, ginko, ispaghula husk with senna (laxative), losartan, salbutamol, ipratropium, allopurinol, and diclofenac.

197-107007 This 85 year old male with neuropathic pain, COPD, thyroidectomy, hypothyroidsm, BPH, TURP, hypertension, bundle branch block, and non specific ST changes, had study hospitalizations for COPD exacerbation and weakness was supposed to discontinue pregabalin on study day 561 when he moved but continued taking pregabalin. Ten days later, he fell and was unable to get up. He was admitted to a hospital with diaphoresis, shortness of breath, weakness, and wheezing. He was diagnosed with septic shock and had hypotension, tachycardia, and hypoxemia. Pregabalin was stopped during the hospitalization. He improved, and was discharged to a skilled nursing facility. Approximately one month later (post therapy date 53) he died and the reported causes of death were respiratory failure, septic shock, and COPD, Pfizer did not know if an autopsy was performed. Concomitant medications prior to hospitalization were cilostazol and pentoxifylline.

197-132001 This 83 year old male with neuropathic pain, hypertension, hiatal hernia and bradycardia presented to an ED on study day 833 with complaint of chest pain, weakness, shortness of breath, pain radiating to the back and under the right shoulder blade. He was diagnosed with an acute myocardial infarction. He was treated with aspirin, Lopressor, Pepcid, and heparin. He was transferred to another hospital for possible catheterization and on arrival was asystolic. He was treated with epinephrine, atropine, vasopressin, and dopamine. He did not respond to these therapies and was pronounced dead. The reported cause of death was myocardial infarction. An autopsy was not performed. Concomitant medications prior to the event were omeprazole, lisinopril, and aspirin.

Sponsor's Summary of Deaths in SU3

149-354028 This 84 year old male with a history that included diabetes, diabetic peripheral neuropathy, asthma, arthritis, hypertension, hyperlipidemia, retinopathy, psoriasis, peripheral vascular disease, and cerebrovascular disease experienced numerous AEs during participation in pregabalin studies including a Mallory Weiss tear that occurred during "withdrawal syndrome" during a mandatory pregabalin drug holiday, recurrent pneumonia, episodes of acute renal failure, myocardial infarction, and infected foot ulcers. He was transferred from a rehabilitative facility on study day 966 with increased confusion and falls. He was admitted to the acute care hospital with acute renal failure, chest infection, acute pulmonary edema, and infected foot ulcer. He was subsequently diagnosed with sepsis. His hospitalization was complicated by recurrent pulmonary edema, hyperkalemia, and hyponatremia. He recovered from the acute renal failure and sepsis and pulmonary edema and underwent amputation of his left great toe. He was transferred back to the rehabilitation hospital but was readmitted to the acute care hospital within one week with decreased consciousness and was diagnosed with a myocardial infarction, left lower lobe pneumonia, and acute renal failure. He experienced ventricular fibrillation and four days later died with cardiac failure as the reported cause of death. No autopsy was performed. Concomitant medications prior to death included fractionated heparin, aspirin, pantoprazole, iron, folic acid, docusate, lactulose, perindopril, digoxin, furosemide, salbutamol, temazepam, morphine, paracetamol, insulin, vancomycin, meropenem, rifampicin, fusidic acid, spironolactone, glceryl trinitrate, fluticasone propionate/salmeterol, bisacodyl, ipratropium, simvastatin, acitretin, latanoprost, and tramadol.

132-106006 This 79 year old male with a history that included neuropathic pain, hypertension, hypercholesterolemia, insomnia, depression, peripheral vascular disease, recurrent pneumonia, and pleural scarring, presented to an ED on study day 1083 after a fall at home. He was confused and the narrative reported that his alcohol level was high. A CT and an MRI documented acute intracranial hemorrhage. A repeat MRI on the next day documented worsening with development of a left frontal hematoma. The subject underwent a craniotomy for evacuation of the hematoma. He subsequently developed bilateral pneumonia, sepsis, and became comatose. Treatment included tube feedings, antibiotics, antiepileptic agents, steroids and nitroprusside. He was transferred to a hospice and died. No autopsy was performed. Concomitant medications prior to the intracranial hemorrhage were atenolol, zolpidem, escitalopram, ezetimibe, aspirin, atorvastatin, zinc, multivitamins, and nortriptyline.

196-803002 This 69 year old male with a history that included post herpetic neuralgia, prior tobacco abuse, peripheral vascular disease, and bifemoral bypass was admitted to a hospital on study day 679 for a myocardial infarction. When the ambulance arrived his heart rhythm was ventricular fibrillation. He received CPR and DC cardioversion. He was admitted to an ICU and diagnosed with an extended anterolateral myocardial infarction with cardiogenic shock. He experienced anoxic encephalopathy and was comatose. The subject died on study day 682 and the cause of death was reported as myocardial infarction

034-017002 This 53 year old male had a history of partial seizures, atherosclerotic cardiovascular disease, asthma, osteoporosis, spinal spondylosis, back pain, sleep apnea, and obesity. Two months, and again one month prior to death, the subject was hospitalized for asthma exacerbations. The subject died at home on study day 1956 and the reported causes of death were morbid obesity and atherosclerotic cardiovascular disease. Pfizer did not know if an autopsy had been performed. Concomitant medications at the time of the last hospitalization prior to death were carbamazepine, clobazam, topiramate, ergocalciferol, salbutamol, and calcium carbonate.

112-147001 This 52 year old female had a history of partial seizures, hyponatremia, hysterectomy, appendectomy, tonsillectomy, adenoidectomy, hypertension, myocardial infarction, osteoporosis, and migraine headaches. Her study treatment experience was notable for diagnosis with a parathyroid adenoma with resection (study day 49) and hospitalizations for hyponatremia (study days 509-13, serum sodium 123; 561-5, serum sodium 119). The subject died on study day 677 and the cause of death was unknown. An autopsy was performed but Pfizer did not have the results. Concomitant medications at the time of death were carbamazepine, primidone, aspirin, metoprolol, amlodipine, prednisone, diclofenac/misoprostol, methotrexate, folate, and vitamin B.

010-002001 This 42 year old male with a history of psoriasis, partial seizures and a >54 pack year history of smoking was diagnosed with large-cell, undifferentiated, lung cancer. Concomitant medications included carbamazepine, topiramate, fish oil, ulobetasol propionate and fluocortolone caproate. He underwent a partial lobectomy and radiotherapy. The subject subsequently died and the reported cause of death was lung cancer. An autopsy was not performed. He received a total of 2031 days of pregabalin.

045-070006, 061-070006 This 60 year old male had post herpetic neuralgia, chronic pain. The subject was hospitalized for prostate cancer and subsequently was diagnosed with metastases to the skull, ribs, and spine. He underwent radiation therapy. Pfizer report that the subject initially continued pregabalin but later discontinued from the study because his pain resolved. Concomitant medications were amitriptyline, cyproterone, atorvastatin, insulin, salicylic acid, metformin, naproxen, dihydrocodeine, fenofibrate, paracetamol/dextropropoxyphene hydrochloride, gliclazide, medroxyprogesterone, and lactulose. Two months after discontinuing pregabalin, the subject died and the reported cause of death was progression of prostate cancer. No autopsy was performed.

149-418005, 165-418005 This 57 year old male with diabetes mellitus, diabetic peripheral neuropathy, hypertension, hyperlipidemia, and smoking cigarettes for >30 years was diagnosed with "microcellular" carcinoma of the left lung on study day 349. He was treated with cisplatin and etoposide, and he died on study day 790.

155-132005, 166-132005 This 66 year old male with a history that included diabetes mellitus, heart disease, CABG, and asthma, experienced multiple AEs during pregabalin studies including seizures, hyperkalemia, second degree heart block and pacemaker insertion, atrial fibrillation, fluid overload, impaired renal function, myocardial infarction, phlebitis, and cellulitis. On study day 1008 he died and an autopsy reported ischemic heart disease with coronary atheroma as the cause of death. Concomitant medications at the time of death were insulin, codeine/paracetamol, diclofenac, zopiclone, sildenafil, aspirin, salbutamol, beclometasone, lactulose, ramipril, mometasone, omeprazole, glyceryl trinitrate, bendroflumethiazide, iron, furosemide, and warfarin.

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/s/

Jerry Boehm
6/6/05 02:04:36 PM
MEDICAL OFFICER

Judith Racoosin
6/6/05 03:48:51 PM
MEDICAL OFFICER

Memorandum of Consultation

To:	Russell Katz, MD Director, HFD-120 (Courtney Calder, Project Manager)
From:	Olivia Easley, MD, Medical Officer, DRUDP (HFD-580) George S. Benson, MD, Team Leader, DRUDP (HFD-580) Dan Shames, MD, Director, DRUDP (HFD-580)
Re:	Consultation concerning male reproductive effects of pregabalin
Date received:	April 8, 2005

Date of consultation: May 13, 2005

Background: Pregabalin is a GABA analogue which is the subject of NDA's 21-446 (pain associated with diabetic peripheral neuropathy), 21-723 (neuropathic pain), 21-724 (epilepsy).

In preclinical rat studies, pregabalin was found to have adverse effects on male reproductive parameters. Because of the pre-clinical findings, the sponsor conducted a clinical study (Study 072) of the effects of pregabalin on semen parameters in 30 healthy men (plus 16 placebo subjects).

DRUDP reviewed the results of study 072 in a consultation to DACCADP (HFD-170) dated April 30, 2004. DRUDP determined that "study 072 in healthy men does not provide reassurance that pregabalin has no adverse effect on human sperm," and recommended that an additional clinical trial should be performed but could be done as a Phase 4 commitment.

NDA 21-724 received an approvable action by DNDP on August 24, 2004. In the approvable letter to the sponsor, DNDP conveyed DRUDP's comments on study 072, and asked the sponsor to commit to conducting a post-approval placebo-controlled clinical trial to further assess the effects of pregabalin on male reproductive function.

The sponsor submitted a response to DNDP's request for an additional male reproductive clinical trial on March 11, 2005. DNDP has requested that DRUDP comment on the sponsor's arguments against the need for a second male reproductive study.

Materials reviewed:

1) DRUDP memorandum of consultation regarding male reproductive effects of pregabalin, dated April 30, 2004.
2) The sponsor's response to DNDP's request for a second male reproductive study.

3) Review of preclinical reproductive and developmental toxicology by HFD-120 pharmacology/toxicology reviewer.
4) Teleconference with the HFD-120 pharmacology/toxicology reviewer on May 5, 2005.
5) Discussion of statistical analysis of Trial 072 with DRUDP statistician.

Medical Officer Review:

The initial DRUDP consultation contained the following comments regarding study 072:

1) The pre-clinical rat studies show reproductive changes at pregabalin doses of 4 times the expected human dose. The two monkey studies show conflicting results.

2) The clinical study was powered to detect a 13% decrease in WHO "a+b+c" sperm motility compared to placebo. This trial did not demonstrate any clinical meaningful changes in semen parameters, but was not powered to detect a significant effect in sperm concentration (percentage of patients with a 50% change in sperm concentration or percentage of patients with lower than "normal" concentration of $20x10^6$/ml).

3) A decision concerning further studies of the effect of pregabalin on male reproductive function depends on the risk/benefit ratio. If a part of the target population is younger men of reproductive age and potential, DRUDP believes that an additional clinical trial should be performed, but could be done as a Phase 4 commitment. The study should be a parallel, placebo-controlled trial. The primary endpoint should be either percentage of patients with a 50% reduction from baseline in sperm concentration or percentage of patients with lower than normal (20×10^6/ml) sperm concentration. Drug or placebo should be given for 3 months and semen analyses should be obtained at baseline, month 3 and month 6. Because of the effects on FSH seen in pregabalin subjects in study 072, the sponsor should also measure FSH and testosterone levels at baseline, month 3 and month 6. Depending upon the non-inferiority margin, these studies require approximately 100 patients per group.

DRUDP also suggested the following labeling:

The sponsor provides the following three arguments against conducting a **second male reproductive study:**

1) The sponsor concludes that it is unlikely that pregabalin has a significant effect on sperm concentration because:
    - Although epididymal sperm content was reduced in rats, testicular spermatogenesis was unaffected, consistent with a direct effect of pregabalin on the epididymis or on sperm maturation in the epididymis in rats.
    - There were no drug-related effects on male reproductive organs in mouse and monkey toxicology studies.

Reviewer's comment: The preclinical reproductive data were discussed with the HFD-120 pharmacology/toxicology reviewer on May 5, 2005. The reviewer disagrees with the sponsor's conclusions that there were no drug-related effects on male reproductive organs in the mouse or monkey and that the effects in rats were limited to the epididymis.

According to the pharmacology-toxicology reviewer, in a 2-year rat carcinogenicity study, "decreased reproductive organ size (i.e. gross findings of small testes and seminal vesicles) and weight and increased incidences of atrophy of the seminiferous tubules and aspermatogenesis in the testes and aspermia in the epididymides were seen at all doses." In a second rat carcinogenicity study, "atrophy and degeneration of the testicular germinal epithelium were increased at all doses." In addition, in an electron microscopic evaluation of male rat reproductive effects of pregabalin, "the presence of ...cytoplasmic lobes in the epididymal lumen again suggested a possible testicular effect."

The pharmacology-toxicology reviewer believes that testicular changes also occurred in a 2-year mouse carcinogenicity study.

In the 4-week monkey study, hypospermia of the testis and epididymis associated with small testes and low testicular weights was observed in 1 monkey at 100 mg/kg/d and 2 monkeys at 500 mg/kg bid. The one-year monkey study demonstrated no effects on sperm parameters or reproductive organ histopathology. The pharmacology-toxicology reviewer considers the results of the monkey studies inconclusive because of study design (small sample size, lower drug exposure).

The pharmacology-toxicology reviewer believes that the preclinical mouse and rat data are concerning that pregabalin may adversely affect the testes and not only the epididymis, as the sponsor suggests.

    - The mean sperm concentration increased in both the pregabalin and placebo groups from baseline to endpoint.

- No pregabalin-treated subject had a decrease in sperm concentration of 50% or more at the end of the study.
- No subject had a concentration of <20 X 10^6/ml, the WHO threshold for oligozoospermia.

Reviewer's comment: Outlier values were not provided in the study report.

- If pregabalin did reduce sperm concentration in 6% of subjects, the study would have provided a >80% chance of observing at least one subject with a reduction in sperm concentration; if the rate were 10%, there would be a 95% chance of observing at least one subject with a reduced sperm concentration.

Reviewer's comment: Study 072 was not powered to detect a significant change in sperm concentration.

2) Preclinical epididymal and sperm findings in rats are not consistent with an FSH effect since decreased FSH would cause primary testicular rather than epididymal effects. In addition, "none of the subjects who had low FSH levels (<0.9 mIU/mL) at the end of treatment showed any adverse effect on sperm motility, morphology or concentration."

Reviewer's comment: Those pregabalin subjects whose FSH levels decreased from baseline (N=5) also had reductions in WHO "a+b+c" sperm motility between -1% to -11% from baseline. There were, however, no changes in motility seen with computer aided sperm analysis (CASA). The clinical significance of the observed decrease in FSH and reduction in WHO motility without a correlation with CASA motility is not clear.

3) Oligozoospermia alone has a low positive predictive value for infertility. The most sensitive assessment of human male reproductive function would be monitoring all three sperm parameters (concentration, morphology and motility) as was done in study 072.

Reviewer's comment: The reviewer agrees that the most sensitive assessment of human male reproductive function is measurement of multiple semen parameters, including sperm concentration, morphology and motility. However, study 072 was powered only to detect a significant change in sperm motility. No conclusions regarding pregabalin's effects on sperm concentration or morphology can be reached based on available data.

Furthermore, the study design also limits conclusions that can be made regarding pregabalin's effects on sperm motility. The sponsor's definition of "normal" motility as percentage of sperm with World Health Organization (WHO) "a+b+c" motility allows sperm with non-progressive motility ("c") to be considered "normal." The WHO (1999)

defines normal motility as 50% or more sperm with grade "a+b" motility or 25% or more with grade "a" motility. [1]

A secondary outcome measure in study 072 was the percent of sperm with normal WHO class "a" motility at the end of the double-blind treatment period. There was no significant change from baseline in percentage of sperm with WHO "a" motility in either the pregabalin or placebo groups (mean change from baseline: +4.8% for placebo and +1.6% for pregabalin).

Data for percentage of sperm with "a+b" motility were not submitted.

Summary and Conclusions:

1. Preclinical studies in rats and mice suggest that pregabalin may have adverse effects on the testes and may cause reduced sperm concentration. Data in the monkey are conflicting.

2. The results of study 072 do not raise any specific male reproductive concerns. However, the trial design limits any conclusion regarding pregabalin's effect on sperm concentration and does not allay our initial concerns that were raised from the preclinical mouse, rat and monkey data.

3. While the likelihood of pregabalin having a significant effect on human male reproductive function appears to be low, this trial was powered only to detect a change in sperm motility (WHO a+b+c) and not to detect a change in sperm concentration. Although an effect on sperm concentration was not seen in study 072, the Division continues to believe that insufficient data were submitted to conclude that pregabalin has no effect on sperm concentration.

4. The recommended study design for a trial to evaluate the effect of a drug on human sperm concentration was outlined in our consult of April 30, 2004. The decision regarding the need for an additional semen study must be based on a risk/benefit assessment acknowledging that the likelihood of pregabalin having a negative impact on semen analysis is low but, nevertheless, does exist.

Olivia J. Easley, MD
Medical Officer
Division of Reproductive and Urologic Drug Products
HFD-580

[1] Wash: Campbell's Urology, 8th ed. 2002.

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/s/

Olivia Easley
5/16/05 04:46:36 PM
MEDICAL OFFICER

George Benson
5/16/05 04:55:54 PM
MEDICAL OFFICER

Daniel A. Shames
5/16/05 06:10:23 PM
MEDICAL OFFICER

MEMORANDUM

NDA 21-724 Lyrica (Pregabalin)

FROM: John Feeney, M.D.
Neurology Team Leader

SUBJECT: Original NDA for the Adjunctive Treatment of Partial Seizures

DATE: August 26, 2004

Introduction

The sponsor has proposed the use of Lyrica 150-600 mg/day as adjunctive treatment of partial seizures. The sponsor has submitted the results from 3 add-on efficacy trials to support approval. In addition, the sponsor has submitted an integrated safety summary, encompassing the use of Lyrica across a range of indications, to include epilepsy, anxiety, and neuropathic pain.

Lyrica is a new chemical entity and NDAs for its use in post-herpetic neuralgia, diabetic neuropathic pain, [redacted] were submitted simultaneously with the specific application for epilepsy discussed in this memo. Because there are no drugs approved for marketing in the U.S. for the treatment of neuropathic pain associated with diabetic neuropathy, that application received a priority review in the Division of Anesthetic, Critical Care, and Addiction Drug Products and an Approvable letter issued on July 29 of this year (signed by Robert Meyer, M.D./Office of Drug Evaluation II). Proposed labeling accompanied that letter.

Lyrica is a new chemical entity, but the chemical structure of pregabalin is remarkably similar to the currently-marketed drug Neurontin (gabapentin). Both pregabalin and gabapentin have a backbone of γ-aminobutyric acid (GABA). Pregabalin has a 4-carbon chain extending from the backbone, while gabapentin has a 5-carbon chain that completes a hexane ring. The molecular weights are very similar. Somewhat surprisingly, neither pregabalin nor gabapentin is active at GABA receptors.

Neurontin was one of three new anticonvulsants approved in the early 1990s after roughly a decade without any approvals for new anticonvulsants. Neurontin was originally approved for the treatment of partial seizures (at dose of 900-1800 mg/day) and, later, was approved for the treatment of post-herpetic neuralgia. In 1993, at the time of its approval, the mechanism of action of gabapentin was unknown. Subsequently, a binding protein was discovered and identified as an auxiliary part of the multi-protein assembly that comprises voltage-gated calcium channels. This binding protein has been named the $\alpha_2\delta$ protein, is associated with cell membranes in excitable cells, and is found in brain tissue, striatal muscle, smooth muscle, and cardiac muscle. Pregabalin also has been found to bind to $\alpha_2\delta$ protein.

Gabapentin has poor bioavailability compared to pregabalin, and as the dose of gabapentin is increased, the bioavailability decreases. Bioavailability of gabapentin is roughly 60%, 47%, 34%, 33%, and 27% following 900, 1200, 2400, 3600, and 4800 mg/day given as 3 divided doses, respectively. In contrast, the bioavailability of pregabalin is about 90%. The daily systemic exposure of pregabalin at a dose of 600 mg/day is roughly the same as the exposure of gabapentin at a dose of 1800-2400 mg/day.

Both pregabalin and gabapentin readily penetrate the blood brain barrier (BBB). Both are substrates of the system L neutral amino acid transporter in CNS tissues. A human study with gabapentin showed that CSF levels were about 20% of plasma levels. A comparable human study has not been done with pregabalin, but animal data suggests comparable BBB penetration.

Neither pregabalin nor gabapentin is metabolized significantly in the body. Both are primarily excreted unchanged in the urine.

During the clinical development of pregabalin, a carcinogenicity study in one strain of mice revealed the frequent occurrence of dose-related hemangiosarcomas, even at exposures comparable to those expected in patients dosed at 600 mg/day. The hemangiosarcomas were aggressive, with metastasis and decreased survival in affected animals. Because of this finding, clinical trials were for the most part suspended and the sponsor was encouraged to develop trials for only patients refractory to available drugs. The sponsor subsequently completed a second mouse carcinogenicity study in a different strain, showing once again the finding of hemangiosarcomas.

The sponsor performed numerous studies to elucidate the mechanism of hemangiosarcoma formation. The sponsor believes they have shown that a mechanism involving platelet activation with release of endothelial growth factors is active in mice, leading to hemangiosarcoma formation. The sponsor also believes they have shown that the mechanism is not active in humans.

Because of the multiple clinical indications under review and because of the complexity of the mechanistic studies relating to the carcinogenicity studies, numerous reviews have been written about different aspects of pregabalin. Some of the reviews pertinent to the epilepsy indication include:

Efficacy Review	Howard Chazin, M.D.
Statistical Review	Tristan Massie, Ph.D.
Clinical Safety Review	Jerry Boehm, M.D., M.P.H. and Alice Hughes, M.D.
Clinical Efficacy and Safety/Neuropathic Pain	Mwango Kashoki, M.D., M.P.H.
Consult on Male Reproductive Effects	Olivia Johnson, M.D.
Consult on Ophthalmologic Effects	Wiley Chambers, M.D.

Consult on Abuse Potential	Katherine Bonson, Ph.D.
Pharm/Tox Review (Overall)	Jerry Cott, Ph.D.
Pharm/Tox Review (Carcinogenicity/Reproductive Toxicology)	Edward Fisher, Ph.D.
Pharm/Tox Team Leader Memorandum	Lois Freed, Ph.D.
Biopharmaceutics Review	Sue-Chih Lee, Ph.D.
Biopharmaceutics Review	Veneeta Tandon, Ph.D.
Clinical Site Inspections/DSI (GCP)	Ni Khin, M.D.

Efficacy

Study 009 (US and Canada)

This was a randomized, double-blind, placebo-controlled trial of pregabalin as add-on therapy in patients with partial seizures. Patients, 18 years of age or older, were randomized to: pregabalin 200mg tid, pregabalin 300mg bid, or placebo. After an 8 week baseline period, patients were titrated over 1 week to their assigned dose regimen and maintained on that regimen for 11 weeks. The inclusion/exclusion criteria were standard for this type of trial. Patients already taking Neurontin were excluded, however. Also, patients taking proarrhythmic drugs were excluded.

Roughly 300 patients were randomized, 100 to each of the three groups.

The primary outcome assessment was the Response Ratio (RR), a comparison of the seizure rate during treatment to the seizure rate during baseline. The RR = [(T – B)/(T + B)] x 100. The primary analysis was based on ranks of the RR, which Dr. Massie points out yields the same result as if ranks of percent change from baseline were used. The primary analysis consisted of pairwise comparisons for the two dose groups vs. placebo (ANOVA), using the Hochberg adjustment for multiple comparisons. Secondary outcome assessments were: 1) the Responder Rate defined as the percent of patients with a 50% reduction in seizure frequency on treatment compared to baseline, and 2) the percent change in seizure frequency.

The mean RRs were 0.6, -36, and -28 for placebo, pregabalin 200mg tid, and pregabalin 300mg bid respectively. The results were highly statistically significant for both dose groups.

The Responder Rates were 9%, 49%, and 43% for placebo, pregabalin 200mg tid, and pregabalin 300mg bid respectively.

The median percent changes in seizure frequency were -1%, -48%, and -36% for placebo, pregabalin 200mg tid, and pregabalin 300mg bid respectively.

Study 011 (Europe)

This was a randomized, double-blind, placebo-controlled trial of pregabalin as add-on therapy in patients with partial seizures. Patients, 18 years of age or older, were randomized to: pregabalin 50mg tid, pregabalin 200mg tid, or placebo. After an 8 week baseline period, patients were titrated over 1 week to their assigned dose regimen and maintained on that regimen for 11 weeks. The inclusion/exclusion criteria were standard for this type of trial. Patients already taking Neurontin were excluded, however. Also, patients taking proarrhythmic drugs were excluded.

Roughly 300 patients were randomized, 100 to each of the three groups.

The primary outcome assessment was the Response Ratio (RR), a comparison of the seizure rate during treatment to the seizure rate during baseline. The RR = [(T – B)/(T + B)] x 100. As in Study 009, the primary analysis was based on ranks of the RR, which Dr. Massie points out yields the same result as if ranks of percent change from baseline were used. The primary analysis consisted of pairwise comparisons for the two dose groups vs. placebo (ANOVA), using a step-down procedure to adjust for multiple comparisons. Secondary outcome assessments were: 1) the Responder Rate defined as the percent of patients with a 50% reduction in seizure frequency on treatment compared to baseline, and 2) the percent change in seizure frequency.

The mean RRs were 0.9, -11.5, and -31.4 for placebo, pregabalin 50mg tid, and pregabalin 200mg tid respectively. The results were highly statistically significant for both dose groups.

The Responder Rates were 6%, 14%, and 43% for placebo, pregabalin 50mg tid, and pregabalin 200mg tid respectively.

The median percent changes in seizure frequency were 1%, -17%, and -43% for placebo, pregabalin 50mg tid, and pregabalin 200mg tid respectively.

None of the pair-wise comparisons in the conditional analysis for secondarily generalized tonic-clonic seizures were statistically significant.

Study 034 (US and Canada)

This was a randomized, double-blind, placebo-controlled trial of pregabalin as add-on therapy in patients with partial seizures. Patients, 12 years of age or older, were randomized to: pregabalin 25mg bid, pregabalin 75mg bid, 150mg bid, 300mg bid, or placebo. After an 8 week baseline period, patients were started on their assigned dose regimen (with no titration) and maintained on that regimen for 12 weeks. The

inclusion/exclusion criteria were standard for this type of trial. Patients already taking Neurontin were excluded, however.

A total of 455 patients were randomized, roughly equally, to the five treatment groups.

The primary outcome assessment was the Response Ratio (RR), a comparison of the seizure rate during treatment to the seizure rate during baseline. The RR = [(T – B)/(T + B)] x 100. As in the previous two studies, the primary analysis was based on ranks of the RR, which Dr. Massie points out yields the same result as if ranks of percent change from baseline were used. The primary analysis consisted of pairwise comparisons for the multiple dose groups vs. placebo (ANOVA), using a step-down procedure to adjust for multiple comparisons. Secondary outcome assessments were: 1) the Responder Rate defined as the percent of patients with a 50% reduction in seizure frequency on treatment compared to baseline, and 2) the percent change in seizure frequency.

The mean RRs were -4, -6, -21, -28, -37 for placebo, pregabalin 50 mg/day, 150 mg/day, 300 mg/day, and 600 mg/day respectively. The results were highly statistically significant for the three highest dose groups.

The Responder Rates were 14%, 15%, 31%, 40%, and 51% for placebo, pregabalin 50 mg/day, 150 mg/day, 300 mg/day, and 600 mg/day respectively.

The median percent changes in seizure frequency were 0%, -9%, -35%, -37%, and -51% for placebo, pregabalin 50 mg/day, 150 mg/day, 300 mg/day, and 600 mg/day respectively.

Monotherapy Study 007 (US and Germany)

This was a randomized, double-blind comparison of pregabalin 600 mg/day versus a low-dose active control, gabapentin 300 mg/day, in hospitalized patients with complex partial seizures who were withdrawn from all background AEDs for pre-surgical epilepsy monitoring. ——————————— maintained on study medication for a maximum of 8 days or until they reached an exit criterion, to include a total of 4 seizures, status epilepticus, prolongation of usual seizures, or new onset generalized seizures. The inclusion/exclusion criteria required patients to have a minimum of 4 seizures and a maximum of 15 seizures in the 5 days prior to randomization. The time for previous AED taper was highly variable prior to randomization.

A total of 93 patients were randomized, 51 to gabapentin and 42 to pregabalin.

The primary outcome assessment was the time to exit using the log-rank statistic.

Roughly 57% of patients assigned to pregabalin completed the study, while only 23% of patients assigned to gabapentin completed the study. Results on the protocol-specified log-rank analysis favored pregabalin, but did not reach statistical significance, p=0.08.

The Kaplan-Meier curves for the two groups appear superimposable until 40% attrition is reached in both groups (3 days). After 3 days, attrition continued in the gabapentin group, but not the pregabalin group.

Inspections

FDA inspected 3 domestic clinical sites: [redacted] for Study 009; [redacted] for Study 034. The inspections revealed a small number of discrepancies in the adverse event recording both at the investigator and sponsor level, but the data appeared acceptable overall. No discrepancies in the recording of efficacy data were noted.

Comments on Efficacy

1. The sponsor has demonstrated the efficacy of pregabalin 150-600 mg/day in the adjunctive treatment of partial epilepsy.

2. Only [redacted] 18 years of age were enrolled in these efficacy studies. Therefore, the claim in labeling should be limited to patients 18 years of age or older.

3. The contingent analysis for secondary generalization in Study 011 does not support a claim for [redacted]

4. The protocol-specified analysis in the monotherapy study did not reach statistical significance. The Kaplan-Meier curve for the pregabalin group was flat after 3 days, a somewhat unusual finding.

5. No clinically significant differences in efficacy by age, gender, or ethnicity were identified during the review process.

6. Patients taking Neurontin were excluded from the controlled trials. Therefore, the safety and efficacy of the combination, Lyrica and Neurontin, has not been established. Likewise, the use of felbamate or vigabatrin was a reason for exclusion.

7. The adjunctive medications used most commonly in the efficacy studies were carbamazepine, lamotrigine, phenytoin, topiramate, valproate, and tiagabine. Dr. Massie investigated the estimates of the treatment effect for pregabalin when added to each of these medications and found similar trends for each two-drug combination. Therefore, it seems reasonable to assume that the effects observed in the efficacy studies were not driven by a pharmacodynamic interaction with pregabalin, unique to a particular AED or group of AEDs.

Efficacy of the Newer AEDs

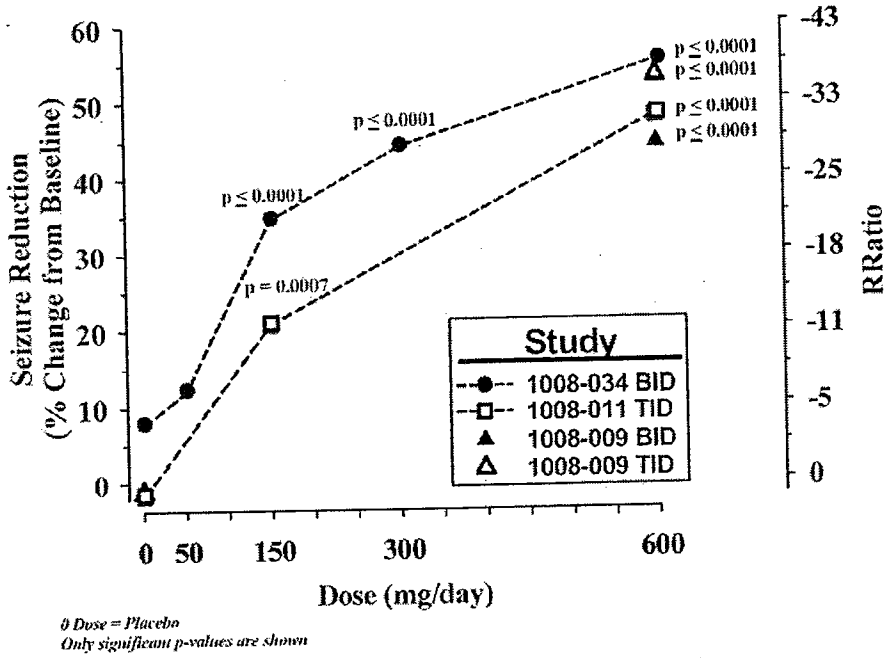
As a preface to this section, across-study comparisons are always hazardous. There may be significant differences between the patient populations enrolled in different studies and the study conditions will also vary. Over the past decade, the newly approved AEDs have almost all been studied in add-on studies in refractory patient populations. The trial designs are often very similar. LaRoche and Helmers (*JAMA*. 2004; 291:605-614) reviewed the clinical trial results for the AEDs approved in the U.S. over the past decade. The following table from their review summarizes the important results for those drugs.

Table 2. Randomized, Placebo-Controlled Trials of the New Antiepileptic Drugs as Adjunctive Treatment for Partial-Onset Seizures*

Source	Study Design	No. of Patients	Study Duration, wk	Daily Dosage, mg†	Responder Rate, %‡	% Decrease in Seizures‡
Gabapentin						
Andrews et al,[26] 1990	Parallel	127	12	1200	25 (P = .04)	29.2
Sivenius et al,[29] 1991	Parallel	43	12	1200	33 (P = .02)	57 (P = .02)
McLean et al,[27] 1993	Parallel	306	12	1800	26.4 (P = .007)	31.9
Anhut et al,[28] 1994	Parallel	272	12	1200	25 (P = .008)	17.8 (P = .005)
Lamotrigine						
Binnie et al,[45] 1989	Crossover	34	12	75-200	6.7	17 (P<.05)
Javad et al,[46] 1969	Crossover	24	12	75-400	66.7	59 (P<.002)
Loiseau et al,[38] 1990	Crossover	23	8	300	34.8	23 (P<.05)
Sander et al,[48] 1990	Crossover	21	12	150-300	NS	NS
Matsuo et al,[40] 1993	Parallel	216	24	300-500	33 (P<.05)	36 (P = .007)
Schapel et al,[42] 1993	Crossover	41	12	150-300	22	26 (P<.01)
Smith et al,[41] 1993	Crossover	81	16	400	17.7	29.7 (P<.05)
Messenheimer et al,[43] 1994	Crossover	98	14	400	20	25 (P<.001)
Boas et al,[44] 1996	Crossover	56	12	75-400	24	30.3 (P = .01)
Topiramate						
Ben-Menachem et al,[66] 1996	Parallel	56	13	800	43 (P = .001)	54 (P<.001)
Faught et al,[64] 1996	Parallel	181	12	400	47 (P = .01)	48 (P = .007)
Privetera et al,[65] 1996	Parallel	190	18	600	44 (P<.001)	41
Sharief et al,[68] 1996	Parallel	47	11	400	35 (P = .03)	41 (P = .06)
Tassinari et al,[67] 1996	Parallel	60	12	600	47 (P = .001)	46 (P = .004)
Yen et al,[69] 2000	Parallel	46	14	300	47.8 (P = .01)	Not reported
Tiagabine						
Sachdeo et al,[79] 1997	Parallel	318	12	32	31 (P<.001)	Not reported
Kalviainen et al,[78] 1998	Parallel	154	16	12-30	14 (P = .17)	12.6 (P<.05)
Uthman et al,[80] 1998	Parallel	297	20	56	29 (P<.001)	Not reported
Levetiracetam						
Ben-Menachem and Falter,[95] 2000	Parallel	286	12	3000	42.1 (P<.001)	39.9 (P<.001)
Betts et al,[97] 2000	Parallel	119	24	2000	48.1 (P<.05)	Not reported
Cereghino et al,[96] 2000	Parallel	294	18	3000	39.8 (P<.001)	37.1 (P<.001)
Shorvon et al,[59] 2000	Parallel	324	18	2000	31.6 (P<.001)	26.5 (P = .003)
Oxcarbazepine						
Houtkooper et al,[86] 1987	Crossover	48	12	900-3600	Not reported	NS
Barcs et al,[91] 2000	Parallel	694	28	2400	50 (P<.001)	50 (P<.001)
Zonisamide						
Schmidt et al,[110] 1993	Parallel	139	12	7/kg	29.9 (P<.05)	22.5 (P<.05)
Faught et al,[113] 2001	Parallel	203	12	400	43 (P = .01)	40.5 (P<.001)

Abbreviation: NS, not significant and P value not reported in source.
*Felbamate is excluded because it is not considered first-line therapy due to risk of aplastic anemia and hepatotoxicity.
†If patients were randomized to multiple doses, the most effective dose is listed. A dose range is listed when study allowed titration to various doses based on efficacy and tolerability.
‡Responder rate indicates patients who achieved a 50% or greater reduction in seizure frequency from baseline. P values are included when they were reported.

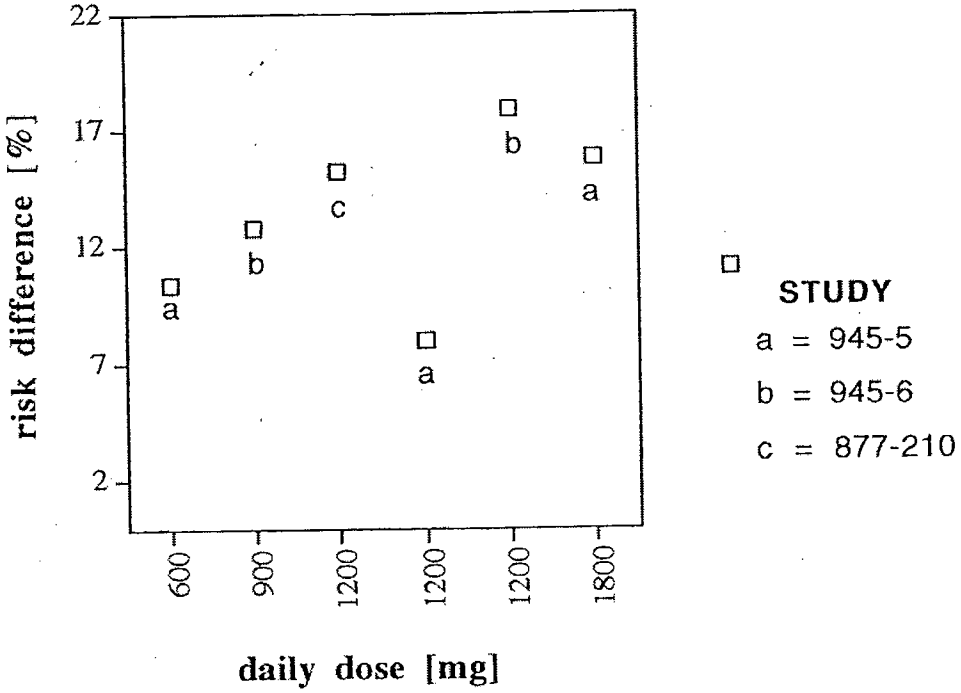
The following graph from the current NDA displays the results of the 3 add-on trials of pregabalin, showing the percent change in seizure frequency/response ratio on the y-axis. The responder rates are not shown; they are as high as 50% for the 600 mg/day dose.



Obviously, the results for pregabalin appear substantial against the historical background. Especially given the similarities between gabapentin and pregabalin, the different trial effect-estimates might seem surprising. The Response Ratio was a parameter also employed in the trials for gabapentin. The Response Ratios observed for gabapentin were roughly -20 to -22 (not adjusted for placebo) compared to -36 to -37 for pregabalin.

At the time of initial approval for Neurontin, the DNDP Division Director Memo (Dr.Paul Leber) included the following graph (incorporated into labeling for Neurontin), showing the responder rates (adjusted for placebo) at the doses studied. Only one of the controlled trials with gabapentin included multiple fixed-dose groups (Study "a" in the graph), and the results did not demonstrate a monotonic dose-response relationship. [Given the decreasing bioavailability of gabapentin at increasing doses, one can imagine that a monotonic dose-response curve might be hard to demonstrate.] However, when the results across all 3 studies were graphed, increasing response with dose was suggested.

Risk Difference (Neurontin Responder Rate – Placebo Responder Rate) vs. Dose



Given the suggestion of increasing efficacy by dose in the graph, it is probably true that the full extent of the dose-response curve with gabapentin has never been fully explored in controlled trials. In practice, much higher doses are routinely used. Doses as high as 3600 mg/day (and higher) have been tolerated by some patients, and, in fact, doses of 3600 mg/day are approved for post-herpetic neuralgia.

Safety

Dr. Kashoki from HFD-170 performed the overall clinical safety review with attention to the safety profile in neuropathic pain. Drs. Boehm and Hughes from HFD-120 performed the clinical safety review with attention to epilepsy. Neither review identifies specific clinical safety concerns that would preclude the approval of pregabalin for the treatment of partial seizures. Dr. Kashoki and the Clinical Team Leader, Dr. Celia Winchell, both expressed concern about the ophthalmologic adverse events observed during development and the impact these might have on diabetic populations with already compromised vision. These ophthalmologic effects of pregabalin were reviewed in a separate consult by Dr. Wiley Chambers and are discussed separately below.

The overall safety database, including all indications, numbers almost 10,000 subjects with 7,000 person-years of experience. With the inclusion of the safety update, 4379 patients have been treated for 6 months or longer, and 2701 have been treated for a year or longer. At the highest dose, 600 mg/day, 1304 have been treated for 6 months or longer, and 751 have been treated for a year or longer. At the same time, there has been minimal pediatric experience, and this has been limited solely to adolescents.

For the epilepsy indication, there have been 1,613 patients exposed, accounting for 2,637 person-years of experience. The safety experience in epilepsy was collected in the four controlled trials discussed in this review along with the open-label extensions of those studies. The open-label studies also enrolled de novo patients without prior exposure in the randomized controlled trials.

Among these 1,613 epilepsy patients, there were 14 (0.9%) deaths. The approximate causes for death were:

Sudden death	4
Seizure-related	3
Strokes	2
Possible MI	1
Cancer	1
Pulmonary Embolus	1
Accident	1
Septicemia	1

Across the entire safety database, there were 55 (0.6%) deaths, but no particular pattern of deaths emerged during the safety review.

Across all indications, the risk of serious adverse events was about 8%, 13% for epilepsy. In controlled trials in epilepsy, the risk of serious adverse events was about 4% in both the placebo and pregabalin groups.

Dizziness, somnolence, and ataxia were the adverse events most commonly leading to discontinuation of pregabalin in the controlled trials ($\geq$ 2% of patients).

Among epilepsy patients, common adverse events that seemed to follow a dose-response pattern included: dizziness, somnolence, ataxia, weight gain, blurred vision, diplopia, tremor, abnormal thinking, and speech disorder.

Edema is associated with pregabalin use. The safety team requests additional analyses of the relationship between edema observed in trials and dyspnea. These analyses should be requested pre-approval.

The safety team identified mean elevations in CPK in pregabalin-treated patients compared to placebo. Across all indications, the difference was very small, only about 5U/L. But in epilepsy studies, the difference was more substantial, about 60U/L. There was one straightforward case of rhabdomyolysis identified in a patient treated for social phobia (Day 16 of treatment).

The safety team also identified mean decreases in platelets in pregabalin-treated patients compared to placebo. Across all indications, 8 patients developed a platelet count less than 30,000. The risk for bleeding, however, did not appear to be increased in pregabalin treated patients overall.

Effects on EKG parameters were assessed in clinical trials. EKGs were not routinely timed to dosing and a single EKG served as the baseline for each patient. Prolongation of the PR interval was identified in these studies, but no significant effect on QT interval was seen. The safety group believes that additional analyses of the PR interval data should be done pre-approval in patients taking concomitant drugs known to prolong the PR interval.

There were 2 cases of interest to me because of the profound mental status changes shortly after starting drug. Both cases were confounded, however, by other medical conditions that were eventually diagnosed. The timing of the mental status changes suggests that pregabalin might have contributed to the effect. These cases are described below.

Pt 012-084108 A 74 year-old patient developed confusion and hallucinations on day 7 of treatment. He later died and his death was attributed to septicemia and pulmonary embolus. He had been placed on 450 mg/day. Although his ultimate death was due to septicemia, the timing of his original confusion after starting drug suggests the possibility of a drug effect.

Pt 009-011006 A 64 year-old patient was hospitalized on day 12 of treatment with confusion and myoclonus. He was diagnosed with cholestatic jaundice, but the lab abnormalities were not impressive. The drug was discontinued and he recovered; he left the hospital within a week. His dose had been 600 mg/day. Again, the timing of his original confusion after starting drug suggests a possible drug effect.

Ophthalmologic Issues

Vigabatrin is an anticonvulsant available worldwide, but not in the U.S. It has not been approved in the U.S. [redacted]. Current evidence suggests that this visual field defect may be irreversible once identified. Vigabatrin is a structural analog of GABA. It has a backbone of GABA, like gabapentin and pregabalin, but it has a vinyl sidechain. Vigabatrin was developed as a selective inhibitor of GABA-transaminase.

Because of the structural similarities between pregabalin and vigabatrin, the sponsor incorporated ophthalmologic monitoring into the clinical development of pregabalin. Formal testing included visual acuity, perimetry, color vision, and fundoscopy. The results of this testing have been reviewed in a consult by Dr. Wiley Chambers.

Dr. Chambers notes that there were increased numbers of patients with abnormal results on visual acuity and visual field testing in the pregabalin-treated groups compared to placebo. While no specific pattern of abnormalities emerged, he believes the sponsor should do a further study to characterize these changes.

No differences between pregabalin and placebo were seen on fundoscopic testing. Dr. Chambers believes the color testing was not the appropriate testing to discern drug-related toxicity and he has made a recommendation for a specific type of color vision testing for a future study.

Including all identified visual acuity abnormalities, these occurred in 4.8% of placebo patients and 6.5% of all pregabalin patients (7.4% at pregabalin 600 mg/day). Visual field abnormalities (considered valid by a panel of experts) occurred in 4.8% of placebo patients and 5.3% of all pregabalin patients (5.3% at pregabalin 600 mg/day and 7.3% at pregabalin 300 mg/day).

The above differences reflect the results across all therapeutic areas. For validated visual field abnormalities, the greatest pregabalin-placebo difference occurred among epilepsy patients (5% vs. 2%). For visual acuity abnormalities, the results are more uniform across indications.

Among the changes seen in pregabalin-treated patients, Dr. Chambers states that "few" would significantly affect activities of daily living, and most would only affect visual function reserve. He believes that the Precautions section of labeling should reflect the above ophthalmologic results along with a statement that the longterm consequences of these changes are unknown. The proposed labeling, sent with the Approvable letter for neuropathic pain in diabetic neuropathy, did not recommend baseline testing, but did recommend routine monitoring of visual acuity and visual fields.

In the two-year carcinogenicity studies in albino rats, dose-related retinal changes were noted. This would also support the need for a further clinical study as described above.

Developmental and Reproductive Toxicity

Dr. Fisher has reviewed the preclinical studies. There appear to be some effects of pregabalin at all stages of these studies. Dr. Fisher comments in his review on the degree of reproductive impairment and the high rates of embryofetal and pup mortality observed in these studies. A signal for in utero teratogenicity was observed in two species. An increased incidence of fetal abnormalities was also observed in the offspring of pregabalin-treated *male* rats and untreated female rats, an unusual finding. The relevance of this finding for men with epilepsy is unknown.

Because of the effects noted on male reproductive function preclinically, the sponsor performed a study of pregabalin in normal male volunteers to assess effects on sperm motility. No effect on sperm motility was noted. This study was reviewed by Dr. Johnson from the Reproductive Drugs Division. She believes further study is needed if the drug will be given to younger men of reproductive age. Her review recommends a fairly large controlled trial (100 per group) to assess the effects of pregabalin on sperm and hormonal function.

Carcinogenicity

Hemangiosarcomas occurred in two different strains of mice in carcinogenicity studies. The tumors were aggressive and caused early mortality. As mentioned above in the introduction, the sponsor devoted considerable effort to discerning a mechanism by which pregabalin caused the tumors in mice. These efforts are the subject of considerable discussion in different FDA pharm/tox reviews. The position of agency reviewers is that the associations described between the tumors and different parameters are not strong. A good mechanistic understanding of the tumor formation is not supported by the data. Therefore, the possible significance for humans cannot be dismissed.

In the clinical safety database, seventy patients developed a neoplasm (0.8% of all patients). No consistent pattern of tumor formation was observed.

Gabapentin, with its similar chemical structure, was also associated with the occurrence of tumors in carcinogenicity studies. In male rats, pancreatic acinar cell cancers were observed. The tumors in that case did not cause early mortality and a small safety margin of 5 was observed for human exposures at doses of 3600 mg/day. That finding was concerning during the clinical development of gabapentin and led to suspension of clinical study in much the same way the hemangiosarcoma finding affected pregabalin's development. After the approval of gabapentin, the sponsor performed some mechanistic studies which suggested that gabapentin might act as a tumor promoter in pancreatic acinar cells, increasing DNA synthesis.

The relevance of the hemangiosarcomas in mice with pregabalin is of uncertain significance for humans just as the pancreatic acinar cancers with gabapentin are of uncertain significance for humans. Of course, the more aggressive nature of the tumors and the lack of a safety margin with pregabalin draw more attention to the finding. Nevertheless, both drugs were negative in the genotoxic assays and our understanding of these isolated findings in carcinogenicity studies is too limited to draw too many conclusions. The finding with pregabalin should be described in labeling but should not preclude the approvability of the drug for epilepsy.

Of note, the tumorigenic potential of Neurontin is described separately in the Warnings section of labeling. This pattern is not followed in the proposed labeling that issued with the Approvable letter for pregabalin for neuropathic pain.

Drug Abuse and Dependence

This is the subject of a review by Katherine Bonson, Ph.D. of the Controlled Substances Staff (CSS). The CSS has recommended that pregabalin be a Schedule IV drug, comparable to diazepam. Pregabalin caused euphoria in patients; in anxiety studies, 12% of patients treated with pregabalin 450 mg/day and 1.2% of placebo patients reported this effect. In epilepsy patients, pregabalin 600 mg/day led to reports of euphoria in 2% of patients (0.3% for placebo).

Pregabalin was reinforcing in some animal studies and it was associated with withdrawal symptoms in patients when the medication was stopped. CSS also points to a number of deficits in the preclinical behavioral studies that could render them difficult to interpret.

The sponsor disagrees with the recommendation of the CSS and has requested a Formal Dispute Resolution from the Office of the Center Director.

Overall Conclusions

Pregabalin is very similar to gabapentin structurally and pharmacologically. One of the main differences between the two drugs is that pregabalin is considerably more bioavailable than gabapentin. Although direct comparisons of the two drugs have not been performed within the same study in epilepsy patients, the results of studies conducted suggest a greater effect size with pregabalin. I have explained above that apparent differences in efficacy may in part be explained by the fact that higher doses of gabapentin than those studied might impart greater efficacy. The upper range of the dose-response curve for gabapentin has never been fully explored. Controlled trials of gabapentin studied doses as high as 1800 mg/day, but doses much higher are probably used routinely in clinical practice. At dose higher than 1800 mg/day, the side effect profile of gabapentin appears similar to pregabalin; we know this because doses of 2400-3600 mg/day of gabapentin were studied in postherpetic neuralgia and are described in labeling.

In the current NDA, the sponsor has provided evidence to support the efficacy of Lyrica 150-600 mg/day as adjunctive treatment for partial epilepsy.

Ophthalmologic monitoring in controlled trials of pregabalin demonstrated small between-group differences on visual acuity and visual fields. These appear to be very small differences and no consistent pattern of change on visual fields was identified. While monitoring of these parameters can be recommended in labeling (and it was in the proposed labeling that accompanied the Approvable letter for neuropathic pain in diabetes), I wonder how helpful this monitoring will be in practice since most, if not all, of the changes identified will be background changes unrelated to drug.

The safety review identified a signal for drug-induced muscle damage in the NDA. At least one case of rhabdomyolysis in the NDA appeared to be induced by pregabalin. This should be described in labeling and deserves special attention in postmarketing surveillance.

Because of the results of the carcinogenicity studies in mice, the safety review team has asked the sponsor to perform a more detailed analysis of the cancer cases in the safety database. Pending an adequate analysis of this issue, the sponsor should be sent an Approvable letter at this time.

Recommendations

An Approvable letter should be sent requesting that the sponsor complete an analysis of the cancer cases in the NDA in light of expected background incidences of different cancer types.

The Safety Group has several requests for other analyses that should be included in the Approvable letter. These are described earlier in this memo.

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/s/

John Feeney
8/26/04 09:02:24 PM
MEDICAL OFFICER