

**NDA 21-446, Lyrica® (pregabalin) Capsules c-v  
NDA 20-235, Neurontin® (gabapentin) Capsules  
NDA 20-882, Neurontin® (gabapentin) Tablets  
NDA 21-129, Neurontin® (gabapentin) Oral Solution**

**Background Package for July 10 Advisory Committee**

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**JOINT MEETING OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM AND  
THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE**

**ANALYSIS OF SUICIDALITY FROM PLACEBO-CONTROLLED CLINICAL STUDIES  
OF NEURONTIN® (GABAPENTIN) and LYRICA® (PREGABALIN) CAPSULES CV**

**BRIEFING DOCUMENT**

**JULY 10, 2008**

**AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION**

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## EXECUTIVE SUMMARY

This briefing document serves to provide background information to the members of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee (AC) scheduled for 10 July 2008. This document represents Pfizer's analysis and perspective on the issue.

In 2005, Pfizer acted on a request from the U.S. Food and Drug Administration (FDA) and other Health Agencies regarding the evaluation of possible suicide-related adverse events from placebo-controlled trials for NEURONTIN® (gabapentin) and LYRICA® (pregabalin) capsules CV. This request originated from the U.S. Food and Drug Administration (FDA) as a general issue for all Sponsors of marketed antiepileptic drugs (AEDs) and not as an issue for any specific AED. Once a list of studies was identified by the FDA, the requested datasets were submitted to FDA in June 2006 for use in their evaluation and the analysis. Updates to the datasets and the analysis were submitted to the FDA with the most recent response sent in April 2008.

Based on their meta-analysis of data from placebo-controlled studies of 11 drugs approved to treat epilepsy, FDA concluded that patients receiving these drugs had "approximately twice the risk of suicidal behavior or ideation compared to patients receiving placebo". In addition, the FDA stated that the results were "generally consistent among the eleven drugs." This AC Briefing Document has been prepared by Pfizer Inc for consideration by experts and regulatory authorities to carefully and rigorously consider the potential limitations of the methods used to suggest that all anticonvulsants identified in the FDA analysis are associated with an increased risk for suicide or related behaviors.

With this Briefing Document, the sponsor intends to highlight the following issues:

- 1) The compounds included in this FDA analysis have a wide range of mechanisms of action. The major element common to all is that treatment of some form of epilepsy is an approved indication in the United States. While some of these anticonvulsants share a similar mechanism of action (e.g. phenytoin and carbamazepine) or multiple and overlapping mechanisms of action (e.g., valproic acid, felbamate and topiramate), others such as levetiracetam and the  $\alpha 2\delta$ -ligands, gabapentin and pregabalin, bind to unique molecular targets on voltage-gated calcium channels. *While gabapentin and pregabalin have often been mistakenly referred to as GABA-mimetics by virtue of their structural similarity to GABA, they do not affect GABA-ergic function, as described in [section 2.2](#).* Because of the differences in mechanism of action, one would expect these drugs to have different profiles of activity across epilepsy, other neurological and psychiatric disorders, and also to have different adverse event profiles. Indeed, the current prescribing information for these agents reflects these differences.

Given the availability of a large amount of placebo-controlled clinical trial data that share the same pharmacologic class, i.e., gabapentin and pregabalin, it is scientifically meaningful and appropriate to assess the risk of suicide for these products separately

from the others. Pfizer believes that the analyses of clinical trial data with gabapentin and pregabalin do not support the conclusion that there is an increased risk of suicidal behavior and thinking as a result of treatment with these  $\alpha 2\delta$  ligands.

- 2) The rarity of potential suicide-related events in the  $\alpha 2\delta$ -ligand dataset, combined with methods utilized by the FDA that *exclude* studies with no such events result in several biases that diminish the ability to assess whether treatment differences exist. Studies with no events, as well as the rarity of events overall is, in fact, quite informative in a descriptive manner. Statistically, the lack of precision (very wide confidence intervals) generated by the reported methods severely limits the confidence of the resulting point estimates. Methods that exclude the majority of clinical trials data based on lack of events results in diminished precision of point estimates and, more importantly, an exaggeration of risk that is introduced by ascertainment bias. Ultimately, the lack of events and the resultant uncertainty in both point estimates and confidence intervals for the  $\alpha 2\delta$  studies prevent a conclusion of increased risk.

Clinically, the lack of events within the clinical trials is informative, as many of the disease states studied for both gabapentin and pregabalin involved populations at increased risk for suicide and related behaviors. Excluding studies with no events will tend to inflate the risk estimate for active treatments. This bias can be demonstrated for ratio-based risk estimates, such as odds ratios, using Bayesian methods, in which all studies are included in the analysis, and the effect of excluding studies with no events can be quantified (see [Section 5.3.1.1](#), [Table 19](#) through [21](#)). Assessments of risk differences confirm both the lack of significant risk for  $\alpha 2\delta$  ligands and the effect of excluding trials with no events on the estimate of risk ([Table 22](#)).

- 3) While the population of patients taking medications for treatment of epilepsy is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that the analyses presented within this document support the conclusion that neither pregabalin nor gabapentin is associated with an increased risk of suicidal behavior or thinking, including completed suicide, suicide attempt, preparatory acts toward imminent suicide, and suicide ideation.

**LIST OF ABBREVIATIONS**

$\alpha 2\delta$	alpha2 delta – an protein subunit of the voltage-gated calcium channel
AED	antiepileptic drug
AMPA	$\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
$Ca^{2+}$	calcium ion
CHMP	The Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
EMA	European Medicines Agency
FDA	Food and Drug Administration
GAB	gabapentin
GABA	gamma-aminobutyric acid
GAD	glutamic acid decarboxylase
GAT-1	GABA Transporter 1
$Na^+$	sodium ion
NMDA	N-methyl-D-aspartic acid
PBO	placebo
PGB	pregabalin
PY	patient-year

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## 1. Introduction and Overview

### 1.1. Overview of suicide and related behaviors

Suicide is a significant cause of death worldwide and accounted for 32,637 deaths in the United States in 2005<sup>1</sup> and represents an estimated lifetime prevalence of 1.1-1.2%<sup>2</sup>. It is further estimated that there are 8 to 25 suicide attempts for every one completed suicide and in one study of high school students, over the year prior to the survey 19% had at least one episode of suicidal ideation, 14.8% admitted to a developed plan, 8.8% attempted suicide, and 2.6% had a significant enough suicide attempt to require medical intervention<sup>3</sup>.

Though the general consensus is that there is a progression of behaviors from suicidal ideation through completed suicide, this is not a uniformly accepted opinion. In a study examining suicidal behavior in 13 countries, Voracek found a poor correlation between completed suicide and other suicidal behaviors<sup>4</sup>. Similarly, Weissman et al, in a nine country study, found no correlation between suicidal ideation in males and national suicide rates but did report a positive correlation in females ( $r=0.52$ )<sup>5</sup>. Negative correlations were seen in both sexes for the prevalence of suicide attempts and national suicide rates.

The causes of the poor correlation between other suicidal behavior and completed suicide are unknown but authors have suggested variable rates of reporting for less obvious behaviors<sup>4</sup> and the lack of standard nomenclature regarding suicidal behavior<sup>6</sup>. Furthermore, there are few reports to suggest any predictive validity of rating scales designed to assess suicidal behavior and ultimate completion of suicide<sup>6</sup>. This poor predictive value was highlighted in a prospective 5-year study by Pokorny et al of 4800 patients who were examined and rated on instruments reported to be predictive of suicide<sup>7</sup>. Of the 803 identified as being at increased risk for suicide, only 30 (3.7%) completed suicide, however, 37 who were not identified as being at increased risk also committed suicide. Therefore, the false positive rate in this study exceeded 96%, and most of the patients who did commit suicide were not identified as being at an increased suicide risk.

One of the difficulties in assessing suicide risk in study populations is the increased background rate of suicidal behavior in many of the populations studied. Thus, in addition to the risks known to occur with mood disorders, personality disorders, and substance abuse<sup>8,9,10</sup>, increased incidences of suicide and related behavior have been reported for patients with both epilepsy<sup>11,12,13</sup> and chronic pain<sup>14,15,16</sup>. Rates of suicide in epilepsy patients have been reported to increase by a factor of 3 to 10, depending on the existence of comorbid psychiatric conditions, which are also common. Because of the increased incidence of suicidal behavior in these populations, ascertainment bias becomes a concern in assessing risk, particularly with low incidences of these events in clinical trials. This bias favors placebo, as active treatments tend to be associated with higher

rates of adverse events and the patient may be more likely to report other events in the same context. Unequal randomization between drug and placebo may further compound this problem

Two additional factors to consider are the effects of overly broad product warnings on the public health. The first is the direct impact of increased media attention to suicide as a topic. Pirkis et al studied the impact of Australian media attention on subsequent rates of suicide within the population and found that, particularly with television coverage, an increased incidence of suicide could be detected in the media catchment area following the coverage<sup>17</sup>.

The second consideration, perhaps more importantly, is the impact of product labeling changes on prescribing patterns and subsequent suicide rates. Following the imposition of bolded warnings for a possible relationship between antidepressant medications and suicide-related behaviors, several authors have noted an increase in the rates of suicide within the population. Libby et al estimated that the class labeling resulted in a 58% decrease in prescribing of Selective serotonin reuptake inhibitor (SSRI) antidepressants in the pediatric population<sup>18</sup>. Gibbons et al and Nemeroff et al both reported significant decreases in prescribing within the same population following the addition of a boxed warning<sup>19,20</sup>. At the same time, there was a 49% increase in completed suicides in the same age group in the Netherlands and a 14% increase in the United States. The latter increase, between 2003-2005, represented “the largest year-to-year change in suicide rates in this population since the Centers for Disease Control and Prevention began systematically collecting suicide data in 1979.”<sup>19</sup> A recently published article by Katz et al found that, again following imposition of boxed antidepressant warnings, the rate of prescribing in the pediatric population decreased but, moreover, the number of office visits for patients reporting mood and anxiety disorders also decreased<sup>21</sup>. There was a concomitant increase in this population in the relative risk for completed suicide of 1.25 (95% CI, 1.08-1.44).

## 1.2. Background on the Anti-Epileptic Review

Based on an analysis of data from placebo-controlled studies of 11 drugs used to treat epilepsy, the FDA concluded that patients receiving these drugs had “approximately twice the risk of suicidal behavior or ideation compared to patients receiving placebo”. In addition, the FDA stated that the results were “generally consistent among the eleven drugs.” This AC Briefing Document has been prepared by Pfizer Inc for consideration by experts and regulatory authorities to carefully and rigorously consider the potential limitations of the methods used to suggest that all anticonvulsants identified in the FDA analysis are associated with an increased risk for suicide or related behaviors.

Of the 11 anticonvulsants included in the FDA analysis, gabapentin and pregabalin are the only drugs with a mechanism of action mediated by binding at  $\alpha_2\delta$  subunits of voltage-gated calcium channels. While gabapentin and pregabalin have often been mistakenly referred to as GABA-mimetics by virtue of their structural similarity to GABA, they do not affect GABA-ergic function as described in [section 2.2](#). The mechanism of action of these  $\alpha_2\delta$  ligands, which distinguishes them from the other 9

epilepsy medications, is discussed in [Section 2](#) of this Briefing Document. The use of all 11 of these drugs for epilepsy is compared with their use in non-epilepsy indications in [Section 3](#).

The clinical trial data analyzed by the FDA included data from gabapentin and pregabalin clinical trials that was submitted to the Agency by Pfizer in June 2006. Pfizer subsequently responded to queries from FDA to clarify certain information; the last response before the 31 January 2008 FDA Alert was sent on 16 November 2007. The submitted information included data on the occurrence of possibly suicide-related adverse events, which were identified in the patient data using the FDA's prespecified search criteria. These events were subsequently assessed and classified using Columbia University Suicidality Classification Methodology as specified by the FDA. The Columbia categories are 1: completed suicide; 2: suicide attempt; 3: preparatory acts toward imminent suicidal behavior; 4: self-injurious behavior, intent unknown; 5: suicidal ideation; 6a: not enough information; fatal; 6b: not enough information; nonfatal; 7: self-injurious behavior; no suicidal intent; 8: other: accident; psychiatric; medical. Pfizer analyzed the occurrence of possibly suicide-related events in Columbia categories by treatment group, and concluded that there is no increased risk of suicidal behavior or thinking as a result of treatment with either gabapentin or pregabalin. Reports detailing these analyses were submitted to the FDA and European Regulatory Agency (EMA), as well as other international Health Agencies and are included in this Briefing Document as [Appendix 1](#) (gabapentin) and [Appendix 2](#) (pregabalin).

As stated in FDA's document "Statistical Review and Evaluation of Antiepileptic Drugs and Suicidality" dated 23 May 2008<sup>22</sup>, their analysis was based on 199 placebo-controlled trials consisting of a total of 43,892 patients (27, 863 in drug arms and 16, 029 in placebo arms). There were 4 completed suicides among drug-treated patients and none among placebo-treated patients. The combined dataset for gabapentin and pregabalin trials submitted to the FDA by Pfizer included 18,764 active drug- or placebo-treated patients of which 15,258 were used in the FDA analyses or 34.8% of the data analyzed by the FDA. Only 1 of the 4 completed suicides included in the FDA's aggregated dataset occurred in drug-treated patients in the gabapentin or pregabalin clinical trials; therefore, the remaining 3 suicides must have been reported for drug-treated groups in trials with the other epilepsy medications. Despite the similar total number of patients, the discrepancy in number of completed suicides in the  $\alpha_2\delta$  dataset compared with the data from the 9 other epilepsy drugs suggests that the occurrence of suicide is not homogeneous among the drug treatment groups. The amount of controlled clinical data in the FDA meta-analysis which may potentially be accounted for by the  $\alpha_2\delta$  data is summarized in [Section 4](#).

Given the common mechanism of action of the  $\alpha_2\delta$  ligands compared with other drugs used to treat epilepsy, the large amount of patient data available for the  $\alpha_2\delta$  ligands, and the apparent lack of homogeneity in suicide among the clinical trial populations, Pfizer considers it scientifically appropriate and meaningful to analyze pregabalin and gabapentin data separately, as an  $\alpha_2\delta$  ligand class unto themselves and distinct from the other epilepsy medications, for the occurrence of possible suicide-related adverse events.

Pfizer has comprehensively analyzed the  $\alpha_2\delta$  ligand data based both on the methodology described by the FDA statistical analysis, and on meta-analytic methods described by Normand<sup>23</sup>. Methods used by Pfizer to analyze these data are described in [Section 5.1](#).

Data summaries of Columbia category events by treatment group and indication for pregabalin, gabapentin, and the  $\alpha_2\delta$ -ligand dataset (combined pregabalin and gabapentin) are presented in [Section 5.2.1](#), [Section 5.2.2](#), and [Section 5.2.3](#), respectively. The data discussed in these sections include both the dataset submitted in 2006 and a dataset updated with data from clinical studies completed subsequent to the 2006 dataset cut-off and prior to 01 January 2008. A preliminary assessment of potential suicide-related events was done for the compilation of this document. The list of event terms is included in [Appendix 3](#). The use of Bayesian meta-analytical methods are discussed in [Section 5.3](#). Statistical conclusions are included in [Section 5.4](#), and an overall discussion with conclusions is found in [Section 6](#).

## 2. Mechanism of Action of Anti-Epileptic Drugs (AEDs)

### 2.1. Anti-epileptic Drugs not Binding to the $\alpha_2\delta$ Subunit

Epilepsy is the term used to describe a collection of disorders with diverse etiologies and behavioral phenotypes in which recurrent seizures are the defining characteristic. A number of drugs have been shown to be clinically effective and approved for the treatment of epilepsy, but show differences in effectiveness of treatment across the different seizure types<sup>24,25</sup>. For instance, valproic acid has been shown to be clinically effective across a broad range of seizure disorders, including partial seizures, generalized tonic-clonic seizures, absence seizures, and myoclonic seizures and approved specifically for complex partial seizures as well as simple and complex partial seizures in the US. Levetiracetam shows a similar broad spectrum of activity in the clinic, but is only approved specifically in the US for adjunctive treatment for partial onset seizures, myoclonic seizures and primary generalized tonic clonic seizures. Ethosuximide on the other hand, appears to be only affective against absence seizures<sup>24,25</sup>. In addition to the effects of these drugs on seizure disorders, a number of these drugs have also been used, and in some instances approved, to treat non-epileptic conditions, including neuropathic pain, mood disorders, migraine and other neurologic and psychiatric indications<sup>26</sup>. As all AEDs do not share a single common molecular target it might be expected these compounds would have different neurological, psychiatric, and side effect profiles.

Rogawski & Loscher have loosely categorized the potential mechanism of action(s) of AEDs into those that involve one or more of the following: 1) modulation of voltage-gated ion channels; 2) enhancement of synaptic inhibition; and 3) inhibition of synaptic excitation<sup>27</sup>. The mechanism of action of antiepileptic medications will be reviewed within this context to demonstrate that while some AEDs do share similar or overlapping mechanisms of action, others have unique mechanisms of action. This would confer different spectrums of activity in patients with respect to efficacy across seizure disorders, activity in other neurological and psychiatric disorders, and perhaps differences in adverse event profiles.

Voltage-gated channels are a common target of a number of drugs approved for the treatment of epilepsy. Phenytoin and carbamazepine at clinically relevant concentrations appear to produce a frequency dependent block of recombinant or native Na<sup>+</sup> channels that result from a selective affinity for the inactivated state of the channel. This selectivity for the inactivated state of the Na<sup>+</sup> channel translates into a block of high-frequency repetitive spike firing, such as occurs during a seizure, with limited effect on normal on-going neuronal activity (reviewed in [reference 27](#)). There is little evidence that these two drugs act at other targets at clinically relevant concentrations.

A second set of AEDs can be roughly grouped together that combine block of voltage-gated Na<sup>+</sup> channel with activity at additional targets. Thus, lamotrigine produces a state-dependent block of voltage-gated Na<sup>+</sup> channels<sup>27</sup> but also inhibits N and P type voltage-gated Ca<sup>2+</sup> channels in neurons at similar concentrations<sup>28</sup>. Likewise, valproate has been shown to inhibit voltage-gated Na<sup>+</sup> channels<sup>29,30</sup>, produce a modest inhibition of T-type voltage-gated Ca<sup>2+</sup> channels<sup>31</sup>, and at higher concentrations both elevates brain GABA concentrations by blocking GABA transaminase and also enhances GABA<sub>A</sub> receptor responses<sup>32</sup>. Zonisamide, at clinically relevant concentrations, blocks voltage-gated Na<sup>+</sup> channels in squid giant axons<sup>33</sup> and, like other Na<sup>+</sup> channel antagonists, inhibits sustained repetitive firing in cultured neurons<sup>34</sup>. In addition to its effects on Na<sup>+</sup> channels, zonisamide has also been shown to inhibit T-type and voltage-gated Ca<sup>2+</sup> channels<sup>35,36</sup>. Topiramate has been shown to inhibit voltage-gated Na<sup>+</sup> channels<sup>37,38</sup> as well as both enhance synaptic inhibition and reduce synaptic excitation through an interaction with GABA<sub>A</sub><sup>39</sup> and AMPA/kainite receptors<sup>40</sup>, respectively. Likewise, data suggests that felbamate inhibits voltage-gated Na<sup>+</sup> channels as it inhibits sustained repetitive firing in culture mouse neurons<sup>41</sup> and at high concentrations inhibits voltage-gated Na<sup>+</sup> channels when applied to the intracellular side of the membrane<sup>42</sup>. Felbamate has also been shown to enhance GABA<sub>A</sub><sup>43,44</sup> receptor responses and at higher concentrations inhibits NMDA receptor function<sup>43,45</sup>.

A third group of AEDs function predominately to enhance GABA-ergic synaptic inhibition. Benzodiazepines and barbiturates potentiate GABA<sub>A</sub> receptor function through allosteric interactions at different sites on the GABA<sub>A</sub> receptor complex<sup>46</sup>. Effects of barbiturates have also been described at AMPA and kainate receptor currents<sup>47,48</sup> and voltage gated Na<sup>+</sup> and Ca<sup>2+</sup> channels<sup>49,50</sup>. However, these effects occur at somewhat higher concentrations than those required to modulate GABA<sub>A</sub> receptor function, thus it is unclear whether these additional activities are relevant to the therapeutic effects of barbiturates in the clinic. Other AEDs act by elevating the level of GABA. Tiagabine inhibits the reuptake of GABA by binding to and blocking GAT-1, the most abundant of the GABA transporters<sup>51</sup>. Vigabatrin inhibits GABA-transaminase<sup>51</sup>, the enzyme that converts GABA to succinic acid, thus elevating brain GABA levels. One might expect the clinical profiles of benzodiazepines and barbiturates to be somewhat different than that of tiagabine and vigabatrin as the former group targets GABA<sub>A</sub> receptor function, while the later group would presumably result in enhanced activation of both GABA<sub>A</sub> and GABA<sub>B</sub> receptors. *While gabapentin and pregabalin have often been mistakenly referred to as GABA-mimetics by virtue of their structural similarity to GABA, they do not affect GABA-ergic function as described in [section 2.2](#).*

A fourth group of AEDs are unique in that they bind to novel targets not previously described for AEDs. Levetiracetam has recently been shown to bind to a novel site in rat brain, that is enriched in the synaptic vesicle membrane fraction<sup>52,53</sup>. This was subsequently identified to be the SV2A protein, a vesicle protein that appears to play a role in vesicle fusion. The anticonvulsant potency of a series of levetiracetam analogs for blocking audiogenic seizures was highly correlated with their potency for binding to the SV2A protein suggesting that the anticonvulsant activity of levetiracetam is related to its interaction with the SV2A protein<sup>54</sup>. No other AED was demonstrated to show high affinity interactions with this site. There is some evidence that levetiracetam interacts with other targets. For instance, while levetiracetam does not inhibit voltage-gated Na<sup>+</sup> channels or low voltage-activated T type calcium channels<sup>55</sup>, it has been shown to produce a small but significant block of N-type calcium channels<sup>56</sup>, and at high concentrations has been shown to produce a small inhibition of AMPA receptor currents in neurons<sup>57</sup>. Given the close correlation between affinity for the SV2A, it seems unlikely that the small block of calcium channels or AMPA receptors contributes to the anticonvulsant effects of levetiracetam *in vivo*. On the other hand, more recent evidence suggests an effect with acute<sup>57</sup> or longer term administration<sup>58</sup> on electrophysiological and imaging markers of presynaptic function *in vitro* that are consistent with effects on SV2A to modulate presynaptic transmitter release machinery.

## 2.2. Drugs that Bind to the $\alpha_2\delta$ Subunit of Voltage-gated Calcium Channels

Studies indicate that gabapentin and pregabalin also bind to a novel site in the CNS, the  $\alpha_2\delta$  protein, an auxiliary subunit of voltage-gated Ca<sup>2+</sup> channels<sup>59</sup>. This site of action was first suggested from the observation of high affinity [<sup>3</sup>H]-gabapentin binding to the  $\alpha_2\delta$  subunit purified from solubilized proteins of porcine brain and similar high affinity binding to membranes prepared from cells expressing recombinant  $\alpha_2\delta$ -1<sup>60</sup>. This binding site is unique for pregabalin and gabapentin as other AEDs including phenytoin, carbamazepine, benzodiazepines, barbiturates, felbamate, vigabatrin and lamotrigine do not displace [<sup>3</sup>H]gabapentin or [<sup>3</sup>H]pregabalin binding to the  $\alpha_2\delta$  protein<sup>61,62</sup>. Three additional  $\alpha_2\delta$  subunits genes were identified ( $\alpha_2\delta$ -2,  $\alpha_2\delta$ -3, &  $\alpha_2\delta$  -4), but [<sup>3</sup>H]-gabapentin was found to only bind to  $\alpha_2\delta$ -1 and  $\alpha_2\delta$ -2<sup>63,64</sup>. The anticonvulsant, anti-hyperalgesic and anxiolytic effects of pregabalin and gabapentin in animal models result from binding to the  $\alpha_2\delta$  as in behavioral studies with pregabalin and structural derivatives, the anticonvulsant, anxiolytic and antihyperalgesic effects were correlated with affinity for the  $\alpha_2\delta$  protein<sup>65</sup>. In addition, a genetically modified strain of mice has been generated in which the wildtype  $\alpha_2\delta$ -1 protein gene is replaced with a mutant form of  $\alpha_2\delta$ -1 in which the arginine at position 217 of the amino acid have been replaced with alanine. This substitution dramatically reduces the affinity of pregabalin and gabapentin for the protein. In mice expressing the  $\alpha_2\delta$ -1R217A mutation, the activity of gabapentin and pregabalin in inflammatory and neuropathic models of pain as well as in models of anxiety and seizures was dramatically reduced, providing additional evidence that the pharmacological actions of these compounds is due to their interaction with the  $\alpha_2\delta$  protein<sup>66,67,68</sup>.

As the  $\alpha_2\delta$  protein is an auxiliary subunit of voltage gated ion channels, it would seem reasonable to expect that pregabalin and gabapentin would modulate voltage-gated  $\text{Ca}^{2+}$  channel function and subsequently, neurotransmitter release. Indeed, several reports indicate that gabapentin reduces voltage-gated  $\text{Ca}^{2+}$  currents in neurons<sup>69,70</sup>. Other studies, however, contradict these findings by showing that gabapentin does not alter  $\text{Ca}^{2+}$  currents measured in neuronal cell bodies<sup>71</sup>, or in recombinant cell systems with artificial expression of mammalian VSCC  $\alpha_2\delta$ ,  $\alpha_1$  and  $\beta_1$  subunits<sup>72</sup>. A recent study might explain these contradictory findings; it indicates that voltage-gated  $\text{Ca}^{2+}$  currents in sensory neurons from wild-type mice were not affected by gabapentin, while  $\text{Ca}^{2+}$  currents in sensory neurons from mutant mice overexpressing the  $\alpha_2\delta$ -1 protein were blocked by gabapentin<sup>73</sup>. Finally, Dolphin and colleagues have most recently demonstrated that chronic treatment with gabapentin inhibits voltage-gated  $\text{Ca}^{2+}$  channels by an intracellular site of action, impairing the ability of  $\alpha_2\delta$  to translocate the  $\text{Ca}^{2+}$  channel complex to the cell surface<sup>74</sup>. Consistent with effects on voltage-gated  $\text{Ca}^{2+}$  channels, gabapentin and pregabalin have been shown to modulate neurotransmitter release<sup>75</sup> in conditions of enhanced excitability<sup>76,77</sup>.

Other sites of action for gabapentin and pregabalin have been proposed. As the compounds are close analogs of GABA, it was initially speculated that they might interact with GABA receptors. This structural similarity to GABA resulted in the unfortunate assignment by USAN of a GAB-stem to their generic names, which suggested that pregabalin and gabapentin were GABA-mimetics. As briefly outlined below, while pregabalin and gabapentin are structurally related to GABA, they are not GABA-mimetic as they do not interact with GABA receptors, inhibit GABA transporters, or interact with GABA synthetic or degradative enzymes at pharmacologically relevant concentrations.

Gabapentin and pregabalin do not alter radioligand binding to  $\text{GABA}_A$  and  $\text{GABA}_B$  receptors<sup>78,79</sup>, nor do they alter  $\text{GABA}_A$  receptor function<sup>80,81</sup>. While initial studies suggested that at high concentrations (supratherapeutic) gabapentin might be a subtype-selective agonist at  $\text{GABA}_B$  receptors<sup>82</sup>, this has not been confirmed in subsequent studies<sup>83,84</sup>. Pregabalin and gabapentin do not inhibit reuptake of GABA<sup>85,86</sup>. At high, supratherapeutic, concentrations, gabapentin inhibits GABA-transaminase<sup>87</sup>, but this has not been seen with pregabalin<sup>88</sup>, and elevations in total brain GABA levels have not been seen in rats, in contrast to the large increases in GABA levels seen with the GABA-transaminase inhibitor, vigabatrin<sup>89</sup>. Three substituted GABA analogs, like gabapentin and pregabalin have been shown to activate glutamic acid decarboxylase (GAD), the enzyme that synthesizes GABA. However, the potency for GAD enhancement is not correlated with anticonvulsant activity, moreover significant effects of gabapentin on GAD activity were only seen at 1 mM and above – much higher than unbound plasma concentrations in patients<sup>90</sup>.

### 2.3. Mechanism of Action Summary

Drugs approved for the treatment epilepsy have a wide range of mechanisms of action. While the mechanism of action of some AED's are similar (such as phenytoin and carbamazepine) or have multiple and overlapping mechanisms of action (such as valproic

acid, felbamate and topiramate), others such as leviteracetam and the  $\alpha 2\delta$ -ligands gabapentin and pregabalin bind to unique targets that are not shared by other AEDs. One would expect that because of the differences in mechanism of action, that AEDs would have different profiles of activity across epilepsy disorders, other neurological and psychiatric disorders and different adverse event profiles.

### 3. Usage of Anti-Epileptic Drugs in Epilepsy vs Non-Epilepsy Indications

Usage patterns for the 11 drugs included in the FDA analysis vary widely. Table 1 shows the projected use (IMS Medical database) for epilepsy and non-epilepsy indications in the year 2007. As can be seen in the table, although these compounds are all approved for the treatment of epilepsy, the usage of these products varies considerably. Hence, nearly all of the usage of pregabalin is for indications other than epilepsy. Similarly, less than 10% of the gabapentin use was for epilepsy indications; greater than 90% of its use was for non-epilepsy indications. The percentage of epilepsy usage for the other drugs ranged from a high of about 97% (felbamate) to a low of about 26% (topiramate).

**Table 1. Use of Anticonvulsant Drugs in for Epilepsy and Non-Epilepsy Indications in 2007**

	Total <sup>a</sup>	Epilepsy		Non-Epilepsy	
		Number <sup>a</sup>	%	Number <sup>a</sup>	%
Pregabalin	10,503	192	1.8	10,311	98.2
Gabapentin	12,784	919	7.2	11,864	92.8
Topiramate	7,053	1,818	25.8	5,236	74.2
Valproate Semisodium	7,428	2,125	28.6	5,303	71.4
Lamotrigine	8,971	2,933	32.7	6,038	67.3
Oxcarbazepine	3,929	1,994	50.8	1,935	49.2
Carbamazepine	24,553	12,952	52.7	11,601	47.3
Tiagabine	147	90	60.7	58	39.3
Zonisamide	4,123	3,242	78.6	881	21.4
Levetiracetam	2,645	2,266	85.7	379	14.3
Felbamate	29	28	97.0	1	3.0

<sup>a</sup>Thousands of prescriptions

In analyses presented by the FDA at the Pediatric Advisory Committee on 25 March 2008, risk differences and relative risks differed by indication (epilepsy, psychiatric, and other). Differential usage of these products should be considered in the overall risk-benefit assessment.

### 4. Percentage of Gabapentin and Pregabalin Data Contributing to the FDA Meta-analysis

The number of patients included in the June 22, 2006 submissions to the FDA are compared with the total number of patients analyzed by the FDA in [Table 2](#) below. The

methodology used by the FDA was recently published in the document titled “Statistical Review and Evaluation of Antiepileptic Drugs and Suicidality“. Based on this report, the  $\alpha 2\delta$  clinical trials contributed 34.8% of the combined drug-treated and placebo-treated total number of patients included in the FDA analysis, though only 8.4% of the potentially suicide-related cases (PSRAEs) were derived from the  $\alpha 2\delta$  clinical trials

**Table 2. Potential Number of Patients from  $\alpha 2\delta$  Clinical Trials Included in the FDA Analysis**

	<b>Drug-Treated</b>	<b>Placebo-Treated</b>	<b>Total</b>
FDA Total	27863	16029	43892
Gabapentin	2903	2029	4932
Pregabalin	7201	3125	10326
$\alpha 2\delta$ Total <sup>a</sup>	10104	5154	15258
$\alpha 2\delta$ Total as % FDA Total	36.3%	32.2%	34.8%

<sup>a</sup> Gabapentin + Pregabalin

## 5. Statistical Analysis of Potentially Suicide-Related Events with the $\alpha 2\delta$ Agents Gabapentin and Pregabalin

### 5.1. Methods used to identify possible suicide-related adverse events

Data derived from the pregabalin and gabapentin FDA responses, dated 22 June 2006 and data included in response to queries from the Division regarding possibly suicide related events within controlled clinical trials of gabapentin and pregabalin were utilized to conduct these analyses. Subsequent analyses conducted by Pfizer include additional data from studies completed after the dataset cut-off for the 22 June 2006 response and prior to 01 January 2008. This updated analysis was submitted to the Division on 30 April 2008.

The data for these two compounds were summarized using the 2006 data sets, the updated pregabalin data set (the 2006 data set plus all qualified studies with final study report prior to January 1, 2008), and with the combined gabapentin and pregabalin data. A revised assessment of potential suicide-related events was done for the compilation of this document. The list of event terms is included in [Appendix 3](#). Reviewers of these terms remain blinded to the treatment assignments.

Traditional methods utilizing ratio-based risk comparisons, such as odds ratios, assess risk within populations reporting an adequate number of events include 1) the Cochran-Mantel-Haenszel (CMH) method, 2) CMH “with a 0.5 correction” as defined in the FDA 2006 Advisory Committee briefing package for antidepressants which states that for “. . . trials with events in one group and no events in its comparison group, a ‘continuity correction’ of 0.5 was added . . .”, 3) logistic regression model, and 4) the Dersimonian-Laird random effects model (using the ‘0.5’ correction). For each method analyses were stratified by study. However, each of these methods excludes studies with no events in

either treatment group. The effect(s) of this exclusion can be explored further, as described below.

Because standard methods for odds ratios do not use data from studies with no events the standard Mantel-Haenszel methods for risk differences were used in a further evaluation of the effects of excluding studies with no events.

Procedural difficulties were already described in the use of point estimates utilizing ratio-based risk comparisons, such as odds ratios. As a result, studies with no events are typically excluded, though this exclusion may ultimately alter the conclusions. Therefore, incorporating all studies (and all data) becomes both clinically and statistically relevant.

An alternative method, using a Bayesian approach based on the event distribution following a Poisson distribution, can be used and may help to inform about the impact of excluding studies. The Bayesian methods were applied both to the updated pregabalin data and the combined pregabalin/gabapentin data. The latter was done in an attempt to explore the risk of  $\alpha 2\delta$  ligands as a class. Data were stratified by study in these analyses, and WinBUGS statistical software was used to perform the analyses. A similar Bayesian approach was applied to odds ratios.

Analyses were conducted using all data from placebo controlled trials in the dataset created in response to the FDA query for information and by excluding the trials that the FDA would presumably have excluded based either on durations of trials shorter than requested or small sample size, see [Table 3](#). For both sets of analyses trials were excluded in the 2006 datasets if they have no placebo arm, see [Table 4](#), or had a single dose/single day treatment duration.

**Table 3. List of Study Exclusions Based in Sample Size or Duration**

<b>Studies In 2006 Databases but Excluded In Some Analyses</b>		
<b>Pregabalin Study</b>	<b>Pregabalin N</b>	<b>Placebo N</b>
Duration < 8 days		
1008-013	100	50
1008-016	99	50
1008-027	68	20
Fewer than 20 per arm or <30 total		
1008-002	45	12
A0081038 (also 1 day duration)	24	6
1008-072	30	16
<b>Total PGB</b>	<b>366</b>	<b>154</b>
<b>Gabapentin Study</b>	<b>Gabapentin N</b>	<b>Placebo N</b>
Duration < 8 days		
1032-001	252	52
1035-001	152	51
1035-001B	81	20
1035-002	101	49
934-324	131	20
934-335	60	30
A9451139	206	103
A9451140	522	262
A9451141	515	258
Fewer than 20 per arm or <30 total		
945-009	27	18
945-010	26	16
945-019	9	12
945-421-222	15	15
945-439	15	15
945-020	5	6
<b>Total GAB</b>	<b>2117</b>	<b>927</b>
<b>Total PGB + GAB</b>	<b>2483</b>	<b>1081</b>

**Table 4. Studies In 2006 Databases but Excluded In All Analyses Because of No Placebo or  $\alpha 2\delta$  Drug**

<b>Pregabalin Study</b>	<b>Pregabalin N</b>	<b>Placebo N</b>
1008-007	42	0
<b>Gabapentin Study</b>	<b>Gabapentin N</b>	<b>Placebo N</b>
945-077	146	0
945-082	181	0
945-088	40	0
945-177	43	0
945-213	75	0
945-448-001	50	0
945-475-283	1	0
945-8J	0	1
<b>Total</b>	<b>578</b>	<b>1</b>

In the analyses the studies in [Table 4](#) and studies with a single dose or single day of treatment were excluded. The following pregabalin studies had a single dose or a single day of treatment with two doses: 1008-013, 1008-016, 1008-027, A0081038, and A0081072. The following gabapentin studies were single dose studies: 1032-001, 1035-001, 1035-001B, 1035-002, 934-324, 934-335, A9451139, A9451140, and A9451141.

## 5.2. Results

### 5.2.1. Summary of Pregabalin Placebo Controlled Data

Table 5 and Table 6 summarize exposure and patient counts for pregabalin studies in the 2006 dataset and the updated dataset, respectively.

**Table 5. Pregabalin Exposure Data from 2006 FDA Response**

	Pregabalin N	Placebo N	PGB Exposure in patient-days	PLA Exposure in patient-days
NeP	2174	989	113111	50013
Epilepsy	1178	507	87142	43615
Fibro	956	321	57115	19654
GAD	1326	580	42795	18978
Other Psych	877	421	46519	22477
Chronic Pain	670	285	32895	15620
Other Studies	95	50	4428	2400

**Table 6. Updated Pregabalin Exposure Data – 2006 FDA Response and Qualified Studies Completed Prior to January 1, 2008**

	Pregabalin N	Placebo N	PGB Exposure in patient-days	PLA Exposure in patient-days
NeP	3320	1586	189282	92995
Fibro	1517	505	99307	33777
Epilepsy	1178	507	87142	43615
GAD	1447	708	48533	25202
Other Psych	877	421	46519	22477
Chronic Pain	670	285	32895	15620
Other Studies	206	87	7470	3436

The number patient-years in the 2006 database were pregabalin 1051.348 and placebo 472.983 (total number of patient days in Table 5 divided by 365.25).

[Table 7](#) summarizes estimates of event rates across indications for the 2006 dataset. It should be noted that, as with other calculations of risk associated with rare events, these estimates have low accuracy and should be viewed primarily as descriptive.

**Table 7. Event Types by Indication in Updated Pregabalin Data – 2006 FDA Response**

	Treatment	Event 1,2,3,5 n/Patient- Years	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
<b>NeP</b>	Pregabalin	0/309.681	0/2174	0	0	0	0
	Placebo	0/136.928	0/989	0	0	0	0
<b>Fibro</b>	Pregabalin	0/156.372	0/956	0	0	0	0
	Placebo	1/53.810 (0.0186)	1/321 (0.0031)	0	0	0	1
<b>Epilepsy</b>	Pregabalin	2/238.582 (0.0084)	2/1178 (0.0017)	1	1	0	0
	Placebo	0/119.411	0/507	0	0	0	0
<b>GAD</b>	Pregabalin	0/117.166	0/1326	0	0	0	0
	Placebo	0/51.959	0/580	0	0	0	0
<b>Other Psych</b>	Pregabalin	5/127.362 (0.0393)	5/877 (0.0057)	0	2	0	3
	Placebo	1/61.539 (0.0163)	1/421 (0.0024)	0	0	0	1
<b>Chronic Pain</b>	Pregabalin	0/90.062	0/670	0	0	0	0
	Placebo	0/42.765	0/285	0	0	0	0
<b>Other Studies</b>	Pregabalin	0/12.123	0/95	0	0	0	0
	Placebo	0/6.571	0/50	0	0	0	0

In the current update (submitted to FDA on 30 April 2008 and which includes data from completed study reports prior to January 1, 2008) the results show only one new event using the FDA criteria and Columbia classification system for the categories analyzed by FDA and in this document – categories 1, 2, 3, and 5. Within the new studies, treatment exposure duration is 1399.838 patient-years for pregabalin and 649.205 patient-years for placebo (total number of patient days in Table 6 divided by 365.25). The corresponding patient-years in the 2006 database were pregabalin 1051.348 and placebo 472.983 (total number of patient days in Table 5 divided by 365.25). Thus, the updated dataset allows for an examination of the effects of a 33% increase in exposure for pregabalin and 37% increase in placebo exposure. Despite this increased duration of exposure, only one new relevant event occurred and this occurred within a placebo-treated subject. The resulting changes in point estimates of calculated risk highlight the extreme uncertainty in defining risk within such rare events.

Table 8 summarizes estimates of event rates across indications based on the revised dataset including patient exposure up through 01 January 2008. The estimates again have low accuracy because of the rarity of events. The rarity of events is further highlighted by the fact that only one event, a completed suicide in a placebo-treated subject, occurred

within the updated analysis. The effect of this additional placebo event on point estimates of risk can be seen in Table 8 and Table 9.

**Table 8. Event Types by Indication in Updated Pregabalin Data – 2006 FDA Response and Qualified Studies Completed Prior to January 1, 2008**

	Treatment	Event 1,2,3,5 n/Patient- Years	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
<b>NeP</b>	Pregabalin	0/518.226	0/3320	0	0	0	0
	Placebo	1/254.606 (0.0039)	1/1586 (0.0006)	1	0	0	0
<b>Fibro</b>	Pregabalin	0/271.888	0/1517	0	0	0	0
	Placebo	1/92.476 (0.0108)	1/505 (0.0020)	0	0	0	1
<b>Epilepsy</b>	Pregabalin	2/238.582 (0.0084)	2/1178 (0.0017)	1	1	0	0
	Placebo	0/119.411	0/507	0	0	0	0
<b>GAD</b>	Pregabalin	0/132.876	0/1447	0	0	0	0
	Placebo	0/68.999	0/708	0	0	0	0
<b>Other Psych</b>	Pregabalin	5/127.362 (0.0393)	5/877 (0.0057)	0	2	0	3
	Placebo	1/61.539 (0.0163)	1/421 (0.0024)	0	0	0	1
<b>Chronic Pain</b>	Pregabalin	0/90.062	0/670	0	0	0	0
	Placebo	0/42.765	0/285	0	0	0	0
<b>Other Studies</b>	Pregabalin	0/20.452	0/206	0	0	0	0
	Placebo	0/9.407	0/87	0	0	0	0

Table 9 summarizes relative risks and risk differences for the indications based on the data in Table 8. There is no consistent pattern to suggest increased risk in drug treated subjects compared to placebo. In the cases of other psychiatric trials and epilepsy trials there is a numeric but not statistically significant increase in risk difference; however, data in neuropathic pain and fibromyalgia trials, where the majority of exposure exists, reveal a negative risk difference and a relative risk of zero. It is also important to realize that all of the epilepsy trials conducted were of adjunctive therapy and patients were taking multiple antiepileptic therapies. Note that there were no events classified in either treatment group as preparatory acts toward imminent suicidal behavior. Overall, the relative risk and risk difference for categories 1,2,3 and 5 for all indications are very close to one and null, respectively.

**Table 9. Summary Statistics for Events by Indication Using the 2006 FDA Response Studies and Qualified Studies Completed Prior to January 1, 2008**

	Treatment	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
<b>NeP</b>	Pregabalin	0/3320	0	0	0	0
	Placebo	1/1586 (0.0006)	1	0	0	0
Risk Difference	drug-placebo	-0.0006				
Relative Risk	drug/placebo	0				
<b>Fibromyalgia</b>	Pregabalin	0/1517	0	0	0	0
	Placebo	1/505 (0.0020)	0	0	0	1
Risk Difference	drug-placebo	-0.0020				
Relative Risk	drug/placebo	0				
<b>Epilepsy</b>	Pregabalin	2/1178 (0.0017)	1	1	0	0
	Placebo	0/507	0	0	0	0
Risk Difference	drug-placebo	0.0017				
Relative Risk	drug/placebo	undefined				
<b>Other Psych</b>	Pregabalin	5/877 (0.0057)	0	2	0	3
	Placebo	1/421 (0.0024)	0	0	0	1
Risk Difference	drug-placebo	0.0033				
Relative Risk	drug/placebo	2.40				
<b>All Studies</b>	Pregabalin	7/9215 (0.0008)	1	3	0	3
	Placebo	3/4099 (0.0007)	1	0	0	2
Risk Difference	drug-placebo	0.0000				
Relative Risk	drug/placebo	1.04				

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### 5.2.2. Summary of Gabapentin Placebo Controlled Data

The gabapentin exposure and event occurrences are summarized here. Only the 2006 data were used as recent gabapentin studies did not have final clinical study reports available prior to the January 1, 2008 date.

**Table 10. Gabapentin Exposure Data from 2006 FDA Response**

	Gabapentin N	Placebo N	GAB Exposure in patient-days	PBO Exposure in patient-days
NeP	1081	785	59043	46622
Epilepsy	778	617	76954	60846
Other Psych	144	145	7848	8129
Chronic Pain	157	53	4250	1336
Other Studies	478	236	21905	11878

N=number of subjects; GAB=gabapentin; PBO=placebo; NeP=neuropathic pain

Table 11 summarizes the events categorized into Columbia classification categories 1, 2, 3, and 5. The extreme rarity of events is immediately obvious. These data do not provide any evidence of an increased risk in any category.

**Table 11. Event Types by Indication Using the 2006 FDA Response Gabapentin Studies**

	Treatment	Event 1-5 n/Patient- Years	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
NeP	Gabapentin	0/161.651	0/1081	0	0	0	0
	Placebo	1/127.644 (0.0078)	1/785 (0.0013)	0	0	0	1
Epilepsy	Gabapentin	2/210.689 (0.0095)	2/778 (0.0026)	0	0	0	2
	Placebo	0/166.587	0/617	0	0	0	0
Other Psych	Gabapentin	0/21.487	0/144	0	0	0	0
	Placebo	0/22.256	0/145	0	0	0	0
Chronic Pain	Gabapentin	0/11.636	0/157	0	0	0	0
	Placebo	0/3.658	0/53	0	0	0	0
Other Studies	Gabapentin	0/59.973	0/478	0	0	0	0
	Placebo	0/32.520	0/236	0	0	0	0

Table 12 summarizes relative risks and risk differences for indications with events. As with the pregabalin data no clear pattern emerges.

**Table 12. Summary Statistics for Events by Indication Using the 2006 FDA Response Gabapentin Data**

Treatment		Event 1,2,3,5 n/N	Suicidal Ideation
NeP	Gabapentin	0/1081	0/1081
	Placebo	1/785	1/785
Risk Difference	drug-placebo	(0.0013)	(0.0013)
Relative Risk	drug/placebo	-0.0013	-0.0013
Epilepsy	Gabapentin	0	0
	Placebo	2/778	2/778
Risk Difference	drug-placebo	(0.0026)	(0.0026)
Relative Risk	drug/placebo	0/617	0/617
Risk Difference	drug-placebo	0.0026	0.0026
Relative Risk	drug/placebo	undefined	undefined
All Studies	Gabapentin	2/2638	
	Placebo	(0.0008)	
Risk Difference	drug-placebo	1/1836	
Relative Risk	drug/placebo	(0.0005)	
Risk Difference	drug-placebo	0.0002	
Relative Risk	drug/placebo	1.39	

### 5.2.3. Summary of Combined Gabapentin and Pregabalin ( $\alpha 2\delta$ ) Placebo Controlled Data

Table 13 summarizes the combined patient counts and exposure for the pregabalin updated data and 2006 gabapentin data combined.

**Table 13.  $\alpha 2\delta$  Exposure Data – 2006 FDA Responses and Qualified Pregabalin Studies Completed Prior to January 1, 2008**

	$\alpha 2\delta$ N	Placebo N	$\alpha 2\delta$ Exposure in patient-days	PBO Exposure in patient-days
NeP	4401	2371	248325	139617
Epilepsy	1956	1124	164096	104461
Fibro	1517	505	99307	33777
GAD	1447	708	48533	25202
Other Psych	1021	566	54367	30606
Chronic Pain	827	338	37145	16956
Other Studies	684	323	29375	15314

N=number of subjects; PGB=pregabalin; PBO=placebo; NeP=neuropathic pain; Fibro=fibromyalgia; GAD=generalized anxiety disorder

Table 14 summarizes the combined event counts and rates for the combined datasets. Once again, the rarity of events renders the accuracy of risk estimates unreliable and, therefore, the results should only be viewed as descriptive. There is, however, no consistent pattern and event rates appear as both decreased and increased in the  $\alpha 2\delta$  class relative to placebo, depending on indication.

**Table 14. Event Types by Indication in  $\alpha 2\delta$  Placebo-Controlled Data – 2006 FDA Responses and Qualified Pregabalin Studies Completed Prior to January 1, 2008**

	Treat- ment	Event 1,2,3,5 n/Patient-Years	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
<b>NeP Studies</b>	$\alpha 2\delta$	0/679.877	0/4401	0	0	0	0
	PBO	2/382.251 (0.0052)	2/2371 (0.0008)	1	0	0	1
<b>Fibro Studies</b>	$\alpha 2\delta$	0/271.888	0/1517	0	0	0	0
	PBO	1/92.476 (0.0108)	1/505 (0.0020)	0	0	0	1
<b>Epilepsy Studies</b>	$\alpha 2\delta$	4/449.270 (0.0089)	4/1956 (0.0020)	1	1	0	2
	PBO	0/285.999	0/1124	0	0	0	0
<b>GAD Studies</b>	$\alpha 2\delta$	0/132.876	0/1447	0	0	0	0
	PBO	0/68.999	0/708	0	0	0	0
<b>Other Psych Studies</b>	$\alpha 2\delta$	5/148.849 (0.0336)	5/1021 (0.0049)	0	2	0	3
	PBO	1/83.795 (0.0119)	1/566 (0.0018)	0	0	0	1
<b>Chronic Pain Studies</b>	$\alpha 2\delta$	0/101.697	0/827	0	0	0	0
	PBO	0/46.423	0/338	0	0	0	0
<b>Other Studies</b>	$\alpha 2\delta$	0/80.424	0/684	0	0	0	0
	PBO	0/41.927	0/323	0	0	0	0

PBO=placebo; NeP=neuropathic pain; Fibro=fibromyalgia; GAD=generalized anxiety disorder.

Table 15 summarizes relative risks and risk differences for only those indications in which a category 1, 2, 3, or 5 event occurred. A consistent pattern of response remains unseen. As before estimates have low precision because of the scarcity of events.

**Table 15. Summary Statistics for Events by Indication- 2006 FDA Responses and Qualified Pregabalin Studies Completed Prior to January 1, 2008**

	Treat- ment	Event 1,2,3,5 n/N	Completed Suicide	Suicide Attempt	Preparatory Acts	Suicidal Ideation
<b>NeP Studies</b>	$\alpha 2\delta$	0/4401	0	0	0	0
	PBO	2/2371	1	0	0	1
		(0.0008)				
	Risk difference ( $\alpha 2\delta$ -PBO)	-0.0008				
Relative risk	( $\alpha 2\delta$ /PBO)	0				
<b>Fibro Studies</b>	$\alpha 2\delta$	0/1517	0	0	0	0
	PBO	1/505	0	0	0	1
		(0.0020)				
	Risk difference ( $\alpha 2\delta$ -PBO)	-0.0020				
Relative risk	( $\alpha 2\delta$ /PBO)	0				
<b>Epilepsy Studies</b>	$\alpha 2\delta$	4/1956	1	1	0	2
	PBO	0/1124	0	0	0	0
		(0.0020)				
	Risk difference ( $\alpha 2\delta$ -PBO)	0.0020				
Relative risk	( $\alpha 2\delta$ /PBO)	Undefined				
<b>Other Psych Studies</b>	$\alpha 2\delta$	5/1021	0	2	0	3
	PBO	1/566	0	0	0	1
		(0.0018)				
	Risk difference ( $\alpha 2\delta$ -PBO)	0.0031				
Relative risk	( $\alpha 2\delta$ /PBO)	2.77				
<b>All Studies</b>	$\alpha 2\delta$	9/11853	1	3	0	5
	PBO	4/5935	1	0	0	3
		(0.0008)				
	Risk difference ( $\alpha 2\delta$ -PBO)	0.0007				
Relative risk	( $\alpha 2\delta$ /PBO)	1.13				

Overall, the risk difference (0.0001) and relative risk (1.13), as shown above, provide no evidence of an increased risk of suicide or related behaviors.

#### 5.2.4. Calculations of Risk Using Traditional Methods

The following tables summarize results using methods that include those described by the FDA in their document “Statistical Review and Evaluation of Antiepileptic Drugs and Suicidality“. In all cases the focus is on the outcome of any event with Columbia criteria score of 1, 2, 3, or 5 (1=completed suicide, 2=suicide attempt, 3=preparatory acts, or 5=suicidal ideation), as categories 4 and 5 were reversed between preparation of the original databases and the present review.

Table 16 summarizes the point estimates and 95% confidence intervals for all placebo-controlled pregabalin trials and Table 17 shows the same information for studies meeting FDA criteria, based on the dataset provided in 2006 in response to the FDA request for information. It can be seen that, depending on the method used to calculate odds ratio, that

the point estimate can vary considerably (by a factor of two) and, furthermore, that the precision of these point estimates is clearly low based on the broad confidence intervals. In no case did the 95% CI exclude 1, suggesting a lack of statistical significance for any of the reported point estimates.

**Table 16. Suicidality Rates from Pregabalin Trials (Event Categories 1, 2, 3, and 5) - Stratification by Trial, All Placebo Controlled Trials Included <sup>a</sup>**

Method	Odds Ratio	95% CI on Odds Ratio	Event Counts	
			Pregabalin N=7276	Placebo N=3153
Mantel-Haenszel with '0.5' correction	0.860	0.281, 2.631	7/1370 <sup>b</sup>	2/663
Mantel-Haenszel	1.781	0.389, 8.157	7/1370 <sup>b</sup>	2/663
Logistic regression	1.891	0.381, 9.381	7/1370 <sup>b</sup>	2/663
Dersimonian-Laird random effects model <sup>c</sup>	0.850	0.258, 2.796	7/1370 <sup>b</sup>	2/663

Events included are completed suicide (1); suicide attempt (2); preparatory acts towards imminent suicidal behavior (3); suicidal ideation (5)

<sup>a</sup> See list of excluded trials in Table 4 and list of trials with single dose/single day of treatment in Table 3.

<sup>b</sup> These methods exclude subjects in trials with no suicidality events.

<sup>c</sup> For Dersimonian/Laird, individual trial log odds ratios and their SEs were determined using Mantel-Haenszel with '0.5' correction.

**Table 17. Suicidality Rates from Pregabalin Trials (Event Categories 1, 2, 3, and 5) - Stratification by Trial, Placebo Controlled Trials Meeting FDA Criteria (Excludes Studies in Table 3 and Table 4<sup>a</sup>)**

Method	Odds Ratio	95% CI on Odds Ratio	Event Counts	
			Pregabalin N=7201	Placebo N=3125
Mantel-Haenszel with '0.5' correction	0.860	0.281, 2.631	7/1370 <sup>b</sup>	2/663
Mantel-Haenszel	1.781	0.389, 8.157	7/1370 <sup>b</sup>	2/663
Logistic regression	1.891	0.381, 9.381	7/1370 <sup>b</sup>	2/663
Dersimonian-Laird random effects model <sup>c</sup>	0.850	0.258, 2.796	7/1370 <sup>b</sup>	2/663

Events included are completed suicide (1); suicide attempt (2); preparatory acts towards imminent suicidal behavior (3); suicidal ideation (5)

<sup>a</sup> See list of excluded trials in Table 3 and Table 4

<sup>b</sup> These methods exclude subjects in trials with no suicidality events.

<sup>c</sup> For Dersimonian/Laird, individual trial log odds ratios and their SEs were determined using Mantel-Haenszel with '0.5' correction.

These techniques are similar to those used in previous FDA reviews of suicidality. Importantly, it should be noted that they exclude much of the data (trials with no events in either treatment group) and this is reflected in the much smaller denominators, compared to the total sample size, of the four different approaches used here. The Mantel-Haenszel (with '0.5' correction) and Dersimonian-Laird methods in which an arbitrary event count (e.g., addition of 0.5 event) is inserted into the numerator lead to a different interpretation as the odds ratios have point estimates below 1 while the other two methods provide point estimates of approximately 1.8. Thus, the methods used to generate odds ratios in which the event count is very low suffer from both variability of the point estimate as well as widely different

confidence intervals. This renders the validity of that point estimate questionable at best and potentially misleading in other circumstances.

Table 18 presents the point estimates and confidence intervals for the combined gabapentin and pregabalin data, using the same methods as described above. Not surprisingly, the point estimates show the same methods-dependent variability, while the increase in denominators leads to better, albeit slight, precision. Again, none of the calculated confidence intervals exclude 1, demonstrating a lack of statistical difference between treatment groups.

**Table 18. Suicidality Rates from  $\alpha 2\delta$  Trials (Events 1, 2, 3, and 5) - Stratification by Trial All Placebo Controlled Trials Included <sup>a</sup>**

Method	Odds Ratio	95% CI on Odds Ratio	Event Counts	
			$\alpha 2\delta$ N=9899	Placebo N=4974
Mantel-Haenszel with '0.5' correction	0.891	0.343, 2.313	9/1771 <sup>b</sup>	3/946
Mantel-Haenszel	1.681	0.479, 5.902	9/1771 <sup>b</sup>	3/946
Logistic regression	1.792	0.473, 6.798	9/1771 <sup>b</sup>	3/946
Dersimonian-Laird random effects model <sup>c</sup>	0.882	0.319, 2.444	9/1771 <sup>b</sup>	3/946

Events included are completed suicide (1); suicide attempt (2); preparatory acts towards imminent suicidal behavior (3); suicidal ideation (5)

<sup>a</sup> See list of excluded trials in [Table 4](#) and list of trials with single dose/single day of treatment in [Table 3](#).

<sup>b</sup> These methods exclude subjects in trials with no suicidality events.

<sup>c</sup> For Dersimonian/Laird, individual trial log odds ratios and their SEs were determined using Mantel-Haenszel with '0.5' correction.

The combined results are numerically similar to those for the individual compounds. Gabapentin results are not analyzed separately because so few events occur in the gabapentin studies that the point estimates become essentially meaningless with these methods.

### 5.3. Calculations of Risk in Rare Events by Bayesian Meta-Analytic Methods and by Consideration of the Risk Difference Using Mantel-Haenszel Techniques

The results for risk difference and relative risks in the [Table 9](#), [Table 12](#), and [Table 15](#) as well as the preceding odds ratio estimate illustrate the low accuracy and precision for the given datasets. When applied to ratio-based risk measures methods such as Mantel-Haenszel or exact procedures do not utilize information from studies in which no events occur. This is because such studies provide no information about the relative risk rates for active treatment and placebo. Nevertheless, studies with no events do provide information about the overall event rates for active and placebo – namely that their rates are likely quite low. Furthermore, in cases of very rare events the stability of ratio-based comparative risk measures may come into question because of the non-negligible probability that no events occur for only one treatment (even under the assumption of equal rates). This can lead to an odds ratio estimate of zero or infinity. One such example is for tiagabine which has an estimated odds ratio of infinity according to data in the FDA Statistical Review and Evaluation of Anti-Epileptic Drugs and Suicidality dated 23 May 2008 (Figure 2, page 24). For these reasons methods which include data from studies with no events warrant investigation especially if the bulk of the studies have no events as is the case for both pregabalin and gabapentin. One such family

of methods comes from Bayesian statistics. These methods can suffer the same limitations regarding instability of ratio-based “point” estimates but they can shed light on the degree of instability because they estimate a distribution for the ratio-based parameter rather than just a point estimate.

Based on discussions with external statistical experts (David Madigan, PhD, Professor of Statistics, Columbia University; Javier Cabrera, PhD, Professor of Statistics, Rutgers University; and Sharon-Lise T. Normand, PhD, Professor of Biostatistics, Harvard School of Public Health), there was a consensus that, in order to minimize meta-analytic bias, as much data should be utilized as possible. Therefore, Bayesian methods were used to help clarify the extent of the uncertainties as well as to illustrate the effect of removing studies with zero events. Two approaches were taken, one that uses patient exposure (in patient days) and looks at ratios of Poisson rates, and one which looks at odds ratios. Both approaches use a Bayesian framework.

In the first set of Bayesian analyses, with patient-days as a measure of risk exposure the events were assumed to follow a Poisson distribution with a different parameter value for each study and treatment. The specifics of the model are as follows for a given treatment in study  $i$ :

$$\begin{aligned} event &\sim \text{Poisson}(\lambda_i) \\ \lambda_i &= E_i \times \exp(\theta_i) \\ \theta_i &\sim N(\mu, \tau) \end{aligned}$$

where  $event$  is the number of events for a given treatment (active or placebo) in study  $i$ ,  $\lambda_i$  is the event rate for the treatment in study  $i$ ,  $E_i$  is the total exposure (in days) for the treatment in study  $i$ . The  $\theta_i$  was assumed to come from a normal distribution with mean  $\mu$  and precision  $\tau$ . The means  $\mu$  (one for each treatment) were assumed to follow a normal distribution with mean=-10 and precision=0.1 based on the low number of events available to model, and the precisions  $\tau$  (one for each treatment) were assumed follow a gamma (0.001,0.001) distribution.

The ratio  $\exp(\mu_{active}) / \exp(\mu_{placebo})$  was used as a measure of overall treatment effect because of the low number of events.

The second set of Bayesian analyses looked at odds ratios in a model that assumes events follow a binomial distribution with a different parameter value for each study and treatment. The specifics of the model are as follows for a given treatment in study  $i$ :

$$\begin{aligned} event &\sim \text{Binomial}(n_i, \pi_i) \\ \pi_i &= \exp(\theta_i) / (1 + \exp(\theta_i)) \\ \theta_i &\sim N(\mu, \tau) \end{aligned}$$

where  $event$  is the number of events for a given treatment (active or placebo) in study  $i$ ,  $\pi_i$  is the event probability for the treatment in study  $i$ ,  $n_i$  is the number of patients for the treatment in study  $i$ . The  $\theta_i$  was assumed to come from a normal distribution with mean  $\mu$  and precision

$\tau$ . The means  $\mu$  (one for each treatment) were assumed to follow a normal distribution with mean=-7 and precision=0.1 based on the low number of events available to model. The precisions  $\tau$  (one for each treatment) were assumed follow a gamma (1,1) distribution. The odds ratio is then  $\exp(\mu_{active}) / \exp(\mu_{placebo})$ .

### 5.3.1.1. Bayesian Model Results

The results in Table 19 show estimates when data from all trials are utilized.

**Table 19. Event Rates for Event in Any of Category 1, 2, 3, or 5 from  $\alpha 2\delta$  Trials - Stratification by Trial, All Placebo Controlled Trials Included, Analyzed Using Bayesian Methods**

Data from 2006 Submission and Studies Completed Prior to January 1, 2008	Median Ratio of Event Rates	95% Credible Interval on Ratio	Event Counts	
			Treatment n/Exposure	Placebo n/Exposure
Pregabalin Studies	0.95	0.07, 7.56	7/511148	3/237122
Pregabalin and Gabapentin Studies	1.14	0.14, 9.99	9/681148	4/365933

Table 20 shows the same analyses but using only data from the studies which had an event.

**Table 20. Event (1,2,3,5) Rates from  $\alpha 2\delta$  Trials - Stratification by Trial Using Placebo Controlled Trials With One or More Event, Analyzed Using Bayesian Methods**

Data from 2006 Submission and Studies Completed Prior to January 1, 2008	Median Ratio of Event Rates	95% Credible Interval on Ratio	Event Counts	
			Treatment n/Exposure (days)	Placebo n/Exposure (days)
Pregabalin Studies	1.37	0.28, 12.8	7/103197	3/52267
Pregabalin and Gabapentin Studies	1.45	0.41, 8.11	9/136682	4/78063

The results in Table 19 and Table 20 illustrate the limited amount of precision in this case with very low event rates as seen with the wide credible intervals from the posterior distribution. Exclusion of studies with no events leads to substantial increase in the length of the credible interval the pregabalin studies but decreases somewhat for the combined pregabalin and gabapentin studies.

The medians of the event rates ratio also suggest a potential bias in a skew to the right for the posterior distribution when excluding studies with no events. The Bayesian analyses provide a semi-quantitative way of assessing the bias introduced by excluding data from the meta-analysis, the degree of imprecision, and, more importantly, highlight the lack of risk of suicide or related behaviors with  $\alpha 2\delta$  ligands compared with placebo.

Because Bayesian methods depend to varying degrees on the prior distributions sensitivity checks were made for the combined pregabalin and gabapentin data using precisions of gamma (0.01,0.01) and gamma (0.0001,0.0001) For the means sensitivity analyses were done with means of -9 and -12. The choice of a mean of -10 was based on it providing rates of similar magnitude to the overall rate in the data. The choices of -9 and -12 represent rates of an order of magnitude higher and lower than that seen in the data. In general the results showed the same lack of precision, though they remain informative and demonstrate a shift to the right in the posterior distribution resulting from exclusion of studies.

In a second Bayesian modeling approach the odds ratio was used instead of the ratio of Poisson event rates. Table 21 shows these results which have similar interpretations as those in [Tables 19](#) and [20](#).

**Table 21. Odds Ratios for Event (1,2,3,5) from  $\alpha 2\delta$  Trials - Stratification by Trial Using Placebo Controlled Trials, Analyzed Using Bayesian Methods Applied to Odds Ratios in a Binomial Model**

Data from 2006 Submission and Studies Completed Prior to January 1, 2008		Median Odds Ratio	95% Credible Interval on Odds Ratio	Event Counts	
				Treatment n/N	Placebo n/N
Pregabalin Studies	All Studies	1.07	0.13 , 10.83	7/9215	3/4099
	Only Studies with Events	1.52	0.24 , 15.09	7/1643	3/761
Pregabalin and Gabapentin Studies	All Studies	1.14	0.18 , 8.42	9/11853	4/5935
	Only Studies with Events	1.57	0.34 , 10.26	9/2044	4/1044

Inclusion of the studies with no events can have a tendency to “shrink” the distribution towards the null case of no treatment difference. However the use of ratio-based measures of risk in these cases of very rare events tends to widen the posterior distribution for both the event rates and odds ratios analyses in [Tables 19](#) to [21](#).

In the next section risk differences were used in an attempt to remedy the instability of the ratios and allow comparison of estimates with and without inclusion of studies with no events using traditional statistical methods and, importantly, the *same measure of risk* (namely the risk difference).

### 5.3.1.2. Risk Differences Including and Excluding Studies with No Events

The risk differences shown in [Table 22](#) display the results of applying a Mantel-Haenszel risk difference estimator, with stratification by study, to the pregabalin 2006 data, the 2008 data and the combined  $\alpha 2\delta$  data. See Agresti and Hartzel<sup>91</sup> for details on the method.

**Table 22. Event (1,2,3,5) Risk Differences from  $\alpha 2\delta$  Trials - Stratification by Trial Using Placebo Controlled Trials**

Data from 2006 Submission and Studies Completed Prior to January 1, 2008	Estimated Risk Difference (per 1000 patients)	95% Confidence Interval on Risk Difference	Event Counts	
			Treatment n/N	Placebo n/N
Pregabalin Studies in 2006 Submission	0.52	-0.71 , 1.75	7/7201	2/3125
Pregabalin Studies with Events in 2006 Submission (excludes zero-event studies)	2.55	-3.50 , 8.60	7/1370	2/663
Pregabalin Studies in 2008 Update	0.13	-0.94 , 1.21	7/9215	3/4099
Pregabalin Studies with Events in 2008 Update (excludes zero-event studies)	0.73	-5.12 , 6.58	7/1643	3/761
Pregabalin and Gabapentin Studies	0.18	-0.73 , 1.09	9/11853	4/5935
Pregabalin and Gabapentin Studies With Events (excludes zero-event studies)	1.02	-4.12 , 6.16	9/2044	4/1044

The results show that excluding studies with no events increases the estimated risk difference while the loss in sample size increases the confidence interval lengths. Risk difference point estimates increase by a factor of 5 for each of the three sets of data when the zero-event trials are excluded. Hence, exclusion of data results both in a loss of accuracy (inflated point estimate of risk) as well as precision (broadening of confidence intervals).

#### 5.4. Statistical Conclusions

There is no basis in the available information to conclude a suicide risk exists in any statistical sense, given: 1) the very low frequency of events both in active and placebo treated groups, 2) the instability of point estimates, and 3) the lack of precision displayed for each of the methods applied here.

Point estimates derived from previously published methods demonstrate considerable instability in this case of very rare events. Additionally statistical methods which exclude studies with no events appear to exacerbate this problem as was shown in [Table 16](#), [Table 17](#), and [Table 18](#).

Based on discussions with external statistical experts, there was a consensus that, in order to minimize meta-analytic bias, as much data should be utilized as possible. Though estimates of these rare events are still relatively unstable with Bayesian methods, these techniques allow both inclusion and exclusion of studies with no events and, as such, can measure the impact of excluding studies on the overall estimate of risk.

Even if one believes that Bayesian analyses have a smoothing effect, traditional Mantel-Haenszel methods applied to the risk differences confirm the finding that considerable increases in the measured effect occur if studies with no events were excluded from analyses. Furthermore, this confirmation is based on the measured differences in risk estimates using the same methodologies (i.e., ratio-based assessments using Bayesian methods or risk differences using traditional Mantel-Haenszel approaches). This contrasts with the FDA sensitivity analysis in Section 6.3.1, in which the comparison of inclusion or exclusion of zero-event studies does not use comparable methods (risk difference for all studies vs. odds ratios for only those studies with at least one event). Nowhere does the FDA analysis utilize the same comparative measure of risk (for example, risk difference) for both all studies and only those with at least one event to assess the effect (or bias) of excluding studies with no events (the majority of studies analyzed).

This combination of results from varied methods of analyses brings into question the usefulness of ratio-based estimates in cases of very rare events and lends support to the idea that exclusion of studies with no events may introduce bias. The magnitude of that bias may be understood by comparing results with and without zero-event studies in [Table 19](#) through [22](#).

Based on discussions with external statistical experts, there was a consensus that, in order to minimize meta-analytic bias, as much data should be utilized as possible. Though risk estimates are still relatively unstable with Bayesian methods, these analyses allow inclusion of studies with no events and were conducted to assess the overall event ratio for all studies. In the current case the results support the idea that exclusion of studies with no events can introduce bias and the magnitude of that bias can be estimated by comparing event ratios between [Table 19](#) and [Table 20](#).

## 6. Discussion and Conclusions

Among drugs used to treat epilepsy, gabapentin and pregabalin share a common mechanism of action as  $\alpha 2\delta$  ligands, and represent a true pharmacological class with a broad evidence base of efficacy in multiple disease states, distinct from other medications approved for management of epilepsy.

Because of the heterogeneity of pharmacology, adverse event profiles, and utilization within the population, description of all drugs used for treatment of epilepsy as a ‘class’ is a misnomer. Risk in this mechanistically diverse group of drugs, therefore, should be assessed at the single-agent level or based on drugs with common mechanisms of action. Within a mechanistically and pharmacologically diverse group of drugs, estimates of risk will not apply uniformly and may lead to unintended, potentially harmful effects within a population that may have otherwise received treatment. The potential harm of overwarning may be most apparent where a putative risk finds support only in statistically heterogeneous data, drawn from methodologically heterogeneous trials, of a pool of pharmacologically heterogeneous compounds. Patients and prescribers may misunderstand the risks, if any, of the subject medications, and underestimate the risks of declining treatment.

The rarity of suicide-related events in gabapentin and pregabalin placebo-controlled clinical trials, combined with methods that exclude studies with no such events in both the treatment and placebo groups, lead to biases that must be considered. First, there is an overstatement of precision and, more importantly, an exaggeration of risk that is introduced by ascertainment bias. The point estimates of risk using traditional methods, however, are unstable due to the extremely low number of events and, therefore, fail to establish an increased risk.

Studies with no events, as well as the rarity of events overall is, in fact, quite informative in both a descriptive manner and statistical manner, as long as that data is included in analyses and meta-analytic techniques that include all or most of the data. Ultimately, the lack of events and the resultant uncertainty in point estimates generated using traditional methods within the  $\alpha 2\delta$  studies precludes a conclusion that a risk exists using these methodologies. However, by using Bayesian methods or traditional methods applied to risk differences one limits the bias introduced by exclusion of data and, based on these analyses, a lack of risk becomes clearer. Additionally, by using the *same measure of risk* (risk difference) to study the effects of excluding zero-event studies the level of bias from excluding them appears to increase by a factor of five.

Pfizer believes that the data do not support the conclusion that either gabapentin or pregabalin is associated with an increased risk of suicidal behavior or thinking, including completed suicide, suicide attempt, preparatory acts toward imminent suicide, and suicide ideation. While the population of patients taking medications for treatment of epilepsy is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that the analyses of clinical trial data with gabapentin and pregabalin do not support the conclusion that there is an increased risk of suicidal behavior and thinking associated with treatment with the  $\alpha 2\delta$ -ligands.

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**Appendix 1. Results of findings in response to regulatory agency requests regarding information on possibly suicide-related events in Neurontin® (Gabapentin) Clinical Trials. Pfizer Inc 24 July 2006**

**Appendix 2. Results of findings in response to regulatory agency requests regarding information on possibly suicide-related events in Lyrica® (Pregabalin) Clinical Trials. Pfizer Inc 24 July 2006**

**Appendix 3. List of Potential Suicide Related Events in Updated Data – Qualified Trials with Completed Clinical Study Reports as of January 1, 2008**



Results of Findings in Response to Regulatory Agency Requests  
Regarding Information on Possibly Suicide-Related Events in  
Neurontin<sup>®</sup> (gabapentin) Clinical Trials

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**Date of Report:** 24 July 2006

## EXECUTIVE SUMMARY

Based on requests from several Regulatory Agencies, Pfizer has conducted a review and evaluation of possible suicide-related adverse events from gabapentin placebo-controlled trials. This request originated as a general issue for all Sponsors of marketed antiepileptic drugs (AEDs) and not as an issue for any specific AED. This report is a summary of the data from 49 Phase 1-4 studies (8,829 patients) for the evaluation of “possibly suicide-related” adverse events occurring in placebo-controlled trials for Neurontin<sup>®</sup> (gabapentin).

The initial Regulatory Agency requesting review of possibly suicide-related adverse events was the Food and Drug Administration (FDA) in the United States. A number of the criteria and specifics of this review were stipulated by the FDA or were derived in correspondence with the FDA. Using prespecified search strategies, to review adverse events that occurred during the double-blind phase of treatment or within 1 day of beginning of taper, switching or stopping treatment, 336 possible cases out of 8,829 patients were identified. A complete set of narrative summaries were prepared for each identified case. The narrative summaries were all subsequently blinded with information blocked out as requested by the FDA prior to any review. Appropriately trained and qualified Pfizer psychiatrists then reviewed and classified the blinded narratives using the approach from the Columbia University Criteria for suicidality. Following the blinded review, 326 of the 336 cases were considered not to be possibly suicide-related. The remaining 10 patients are summarized in the following table:

Category, n (%)	Gabapentin	Placebo	Active Control	Low-Dose Placebo <sup>a</sup>
	(N=5194)	(N=2682)	(N=661)	(N=292)
1: Completed suicide	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
2: Suicide attempt	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
3: Preparatory acts toward imminent suicidal behavior	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
4: Self-injurious behavior, intent unknown	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
5: Suicidal ideation	2 (0.039)	1 (0.037)	0 (0.000)	0 (0.000)
6a: Not enough information: Fatal	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
6b: Not enough information: Non-Fatal	2 (0.039)	3 (0.112)	0 (0.000)	0 (0.000)
Any event (1-5)	3 (0.058)	1 (0.037)	0 (0.000)	0 (0.000)
Any event (1-6b)	6 (0.116)	4 (0.149)	0 (0.000)	0 (0.000)

AED = antiepileptic drug;

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed ‘low-dose placebo’) was used instead of placebo.

Pfizer believes that the data support the conclusion that Neurontin<sup>®</sup> neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture, and suicidal ideation. While the population of patients who use AEDs is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of gabapentin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with gabapentin.

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## Abbreviations

AED	Antiepileptic drug
FDA	Food and Drug Administration
PY	Patient-year

## 1. Introduction

Based on requests from several Regulatory Agencies, Pfizer has conducted a review and evaluation of possible suicide-related adverse events from gabapentin placebo-controlled trials. This request originated as a general issue for all Sponsors of marketed antiepileptic drugs (AEDs) and not as an issue for any specific AED. This report is a summary of the data from 49 Phase 1-4 studies (8829 patients) for the evaluation of “possibly suicide-related” adverse events occurring in placebo-controlled trials for Neurontin<sup>®</sup> (gabapentin).

## Epidemiology

Worldwide, one million people die from suicide every year.<sup>1</sup> Suicide and suicidal behaviors are more frequent in people with depression, personality disorder, alcoholism, schizophrenia, and organic mental disorders.<sup>2</sup> Mortality related to suicide is almost universally higher among men than among women, by a ratio of 3.5 to 1 according to data from 53 countries for which complete data are available, although women are more likely to attempt suicide.<sup>1</sup> The risk of suicide may also be increased in people with physical illness and disabling pain.<sup>3</sup> In people with epilepsy, suicides and suicide attempts occur 3 to 4 times more frequently than in the general population. In patients with temporal lobe epilepsy, the risk of suicide and suicide attempts has been estimated to be even higher, ranging up to 25 times that of the general population.<sup>4</sup>

### 1.1. Procedure and Methods of Pfizer Review of Possibly Suicide-related Adverse Events

The initial Regulatory Agency requesting review of possibly suicide-related adverse events was the Food and Drug Administration (FDA) in the United States. A number of the criteria and specifics of this review were stipulated by the FDA or were derived in correspondence with the FDA. The following sections summarize Pfizer’s procedure and methods for this review and evaluation.

#### 1.1.1. Data Sources: Studies Included, Search Criteria, and Identification of Potential Cases

Data sources included all gabapentin placebo-controlled, parallel group studies with at least 30 patients/subjects. This included data from patients and subjects in studies that, in addition to a placebo treatment group, may have included an active control treatment group. Also included were certain epilepsy studies where a placebo arm may not have been appropriate and where a sub-therapeutic dose of a standard AED (termed ‘low-dose placebo’) was used instead of placebo. Studies included all indications or populations studied regardless of whether the indication was approved or not: epilepsy (add-on therapy and monotherapy), pain (neuropathic pain, osteoarthritis, and post-operative pain), gastrointestinal mucosal injury,

social phobia, panic and bipolar disorders, insomnia (primary, acute, and transient) migraine and spasticity. In addition, the studies included volunteer studies. The entire list of studies included in the search is provided in [Appendix 1 Table 1](#).

### Search Terms and Case Identification Methods of Potential Cases

Potential cases of possibly suicide-related adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment were identified through the review of electronically available datasets, final study reports, and safety summaries for the studies listed in [Appendix 1](#). Programmatic searches in clinical trial databases using the following strategies:

- Search of all preferred terms, verbatim terms, and comments fields for the following text strings: “suic”, “overdos”, “accident-“, “injur”, “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-“, “self damage-“, “self harm”, “self inflict”, “self injur-“, “shoot”, “slash”, “poison”, “asphyxiation”, “suffocation”, “firearm”, “burn”, “drown”, “gun”, “immolat”, “monoxide”.
- All deaths and other serious adverse events.

#### 1.1.2. Classification

A listing of subjects with adverse events fitting the search criteria as defined above in [Section 1.1.1](#) was produced. False positives were identified as those terms that were selected because one of the text strings occurred within that term, but the term had no relevance to suicidality (eg, the text string “cut” would identify the word “acute”). The subjects with false positive adverse events were excluded. A narrative was prepared for each subject identified in the listing, and for all deaths and other serious adverse events that occurred while the subject was on treatment or within 24 hours of discontinuation of treatment. Narratives were written, reviewed, checked for accuracy by quality control processes, blinded and placed in an electronic document management system with controlled access. Blinding of subject data within the narratives was performed by a single individual and included blocking out any of the predefined information that could reveal treatment assignment including the following:

- Identifying patient information, identity of study drug, and patient’s randomized drug assignment;
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial;
- All years with the exception of years in remote history;
- Study drug start and stop dates (month, day, and year);
- All medications, both prescription and non-prescription, whether taken before, during, or after the study (non-pharmaceutical substances [eg, alcohol, tobacco] were not blocked out);
- Names of medications involved in overdoses (the number of pills consumed were not blocked out);

- Indications for medications started during or after the study;
- Indications for study drug.

Blinded narratives were randomly assigned a number from 1 to 336 (the total number of narratives), for identification and reference among the reviewers.

Classification was performed using the approach that was characterized by the Columbia University group for the exploration of the association between pediatric suicide and the use of antidepressants (<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>). Pfizer physicians (5 psychiatrists) reviewed the blinded narratives. All of the physician reviewers received training prior to the review process. Training was administered by a separate Pfizer physician (also a psychiatrist with expertise in the assessment and treatment of impulsive aggressive and suicidal patients) using materials from the presentation given by Kelly Posner, PhD at the FDA Pediatric Advisory Committee, October, 2004, as well as a review of the Regulatory Requests and a review of the assessment form to be used to rate each narrative.

Each blinded narrative was evaluated by 3 separate reviewers and classified by the following codes:

- Code 1: completed suicide,
- Code 2: suicide attempt,
- Code 3: preparatory acts toward imminent suicidal behavior,
- Code 4: self-injurious behavior, intent unknown,
- Code 5: suicidal ideation,
- Code 6a: not enough information; fatal,
- Code 6b: not enough information; non-fatal,
- Code 7: self-injurious behavior; no suicidal intent,
- Code 8: other: accident; psychiatric; medical.

A coordinator (not a reviewer/classifier) collated output from the individual blinded review. For those narratives where the 3 reviewers/classifiers did not agree on their initial rating, an adjudication meeting was held to reach a consensus. As per the methods used by Kelly Posner, the final rating was based on consensus among the 3 reviewers, not simply the majority opinion. If no consensus could be reached during this discussion, the narrative was assigned to 2 additional reviewers who had not been involved in the original classification of that specific narrative. The final classification was the code assigned by the majority of all 5 classifiers. This final consensus classification was used and entered into the database summarizing data from this overall review.

## 1.2. Data Summaries

For this report, the following data were summarized:

- Demographic and exposure information,
- Occurrence of events (number [%] of events in category codes (by category and total Codes 1-5 and total Codes 1-6b) and,
- Events in categories by exposure (by category and total Codes 1-5 and total Codes 1-6b).

## 2. Results

### 2.1. Demographics

There were a total of 8829 patients from all studies combined: 5194 gabapentin-treated patients, 2682 placebo, 661 active control and 292 low-dose placebo<sup>1</sup> patients. The demographic characteristics for all studies combined are summarized in [Table 1](#). Demographic characteristics were generally similar across all treatment groups. Most patients were white and between the ages of 25 to 64 years. The gabapentin and placebo groups included 221 and 204 patients aged 5 to 11 respectively. There was only 1 patient in this category in the low-dose placebo group and none in active control.

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<sup>1</sup> Some trials in epilepsy utilized a subtherapeutic dose of a standard antiepileptic drug as a comparator arm. These trials were included per FDA request if they met the other criteria as described in [Section 1.1.1](#) of this report); per FDA instruction, the subtherapeutic comparator arm was coded as a 'low dose-placebo'.

**Table 1. Summary of Patient Characteristics**

	<b>Gabapentin</b>	<b>Placebo</b>	<b>Active Control</b>	<b>Low-Dose Placebo<sup>a</sup></b>
	<b>(N=5194)</b>	<b>(N=2682)</b>	<b>(N=661)</b>	<b>(N=292)</b>
<b>Gender, n (%)</b>				
<b>N</b>	5194	2682	661	292
Male	2739 (52.73)	1371 (51.12)	352 (53.25)	148 (50.68)
Female	2455 (47.27)	1311 (48.88)	309 (46.75)	144 (49.32)
<b>Age (years)</b>				
<b>N</b>	5194	2682	661	292
Mean (SD)	40 (19.02)	40 (20.18)	33 (16.11)	36 (14.34)
Median	36	37	26	34
Min, Max	5, 90	5, 94	13, 83	11, 83
<b>Age category, n (%)</b>				
<b>N</b>	5194	2682	661	292
5-11 years	221 (4.25)	204 (7.61)	0 (0.0)	1 (0.34)
12-17 years	80 (1.54)	59 (2.20)	16 (2.42)	17 (5.82)
18-24 years	1071 (20.62)	440 (16.41)	276 (41.75)	48 (16.44)
25-64 years	3128 (60.22)	1591 (59.32)	321 (48.56)	213 (72.95)
≥ 65 years	694 (13.36)	388 (14.47)	48 (7.26)	13 (4.45)
<b>Race, n (%)</b>				
<b>N</b>	4507	2153	609	292
White Caucasian	3387 (75.15)	1651 (76.68)	450 (73.89)	242 (82.88)
African-American	564 (12.51)	239 (11.10)	56 (9.20)	32 (10.96)
Hispanic	376 (8.34)	147 (6.83)	78 (12.81)	12 (4.11)
Asian	123 (2.73)	73 (3.39)	15 (2.46)	2 (0.68)
Other	57 (1.26)	43 (2.00)	10 (1.64)	4 (1.37)

AED = antiepileptic drug; SD = standard deviation

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

Source; [Appendix 1, Table 2](#)

As shown in [Table 2](#), the most common background indications in the gabapentin-treated group were transient insomnia (24% of all patients), followed by neuropathic pain (21%), and add on epilepsy (13.5%). Almost all gabapentin patients were outpatients (>97%) and three quarters were treated in North America (75%).

**Table 2. Summary of Trial Characteristics**

	<b>Gabapentin (N=5194)</b>	<b>Placebo (N=2682)</b>	<b>Active Control (N=661)</b>	<b>Low-Dose Placebo<sup>a</sup> (N=292)</b>
<b>Indication, n (%)</b>				
Add-on Epilepsy	704 (13.55)	493 (18.38)	52 (7.87)	0 (0.00)
Monotherapy Epilepsy	609 (11.73)	125 (4.66)	94 (14.22)	292 (100.00)
Neuropathic Pain	1081 (20.81)	785 (29.27)	0 (0.00)	0 (0.00)
Osteoarthritis	157 (3.02)	53 (1.98)	52 (7.87)	0 (0.00)
Post-Operative Pain	586 (11.28)	172 (6.41)	351 (53.10)	0 (0.00)
Gastrointestinal Mucosal Injury	82 (1.58)	42 (1.57)	82 (12.41)	0 (0.00)
Social Phobia	34 (0.65)	35 (1.30)	0 (0.00)	0 (0.00)
Panic Disorder	52 (1.00)	51 (1.90)	0 (0.00)	0 (0.00)
Bipolar Disorder	58 (1.12)	59 (2.20)	0 (0.00)	0 (0.00)
Primary Insomnia	129 (2.48)	21 (0.78)	0 (0.00)	0 (0.00)
Acute Insomnia	191 (3.68)	50 (1.86)	0 (0.00)	0 (0.00)
Transient Insomnia	1243 (23.93)	623 (23.23)	0 (0.00)	0 (0.00)
Migraine	238 (4.58)	143 (5.33)	0 (0.00)	0 (0.00)
Spasticity	15 (0.29)	15 (0.56)	0 (0.00)	0 (0.00)
Healthy volunteers	15 (0.29)	15 (0.56)	30 (4.54)	0 (0.00)
<b>Setting, n (%)</b>				
Inpatient	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Outpatient	5083 (97.86)	2577 (96.09)	661 (100.00)	292 (100.00)
Both (inpatient & outpatient)	111 (2.14)	105 (3.91)	0 (0.00)	0 (0.00)
<b>Location, n (%)</b>				
North America	3918 (75.43)	1912 (71.29)	609 (92.13)	292 (100.00)
Non-North America	1276 (24.57)	770 (28.71)	52 (7.86)	0 (0.00)

AED = antiepileptic drug;

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

Source; [Appendix 1, Table 3](#)

## 2.2. Exposure

The average exposure was similar between gabapentin-treated (42.7 days) and placebo-treated (48.3 days) patients and slightly less in the active control group (28.5 days). The low-dose placebo group had a longer average exposure of 80.7 days. Total exposure and average exposure are shown in Table 3.

**Table 3. Summary of Exposure to Study Medication**

	<b>Gabapentin (N=5194)</b>	<b>Placebo (N=2682)</b>	<b>Active Control (N=661)</b>	<b>Low-Dose Placebo (N=292)<sup>a</sup></b>
<b>Total Exposure</b>				
Patient-Days	221889	129669	18898	23574
Patient-Years	607.5	355.01	51.74	64.54
<b>Average Exposure (days)<sup>b</sup></b>				
	42.72	48.35	28.59	80.73

AED = antiepileptic drug;

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

<sup>b</sup> Average exposure is total exposure in patient-days divided by number of patients per treatment group.

Source; [Appendix 1, Table 4](#)

### 2.3. Events

A total of 336 narratives were written. Following blinded review, 326 of them were considered not to be possibly suicide-related (Code 7 or 8). The incidence of events for the remaining 10 patients by treatment group and category (1-6b) are shown in [Table 4](#). Among the 8,829 patients, there were few events of any category (1-6b) in the gabapentin and placebo groups and none in the active control and low-dose placebo groups. The incidence of ‘any event’ in Categories 1-5 was similar in the gabapentin (0.058%; 0.005 per patient-year [PY] or 5 per 1000 PY) and placebo (0.037%; 0.003 per PY or 3 per 1000 PY) groups.

The incidence of ‘any event’ in Categories 1-6b was similar in the gabapentin (0.116%) and placebo (0.149%) groups. There were no completed suicides, suicide attempts, or preparatory acts towards imminent suicidal behavior, in the gabapentin and placebo groups. One gabapentin patient was categorized with self-injurious behavior, intent unknown (0.019%; 2 per 1000 PY); no placebo patients were in this category. The incidence of suicidal ideation was similar in the gabapentin (0.039%; 3 per 1000 PY) and placebo (0.037%; 3 per 1000 PY) groups.

**Table 4. Summary of Events by Category and Treatment Group**

Category	Gabapentin N=5194; PY=607.5			Placebo N=2682; PY=355.01			Active Control N=661; PY=51.74			Low-Dose Placebo <sup>a</sup> N=292; PY=64.54		
	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY
1: Completed suicide	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000
2: Suicide attempt	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000
3: Preparatory acts toward imminent suicidal behavior	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000
4. Self-injurious behavior, intent unknown	1	0.019	0.002	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000
5. Suicidal ideation	2	0.039	0.003	1	0.037	0.003	0	0.000	0.000	0	0.000	0.000
6a: Not enough information; fatal	1	0.019	0.002	0	0.000	0.000	0	0.000	0.000	0	0.000	0.000
6b: Not enough information; nonfatal	2	0.039	0.003	3	0.112	0.008	0	0.000	0.000	0	0.000	0.000
Any Event (1-5)	3	0.058	0.005	1	0.037	0.003	0	0.000	0.000	0	0.000	0.000
Any Event (1-6b)	6	0.116	0.010	4	0.149	0.011	0	0.000	0.000	0	0.000	0.000

AED = antiepileptic drug; PY=patient-years

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

<sup>b</sup> n/Nx100

Source; [Appendix 1, Table 5](#) and [6](#)

### 3. Conclusions

Pfizer believes that the data support the conclusion that Neurontin<sup>®</sup> neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicidal gesture, and suicidal ideation. While the population of patients who use AEDs is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of gabapentin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with gabapentin.

#### 4. References

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- <sup>1</sup> World Health Organization: The World Health Report 2001. Mental Health: New Understanding, New Hope  
[<http://www.who.int/whr/2001/en/>]
- <sup>2</sup> World Health Organization: Mental and Behavioural Disorders, Department of Mental Health, Geneva, 2000 [WHO/MNH/MBD/00.4].
- <sup>3</sup> World Health Organization: press release, September, 10, 2004:  
<http://www.who.int/mediacentre/news/releases/2004/pr61/en/print.html>
- <sup>4</sup> Barraclough BM. The suicide rate of epilepsy. *Acta Psychiatr Scand.* 1987;76:339-345.

## APPENDIX 1

Table 1. List of Studies Included in Neurontin® (gabapentin) Suicidality Response

Table 2. Summary of Patient Characteristics

Table 3. Summary of Trial Characteristics

Table 4. Summary of Exposure to Study Medication

Table 5. Summary of Number and Percent of Events by Category

Table 6. Summary of Events per Total Patient-Years

**Table 1. List of Studies Included in Neurontin® (gabapentin) Suicidality Response**  
(Page 1 of 2)

Indication	Study	Duration of Double-Blind	Number of Patients Randomized
<b>Add-On Epilepsy in Adults</b>	877-210G	14 weeks	129
	877-210P	14 weeks	127
	945-005	12 weeks	306
	945-006	12 weeks	272
	945-009/10	12 weeks	87
	945-8J <sup>a</sup>	12 weeks	209
	945-448-001	24 weeks	102
<b>Monotherapy Epilepsy in Adults</b>	945-077/177 <sup>b</sup>	24 weeks	375
	945-082 <sup>b</sup>	26 weeks	275
	945-088 <sup>b</sup>	8 days	82
	945-213 <sup>b</sup>	4 months	146
<b>Add-On Epilepsy in Pediatrics Patients</b>	945-086/186	12 weeks	247
<b>Monotherapy Epilepsy in Pediatric Patients</b>	945-19/20	2 weeks	33
	945-094	36 weeks	226
<b>Neuropathic Pain</b>	A9451008	15 weeks	389
	945-210	8 weeks	165
	945-224	7 weeks	325
	945-400-211	8 weeks	229
	945-420-276	10 days	120
	945-430-295	7 weeks	334
	945-430-306	8 weeks	307
	945-448-271	5 weeks	120
	945-468-429	8 weeks	132

- a. Study 945-8J was a 12-week double-blind placebo controlled study conducted in Japan. Although the study report was translated into English, the database is in Japanese and is not conducive to English text string searches. A manual search was performed on the translated adverse event summary table and listing table from the study report
- b. Low-dose placebo studies

**Table 1. List of Studies Included in Neurontin® (gabapentin) Suicidality Response  
(Page 2 of 2)**

<b>Indication</b>	<b>Study</b>	<b>Duration of Double-Blind</b>	<b>Number of Patients Randomized</b>
<b>Osteoarthritis</b>	1032-002	4 weeks	262
<b>Post-Operative Pain</b>	1032-001	Single dose	483
	1035-001	Single dose	325
	1035-001 Addendum B	Single dose	101
	1035-002	Single dose	200
<b>Gastrointestinal Mucosal Injury</b>	1032-004	1 week	206
<b>Social Phobia</b>	945-203	14 weeks	69
<b>Panic Disorder</b>	945-204	9 weeks	103
<b>Bipolar Disorder</b>	945-209	10 weeks	117
	945-421-291	1 year	42
<b>Primary Insomnia</b>	934-325	14 days	150
<b>Acute Insomnia</b>	934-324	Single dose	154
	934-335	Single dose	90
<b>Transient Insomnia</b>	A9451139	Single dose	309
	A9451140	Single dose	777
	A9451141	Single dose	773
<b>Migraine</b>	879-200	12 weeks	87
	945-217	16 weeks	150
	945-400-220	16 weeks	143
	945-475-283	21 weeks	133
<b>Spasticity</b>	945-421-222	3 months	30
<b>Study in Healthy Subjects</b>	945-439 - This study was included in Table per FDA letter of 11 July 2005.	5 days	60

Table 2

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## GABAPENTIN Placebo-Controlled Trials

Studies: 877-210P, 877-210G, 879-200, 934-324, 934-325, 934-335, 945-005, 006, 009, 010, 019, 020, 077, 082, 086, 088, 094, 177, 186, 203, 204, 209, 210, 211, 213, 217, 220, 222, 224, 295, 306, 439, 1032-001, 1032-002, 1032-004, 1035-001, 1035-001B, 1035-002, A9451008, A9451139, A9451140, A9451141, 945-448-271, 945-448-001, 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

## Summary of Patient Characteristics

	Gabapentin N=5194	Placebo N=2682	Active Control N=661	Low-Dose Placebo N=292
Gender, n(%)				
N	5194	2682	661	292
Female	2739 (52.73)	1371 (51.12)	352 (53.25)	148 (50.68)
Male	2455 (47.27)	1311 (48.88)	309 (46.75)	144 (49.32)
Age(years)				
N	5194	2682	661	292
Mean (SD)	40 (19.02)	40 (20.18)	33 (16.11)	36 (14.34)
Median	36	37	26	34
Min, Max	5,90	5,94	13,83	11,83
Age Category, n(%)				
N	5194	2682	661	292
5-11 years	221 (4.25)	204 (7.61)	0 (0.00)	1 (0.34)
12-17 years	80 (1.54)	59 (2.20)	16 (2.42)	17 (5.82)
18-24 years	1071 (20.62)	440 (16.41)	276 (41.75)	48 (16.44)
25-64 years	3128 (60.22)	1591 (59.32)	321 (48.56)	213 (72.95)
>= 65 years	694 (13.36)	388 (14.47)	48 (7.26)	13 (4.45)
Race, n(%)				
N	4507	2153	609	292
White Caucasian	3387 (75.15)	1651 (76.68)	450 (73.89)	242 (82.88)
African-American	564 (12.51)	239 (11.10)	56 (9.20)	32 (10.96)
Hispanic	376 (8.34)	147 (6.83)	78 (12.81)	12 (4.11)
Asian	123 (2.73)	73 (3.39)	15 (2.46)	2 (0.68)
Other	57 (1.26)	43 (2.00)	10 (1.64)	4 (1.37)

Non-electronically available studies are: 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

N for race may be smaller due to some studies either not collecting race or having race not available

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 07JUN2006 Date of Table Generation: 13JUN2006 (12:21)

Table 3

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## GABAPENTIN Placebo-Controlled Trials

Studies: 877-210P, 877-210G, 879-200, 934-324, 934-325, 934-335, 945-005, 006, 009, 010, 019, 020, 077, 082, 086, 088, 094,177, 186, 203, 204, 209, 210, 211, 213, 217, 220, 222, 224, 295, 306, 439, 1032-001, 1032-002, 1032-004, 1035-001, 1035-001B, 1035-002, A9451008, A9451139, A9451140, A9451141, 945-448-271, 945-448-001, 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

## Summary of Trial Characteristics

	Gabapentin N=5194		Placebo N=2682		Active Control N=661		Low-Dose Placebo N=292	
Indication, n(%)								
Bipolar Disorder	58	(1.12)	59	(2.20)	0	(0.00)	0	(0.00)
EPILEPSY - Adjunctive	704	(13.55)	493	(18.38)	52	(7.87)	0	(0.00)
EPILEPSY - Monotherapy	609	(11.73)	125	(4.66)	94	(14.22)	292	(100.00)
Gastrointestinal Mucosal Injury	82	(1.58)	42	(1.57)	82	(12.41)	0	(0.00)
Osteoarthritis	157	(3.02)	53	(1.98)	52	(7.87)	0	(0.00)
Insomnia Acute	191	(3.68)	50	(1.86)	0	(0.00)	0	(0.00)
Post-Operative Pain	586	(11.28)	172	(6.41)	351	(53.10)	0	(0.00)
Insomnia Primary	129	(2.48)	21	(0.78)	0	(0.00)	0	(0.00)
Study in Healthy Subjects	15	(0.29)	15	(0.56)	30	(4.54)	0	(0.00)
InsomniaTransient	1243	(23.93)	623	(23.23)	0	(0.00)	0	(0.00)
Migraine	238	(4.58)	143	(5.33)	0	(0.00)	0	(0.00)
Neuropathic Pain	1081	(20.81)	785	(29.27)	0	(0.00)	0	(0.00)
Panic Disorder	52	(1.00)	51	(1.90)	0	(0.00)	0	(0.00)
Social Phobia	34	(0.65)	35	(1.30)	0	(0.00)	0	(0.00)
Spasticity	15	(0.29)	15	(0.56)	0	(0.00)	0	(0.00)
Setting, n(%)								
Inpatient	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Outpatient	5083	(97.86)	2577	(96.09)	661	(100.00)	292	(100.00)
Both(Inpatient & Outpatient)	111	(2.14)	105	(3.91)	0	(0.00)	0	(0.00)
Location, n(%)								
North America	3918	(75.43)	1912	(71.29)	609	(92.13)	292	(100.00)
Non-North America	1276	(24.57)	770	(28.71)	52	(7.87)	0	(0.00)

Non-electronically available studies are: 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

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Table 4

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## GABAPENTIN Placebo-Controlled Trials

Studies: 877-210P, 877-210G, 879-200, 934-324, 934-325, 934-335, 945-005, 006, 009, 010, 019, 020, 077, 082, 086, 088, 094, 177, 186, 203, 204, 209, 210, 211, 213, 217, 220, 222, 224, 295, 306, 439, 1032-001, 1032-002, 1032-004, 1035-001, 1035-001B, 1035-002, A9451008, A9451139, A9451140, A9451141, 945-448-271, 945-448-001, 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

## Summary of Exposure to Study Medication

	Gabapentin (N=5194)	Placebo (N=2682)	Active Control (N=661)	Low-Dose Placebo (N=292)
Total Exposure				
Patient-Days	221889	129669	18898	23574
Patient-Years	607.5	355.01	51.74	64.54
Average Exposure (days)	42.72	48.35	28.59	80.73

Total exposure in patient-days is the sum of EVENTDAY per treatment group.

Total exposure in patient-years is total exposure in patient-days divided by 365.25.

Average exposure is total exposure in patient-days divided by number of patients per treatment group.

Non-electronically available studies are: 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

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Table 5

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## GABAPENTIN Placebo-Controlled Trials

Studies: 877-210P, 877-210G, 879-200, 934-324, 934-325, 934-335, 945-005, 006, 009, 010, 019, 020, 077, 082, 086, 088, 094, 177, 186, 203, 204, 209, 210, 211, 213, 217, 220, 222, 224, 295, 306, 439, 1032-001, 1032-002, 1032-004, 1035-001, 1035-001B, 1035-002, A9451008, A9451139, A9451140, A9451141, 945-448-271, 945-448-001, 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

## Summary of Number and Percent of Events by Category

Category,n(%)	Gabapentin (N=5194)	Placebo (N=2682)	Active Control (N=661)	Low-Dose Placebo (N=292)
1: Completed suicide	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
2: Suicide attempt	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
3: Preparatory acts toward imminent suicidal behavior	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
4: Self-injurious behavior, intent unknown	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
5: Suicidal ideation	2 (0.039)	1 (0.037)	0 (0.000)	0 (0.000)
6: Not enough information	3 (0.058)	3 (0.112)	0 (0.000)	0 (0.000)
6a: Fatal	1 (0.019)	0 (0.000)	0 (0.000)	0 (0.000)
6b: Non-fatal	2 (0.039)	3 (0.112)	0 (0.000)	0 (0.000)
Any event (1-5)	3 (0.058)	1 (0.037)	0 (0.000)	0 (0.000)
Any event (1-6b)	6 (0.116)	4 (0.149)	0 (0.000)	0 (0.000)

Non-electronically available studies are: 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

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Table 6

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## GABAPENTIN Placebo-Controlled Trials

Studies: 877-210P, 877-210G, 879-200, 934-324, 934-325, 934-335, 945-005, 006, 009, 010, 019, 020, 077, 082, 086, 088, 094, 177, 186, 203, 204, 209, 210, 211, 213, 217, 220, 222, 224, 295, 306, 439, 1032-001, 1032-002, 1032-004, 1035-001, 1035-001B, 1035-002, A9451008, A9451139, A9451140, A9451141, 945-448-271, 945-448-001, 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283

## Summary of Events per Total Patient- Years

	Gabapentin (N=5194)	Placebo (N=2682)	Active Control (N=661)	Low-Dose Placebo (N=292)
Total number of patient-years	607.5	355.01	51.74	64.54
Category, n, n/patient-years				
1: Completed suicide	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
2: Suicide attempt	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
3: Preparatory acts toward imminent suicidal behavior	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
4: Self-injurious behavior, intent unknown	1 (0.002)	0 (0.000)	0 (0.000)	0 (0.000)
5: Suicidal ideation	2 (0.003)	1 (0.003)	0 (0.000)	0 (0.000)
6: Not enough information	3 (0.005)	3 (0.008)	0 (0.000)	0 (0.000)
6a: Fatal	1 (0.002)	0 (0.000)	0 (0.000)	0 (0.000)
6b: Non-fatal	2 (0.003)	3 (0.008)	0 (0.000)	0 (0.000)
Any event (1-5)	3 (0.005)	1 (0.003)	0 (0.000)	0 (0.000)
Any event (1-6b)	6 (0.010)	4 (0.011)	0 (0.000)	0 (0.000)

Non-electronically available studies are: 945-08J, 945-420-276, 945-468-429, 945-421-291 and 945-475-283  
 PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 07JUN2006 Date of Table Generation: 23JUN2006 (08:21)



Results of Findings in Response to Regulatory Agency Requests  
Regarding Information on Possibly Suicide-Related Events in Lyrica®  
(Pregabalin) Clinical Trials

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**Date of Report:** 24 July 2006

## EXECUTIVE SUMMARY

Based on requests from several Regulatory Agencies, Pfizer has conducted a review and evaluation of possible suicide-related adverse events from pregabalin placebo-controlled trials. This request originated as a general issue for all Sponsors of marketed antiepileptic drugs (AEDs) and not as an issue for any specific AED. This report is a summary of the data from 44 Phase 1-3 studies (11,946 patients) for the evaluation of “possibly suicide-related” adverse events occurring in placebo-controlled trials for Lyrica. (pregabalin).

The initial Regulatory Agency requesting review of possibly suicide-related adverse events was the Food and Drug Administration (FDA) in the United States. A number of the criteria and specifics of this review were stipulated by the FDA or were derived in correspondence with the FDA. Using prespecified search strategies to review adverse events that occurred during the double-blind phase of treatment or within 1 day of beginning of taper, switching or stopping treatment, 706 possible cases out of 11,946 patients were identified. A complete set of narrative summaries were prepared for each identified case. The narrative summaries were all subsequently blinded with information blocked out as requested by the FDA prior to any review. Appropriately trained and qualified Pfizer psychiatrists then reviewed and classified the blinded narratives using the Columbia University Criteria for suicidality (<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>). Following blinded review, 675 of the 706 cases were classified as not related to suicide or possible suicide. The remaining 31 patients are summarized in the following table:

Category	Pregabalin (N = 7609) n (%)	Placebo (N = 3279) n (%)	Active Control (N = 1007) n (%)	Low-Dose Placebo <sup>a</sup> (N = 51) n (%)
Completed suicide (Code 1)	1 (0.013)	0	0	0
Suicide attempt (Code 2)	3 (0.039)	0	1 (0.099)	0
Preparatory acts towards imminent suicidal behavior (Code 3)	0	0	0	0
Self-injurious behavior, intent unknown (Code 4)	0	1 (0.030)	0	0
Suicidal ideation (Code 5)	3 (0.039)	2 (0.061)	1 (0.099)	0
Not enough information: Fatal (Code 6a)	0	0	0	0
Not enough information: Non-fatal (Code 6b)	15 (0.197)	4 (0.122)	0	0
Any Event 1-5	7 (0.092)	3 (0.091)	2 (0.199)	0
Any Event 1-6b	22 (0.289)	7 (0.213)	2 (0.199)	0

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a subtherapeutic dose of a standard AED (termed ‘low-dose placebo’) was used instead of placebo.

Pfizer believes that the data support the conclusion that Lyrica neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicide gesture, and suicidal ideation. While the population of patients who use AEDs is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of pregabalin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with pregabalin.

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## 1. Introduction

Based on requests from several Regulatory Agencies, Pfizer has conducted a review and evaluation of possible suicide-related adverse events from pregabalin placebo-controlled trials. This request originated as a general issue for all Sponsors of marketed antiepileptic drugs (AEDs) and not as an issue for any specific AED. This report is a summary of the data from 44 Phase 1-3 studies (11,946 patients) for the evaluation of “possibly suicide-related” adverse events occurring in placebo-controlled trials for Lyrica. (pregabalin).

### Epidemiology

Worldwide, 1 million people die from suicide every year. [1] Suicide and suicidal behaviors are more frequent in people with depression, personality disorder, alcoholism, schizophrenia, and organic mental disorders. [2] Mortality related to suicide is almost universally higher among men than among women, by a ratio of 3.5 to 1 according to data from 53 countries for which complete data are available, although females are more likely to attempt suicide. [1] The risk of suicide may also be increased in people with physical illness and disabling pain. [3] In people with epilepsy, suicides and suicide attempts occur 3 to 4 times more frequently than in the general population. In patients with temporal lobe epilepsy, the risk of suicide and suicide attempts has been estimated to be even higher, ranging up to 25 times that of the general population. [4]

#### 1.1. Procedure and Methods of Pfizer Review of Possibly Suicide-Related Adverse Events

The initial Regulatory Agency requesting review of possibly suicide-related adverse events was the Food and Drug Administration (FDA) in the United States. A number of the criteria and specifics of this review were stipulated by the FDA or were derived in correspondence with the FDA. The following sections summarize Pfizer’s procedure and methods for this review and evaluation.

##### 1.1.1. Data Sources: Studies Included, Search Criteria, and Identification of Potential Cases

Data sources included all pregabalin placebo-controlled, parallel-group studies with at least 30 patients/subjects. This included data from patients and subjects in studies that, in addition to a placebo treatment group, may have included an active control treatment group. Also included were certain epilepsy studies where a placebo arm may not have been appropriate and where a subtherapeutic dose of a standard AED (termed ‘low-dose placebo’) was used instead of placebo. Studies included all indications or populations studied regardless of whether the indication was approved or not: epilepsy (add-on therapy and monotherapy), pain (neuropathic pain, acute dental pain, chronic low back pain, osteoarthritis), fibromyalgia, and psychiatry (generalized anxiety disorder, social anxiety disorder, acute mania, and panic disorder). In addition, the studies included volunteer studies. The entire list of studies included in the search is provided in Appendix 1 ([Appendix 1, Table 1](#)).

**Search Terms and Case Identification Methods of Potential Cases** – Potential cases of possibly suicide-related adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment were identified through the review of electronically available datasets, final study reports, and safety summaries for the studies listed in [Appendix 1](#). Programmatic searches in clinical trial databases using the following strategies:

Search of all preferred terms, verbatim terms, and comments fields for the following text strings: “suic”, “overdos”, “accident-“, “injur”, “attempt”, “cut”, “gas”, “hang”, “hung”, “jump”, “mutilat-“, “self damage-“, “self harm”, “self inflict”, “self injur-“, “shoot”, “slash”, “poison”, “asphyxiation”, “suffocation”, “firearm”, “burn”, “drown”, “gun”, “immolat”, “monoxide”.

All deaths and other serious adverse events.

### 1.1.2. Classification

A listing of subjects with adverse events fitting the search criteria as defined above in Section 1.1.1. was produced. False positives were identified as those terms that were selected because one of the text strings occurred within that term, but the term had no relevance to suicidality (eg, the text string “cut” would identify the word “acute”). The subjects with false positive adverse events were excluded. A narrative was prepared for each subject identified in the listing, and for all deaths and other serious adverse events that occurred while the subject was on double-blind treatment or within 1 day of beginning of taper, switching or stopping treatment. Narratives were written, reviewed, checked for accuracy by quality control processes, blinded and placed in an electronic document management system with controlled access. Blinding of subject data within the narratives was performed by a single individual and included blocking out any of the predefined information that could reveal treatment assignment including the following:

Identifying patient information, identity of study drug, and patient’s randomized drug assignment

All identifying information regarding the sponsor, the clinical trial number, and the location of the trial

All years with the exception of years in remote history

Study drug start and stop dates (month, day, and year)

All medications, both prescription and nonprescription, whether taken before, during, or after the study (nonpharmaceutical substances [eg, alcohol, tobacco] were not blocked out)

Names of medications involved in overdoses (the number of pills consumed were not blocked out)

Indications for medications started during or after the study

Indications for study drug

Blinded narratives were randomly assigned a number from 1 to 706 (the total number of narratives) for identification and reference among the reviewers.

Classification was performed using the approach that was characterized by the Columbia University group for the exploration of the association between pediatric suicide and the use of antidepressants (<http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs>). Pfizer physicians (5 psychiatrists) reviewed the blinded narratives. All of the physician reviewers received training prior to the review process. Training was administered by a separate Pfizer physician (also a psychiatrist with expertise in the assessment and treatment of impulsive aggressive and suicidal patients) using materials from the presentation given by Kelly Posner, PhD at the FDA Pediatric Advisory Committee, October 2004, as well as a review of the Regulatory Requests and a review of the assessment form to be used to rate each narrative.

Each blinded narrative was evaluated by 3 separate reviewers and classified by the following codes:

- Code 1: completed suicide
- Code 2: suicide attempt
- Code 3: preparatory acts toward imminent suicidal behavior
- Code 4: self-injurious behavior, intent unknown
- Code 5: suicidal ideation
- Code 6a: not enough information; fatal
- Code 6b: not enough information; nonfatal
- Code 7: self-injurious behavior; no suicidal intent
- Code 8: other: accident; psychiatric; medical

A coordinator (not a reviewer/classifier) collated output from the individual blinded review. For those narratives where the 3 reviewers/classifiers did not agree on their initial rating, an adjudication meeting was held to reach a consensus. As per the methods used by Kelly Posner, the final rating was based on consensus among the 3 reviewers, not simply the majority opinion. If no consensus could be reached during this discussion, the narrative was assigned to 2 additional reviewers who had not been involved in the original classification of that specific narrative. The final classification was the code assigned by the majority of all 5 classifiers. This final consensus classification was used and entered into the database summarizing data from this overall review.

## 1.2. Data Summaries

For this report, the following data were summarized:

Demographic and exposure information,

Occurrence of events (number [%] of events in category codes (by category and total Codes 1-5 and total Codes 1-6b) and,

Events in categories by exposure (by category and total Codes 1-5 and total Codes 1-6b).

## 2. Results

### 2.1. Demographics and Background Characteristics

There were 11,946 patients in all studies combined: 7609 pregabalin-treated patients, 3279 placebo, 1007 active control, and 51 low-dose placebo [1] patients. The demographic characteristics are summarized in Table 1. Most patients were white and between the ages of 24 to 65 years. Overall there were slightly more women than men.

**Table 1. Summary of Patient Characteristics**

	Pregabalin (N = 7609)		Placebo (N = 3279)		Active Control (N = 1007)		Low-Dose Placebo <sup>a</sup> (N = 51)	
<b>Gender, n (%)</b>								
Female	4252	(55.9)	1792	(54.7)	564	(56.0)	22	(43.1)
Male	3357	(44.1)	1487	(45.4)	443	(44.0)	29	(56.9)
<b>Age (years)</b>								
Mean (SD)	49	(17.07)	49	(17.25)	39	(13.52)	36	(10.28)
Median	48		48		38		35	
Min, Max	12, 100		16, 96		18, 80		19, 56	
<b>Age Category, n(%)</b>								
5-11 years	0		0		0		0	
12-17 years	14	(0.2)	7	(0.2)	0		0	
18-24 years	644	(8.5)	278	(8.5)	155	(15.4)	9	(17.7)
25-64 years	5380	(70.7)	2246	(68.5)	808	(80.2)	49	(82.4)
≥65 years	1571	(20.7)	748	(22.8)	44	(4.4)	0	
<b>Race, n(%)</b>								
White Caucasian	6754	(88.8)	2937	(89.6)	864	(85.8)	47	(92.2)
African-American	325	(4.3)	133	(4.0)	58	(5.8)	1	(2.0)
Hispanic	349	(4.6)	123	(3.8)	56	(5.6)	2	(3.9)
Asian	116	(1.5)	47	(1.4)	10	(1.0)	1	(2.0)
Other	65	(0.9)	39	(1.2)	19	(1.9)	0	

AED = Antiepileptic drug.

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a subtherapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

Source: [Appendix 1, Table 2](#)

As shown in [Table 2](#), the most common background indication in the pregabalin-treated group was generalized anxiety disorder (17% of all patients) followed by diabetic peripheral neuropathy and epilepsy-adjunctive (16%, each), fibromyalgia (13%), and postherpetic neuralgia (12%). Almost all pregabalin patients were outpatients (99%) and approximately two-thirds were treated in North America (67%).

**Table 2. Summary of Trial Characteristics**

	Pregabalin		Placebo		Active Control		Low-Dose Placebo <sup>a</sup>	
	(N = 7609)		(N = 3279)		(N = 1007)		(N = 51)	
<b>Indication, n (%)</b>								
Generalized anxiety disorder	1326	(17.4)	580	(17.7)	412	(40.9)	0	
DPN	1180	(15.5)	507	(15.5)	87	(8.6)	0	
Epilepsy-adjunctive	1178	(15.5)	507	(15.5)	141	(14.0)	0	
Fibromyalgia	956	(12.6)	321	(9.8)	0		0	
PHN	924	(12.1)	415	(12.7)	0		0	
Social anxiety disorder	516	(6.8)	223	(6.8)	95	(9.4)	0	
Chronic low back pain	466	(6.1)	193	(5.9)	0		0	
Panic disorder	333	(4.4)	167	(5.1)	158	(15.7)	0	
Dental pain	267	(3.5)	120	(3.7)	114	(11.3)	0	
Osteoarthritis	204	(2.7)	92	(2.8)	0		0	
Healthy volunteers	119	(1.6)	56	(1.7)	0		0	
Spinal cord injury	70	(0.9)	67	(2.0)	0		0	
Epilepsy-monotherapy	42	(0.6)	0		0		51	(100)
Acute mania	28	(0.4)	31	(1.0)	0		0	
<b>Setting, n (%)</b>								
Outpatient	7539	(99.1)	3248	(99.1)	1007	(100)	0	
Inpatient	70	(0.9)	31	(1.0)	0		51	(100)
<b>Location, n (%)</b>								
North America	5092	(66.9)	2110	(64.4)	497	(49.4)	49	(96.1)
Non-North America	2517	(33.1)	1169	(35.6)	510	(50.6)	2	(3.9)

AED = Antiepileptic drug; DPN = Diabetic peripheral neuropathy; PHN = Postherpetic neuralgia.

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a subtherapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

Source: [Appendix 1, Table 3](#).

## 2.2. Exposure

The average exposure was similar between pregabalin-treated (50.6 days) and placebo (52.7 days) patients and slightly less in the active control group (41.2 days). The low-dose placebo group came from a single study and had a short average exposure of 5.3 days. Total exposure and average exposures are shown in Table 3.

**Table 3. Summary of Exposure to Study Medication**

	Pregabalin	Placebo	Active Control	Low-Dose Placebo <sup>a</sup>
	(N = 7609)	(N = 3279)	(N = 1007)	(N = 51)
<b>Total Exposure</b>				
Patient-Days	384628	172903	41503	268
Patient-Years	1053.05	473.38	113.63	0.73
<b>Average Exposure (days)<sup>b</sup></b>	50.55	52.73	41.21	5.25

AED = Antiepileptic drug.

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a subtherapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

<sup>b</sup> Average exposure is total exposure in patient-days divided by number of patients per treatment group.

Source: [Appendix 1, Table 4](#).

### 2.3. Events

A total of 706 narratives were written. Following blinded review, 675 of the 706 cases were categorized as not related to suicide or possible suicide (ie, Code 7 or 8). The incidence of events for the remaining 31 patients by treatment group and category (1-6b) are shown in [Table 4](#). Among the 11,946 patients, there were few events of any category (1-6b) in any of the treatment groups. The incidence of ‘any event’ in Categories 1-5 was similar in the pregabalin (0.092%; 0.007 per patient-year [PY] or 7 per 1000 PY) and placebo (0.091%; 6 per 1000 PY) groups, and greater in the active control group (0.199%; 18 per 1000 PY). The incidence of ‘any event’ in Categories 1-6b was highest in the pregabalin group due to 15 nonfatal events (0.197%) that did not have enough information available to be categorized by the expert classifiers; there were also 4 of these events (0.122%) in the placebo group.

There were no events among the 51 patients in the low-dose placebo group. In the other 3 treatment groups, there was 1 completed suicide among 7609 pregabalin-treated patients (0.013%; 1 event per 1000 PY) and none in the placebo or active control groups. There were 3 suicide attempts in the pregabalin group (0.039%; 3 per 1000 PY) and 1 in the active control group (0.099%; 9 per 1000 PY). One placebo patient was categorized with self-injurious behavior, intent unknown (0.03%; 2 per 1000 PY); no pregabalin-treated or active control patients were in this category. The incidence of suicidal ideation was lowest in the pregabalin group (0.039%; 3 per 1000 PY) compared with placebo (0.061%; 4 per 1000 PY) and active control (0.099%; 9 per 1000 PY).

**Table 4. Summary of Events by Category and Treatment Group**

Category	Pregabalin N = 7609; PY = 1053.05			Placebo N = 3279; PY = 473.38			Active Control N = 1007; PY = 113.63			Low-Dose Placebo <sup>a</sup> N = 51; PY = 0.73		
	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY	n	% <sup>b</sup>	n/PY
1: Completed suicide	1	0.013	0.001	0			0			0		
2: Suicide attempt	3	0.039	0.003	0			1	0.099	0.009	0		
3: Preparatory acts toward imminent suicidal behavior	0			0			0			0		
4: Self-injurious behavior, intent unknown	0			1	0.030	0.002	0			0		
5: Suicidal ideation	3	0.039	0.003	2	0.061	0.004	1	0.099	0.009	0		
6a: Not enough information; fatal	0			0			0			0		
6b: Not enough information; nonfatal	15	0.197	0.014	4	0.122	0.008	0			0		
Any Event (1-5)	7	0.092	0.007	3	0.091	0.006	2	0.199	0.018	0		
Any Event (1-6b)	22	0.289	0.021	7	0.213	0.015	2	0.199	0.018	0		

AED = Antiepileptic drug; PY = Patient-years.

<sup>a</sup> Low-dose placebo: In certain epilepsy studies where a placebo arm may not have been appropriate a sub-therapeutic dose of a standard AED (termed 'low-dose placebo') was used instead of placebo.

<sup>b</sup>  $n/N \times 100$

Source: [Appendix 1, Table 5](#) and [Table 6](#).

### 3. Conclusions

Pfizer believes that the data support the conclusion that Lyrica neither causes nor is associated with an increased risk of suicidal behavior and thinking, including completed suicide, suicide attempt, suicidal gesture, and suicide ideation. While the population of patients who use AEDs is known to have significantly higher rates of suicide relative to the general population, Pfizer believes that an analysis of pregabalin clinical trial data fully supports the conclusion that there is no increased risk of suicidal behavior and thinking as a result of treatment with pregabalin.

#### 4. References

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## APPENDIX 1

Table 1. Proposed List of Studies to be Included in Lyrica™ (Pregabalin) Suicidality

Table 2. Summary of Patient Characteristics

Table 3. Summary of Trial Characteristics

Table 4. Summary of Exposure to Study Medication

Table 5. Summary of Number and Percent of Events by Category

Table 6. Summary of Events per Total Patient-Years

**Table 1. Proposed List of Studies to be Included in Lyrica™ (Pregabalin) Suicidality Request (Page 1 of 2)**

<b>Indication</b>	<b>Study</b>	<b>Duration of Double-Blind</b>	<b>Number of Patients Randomized</b>
Epilepsy	1008-009	12 weeks	312
	1008-011	12 weeks	287
	1008-034	12 weeks	453
	1008-112	17 weeks	433
	1008-157	12 weeks	341
Neuropathic Pain	1008-014	6 weeks	246
	1008-029	5 weeks	337
	1008-030	5 weeks	255
	1008-040	9 weeks	254
	1008-045	8 weeks	238
	1008-125	12 weeks	137
	1008-127	8 weeks	173
	1008-131	8 weeks	146
	1008-132	12 weeks	216
	1008-149	12 weeks	395
	1008-155	12 weeks	338
	1008-173	12 weeks	147
	1008-196	13 weeks	368
Generalized Anxiety Disorder	1008-021	5 weeks	276
	1008-025	5 weeks	282
	1008-026	5 weeks	271
	1008-083	5 weeks	454
	1008-085	7 weeks	341
	1008-087	7 weeks	421
	1008-90/152	9 weeks	277
Fibromyalgia	1008-105	8 weeks	529
Chronic Low Back Pain	1008-032	7 weeks	253
	1008-104	8 weeks	406
Osteoarthritis	1008-031	12 weeks	296
Dental Pain	1008-013	1 day	200
	1008-016	1 day	198
	1008-027	1 day	103

**Table 1. Proposed List of Studies to be Included in Lyrica™ (Pregabalin) Suicidality Request (Page 2 of 2)**

<b>Indication</b>	<b>Study</b>	<b>Duration of Double-Blind</b>	<b>Number of Patients Randomized</b>
Social Anxiety Disorder	1008-017	11 weeks	135
	1008-080	11 weeks	328
	1008-081/153	11 weeks	371
Acute Mania	1008-022	3 weeks	59
Panic Disorder	1008-091	10 weeks	354
	1008-092/094	9.5 weeks	314

Table 2

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## PREGABALIN Placebo-Controlled Trials

Studies: 1008002, 1008007, 1008009, 1008011, 1008013, 1008014, 1008016, 1008017, 1008021, 1008022, 1008025, 1008026, 1008027, 1008029, 1008030, 1008031, 1008032, 1008034, 1008040, 1008045, 1008072, 1008080, 1008081, 1008083, 1008085, 1008087, 1008090, 1008091, 1008092, 1008094, A0081022, A0081038, 1008104, 1008105, A0081056, 1008112, 1008125, 1008127, 1008131, 1008132, 1008149, 1008155, 1008157, 1008173 and 1008196

## Summary of Patient Characteristics

	Pregabalin N=7609	Placebo N=3279	Active Control N=1007	Low-Dose Placebo N=51
Gender, n(%)				
N	7609	3279	1007	51
Female	4252 (55.88)	1792 (54.65)	564 (56.01)	22 (43.14)
Male	3357 (44.12)	1487 (45.35)	443 (43.99)	29 (56.86)
Age(years)				
N	7609	3279	1007	51
Mean (SD)	49 (17.07)	49 (17.25)	39 (13.52)	36 (10.28)
Median	48	48	38	35
Min, Max	12,100	16,96	18,80	19,56
Age Category, n(%)				
N	7609	3279	1007	51
5-11 years	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
12-17 years	14 (0.18)	7 (0.21)	0 (0.00)	0 (0.00)
18-24 years	644 (8.46)	278 (8.48)	155 (15.39)	9 (17.65)
25-64 years	5380 (70.71)	2246 (68.50)	808 (80.24)	42 (82.35)
>= 65 years	1571 (20.65)	748 (22.81)	44 (4.37)	0 (0.00)
Race, n(%)				
N	7609	3279	1007	51
White Caucasian	6754 (88.76)	2937 (89.57)	864 (85.80)	47 (92.16)
African-American	325 (4.27)	133 (4.06)	58 (5.76)	1 (1.96)
Hispanic	349 (4.59)	123 (3.75)	56 (5.56)	2 (3.92)
Asian	116 (1.52)	47 (1.43)	10 (0.99)	1 (1.96)
Other	65 (0.85)	39 (1.19)	19 (1.89)	0 (0.00)

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 09JUN2006

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Table 3

## PREGABALIN Placebo-Controlled Trials

Studies: 1008002, 1008007, 1008009, 1008011, 1008013, 1008014, 1008016, 1008017, 1008021, 1008022, 1008025, 1008026, 1008027, 1008029, 1008030, 1008031, 1008032, 1008034, 1008040, 1008045, 1008072, 1008080, 1008081, 1008083, 1008085, 1008087, 1008090, 1008091, 1008092, 1008094, A0081022, A0081038, 1008104, 1008105, A0081056, 1008112, 1008125, 1008127, 1008131, 1008132, 1008149, 1008155, 1008157, 1008173 and 1008196

## Summary of Trial Characteristics

	Pregablin N=7609		Placebo N=3279		Active Control N=1007		Low-Dose Placebo N=51	
Indication, n(%)								
Acute mania	28	(0.37)	31	(0.95)	0	(0.00)	0	(0.00)
DPN	1180	(15.51)	507	(15.46)	87	(8.64)	0	(0.00)
Epilepsy-monotherapy	42	(0.55)	0	(0.00)	0	(0.00)	51	(100.00)
Chronic low back pain	466	(6.12)	193	(5.89)	0	(0.00)	0	(0.00)
Dental pain	267	(3.51)	120	(3.66)	114	(11.32)	0	(0.00)
Epilepsy-adjunctive	1178	(15.48)	507	(15.46)	141	(14.00)	0	(0.00)
Generalized anxiety disorder	1326	(17.43)	580	(17.69)	412	(40.91)	0	(0.00)
Panic disorder	333	(4.38)	167	(5.09)	158	(15.69)	0	(0.00)
Fibromyalgia	956	(12.56)	321	(9.79)	0	(0.00)	0	(0.00)
Social anxiety disorder	516	(6.78)	223	(6.80)	95	(9.43)	0	(0.00)
Healthy volunteers	119	(1.56)	56	(1.71)	0	(0.00)	0	(0.00)
Osteoarthritis	204	(2.68)	92	(2.81)	0	(0.00)	0	(0.00)
PHN	924	(12.14)	415	(12.66)	0	(0.00)	0	(0.00)
Spinal cord injury	70	(0.92)	67	(2.04)	0	(0.00)	0	(0.00)
Setting, n(%)								
Inpatient	70	(0.92)	31	(0.95)	0	(0.00)	51	(100.00)
Outpatient	7539	(99.08)	3248	(99.05)	1007	(100.00)	0	(0.00)
Both(Inpatient & Outpatient)	0	(0.00)	0	(0.00)	0	(0.00)	0	(0.00)
Location, n(%)								
North America	5092	(66.92)	2110	(64.35)	497	(49.35)	49	(96.08)
Non-North America	2517	(33.08)	1169	(35.65)	510	(50.65)	2	(3.92)

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 09JUN2006

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Table 4

PREGABALIN Placebo-Controlled Trials

Studies: 1008002, 1008007, 1008009, 1008011, 1008013, 1008014, 1008016, 1008017, 1008021, 1008022, 1008025, 1008026, 1008027, 1008029, 1008030, 1008031, 1008032, 1008034, 1008040, 1008045, 1008072, 1008080, 1008081, 1008083, 1008085, 1008087, 1008090, 1008091, 1008092, 1008094, A0081022, A0081038, 1008104, 1008105, A0081056, 1008112, 1008125, 1008127, 1008131, 1008132, 1008149, 1008155, 1008157, 1008173 and 1008196

Summary of Exposure to Study Medication

	Pregabalin (N=7609)	Placebo (N=3279)	Active Control (N=1007)	Low-Dose Placebo (N=51)
Total Exposure				
Patient-Days	384628	172903	41503	268
Patient-Years	1053.05	473.38	113.63	0.73
Average Exposure (days)	50.55	52.73	41.21	5.25

Total exposure in patient-days is the sum of EVENTDAY per treatment group.

Total exposure in patient-years is total exposure in patient-days divided by 365.25.

Average exposure is total exposure in patient-days divided by number of patients per treatment group.

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 09JUN2006 Date of Table Generation: 13JUN2006 (09:59)

Table 5

Page 1 of 1

## PREGABALIN Placebo-Controlled Trials

Studies: 1008002, 1008007, 1008009, 1008011, 1008013, 1008014, 1008016, 1008017, 1008021, 1008022, 1008025, 1008026, 1008027, 1008029, 1008030, 1008031, 1008032, 1008034, 1008040, 1008045, 1008072, 1008080, 1008081, 1008083, 1008085, 1008087, 1008090, 1008091, 1008092, 1008094, A0081022, A0081038, 1008104, 1008105, A0081056, 1008112, 1008125, 1008127, 1008131, 1008132, 1008149, 1008155, 1008157, 1008173 and 1008196

## Summary of Number and Percent of Events by Category

Category,n(%)	Pregabalin (N=7609)	Placebo (N=3279)	Active Control (N=1007)	Low-Dose Placebo (N=51)
1: Completed suicide	1 (0.013)	0 (0.000)	0 (0.000)	0 (0.000)
2: Suicide attempt	3 (0.039)	0 (0.000)	1 (0.099)	0 (0.000)
3: Preparatory acts toward imminent suicidal behavior	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
4: Self-injurious behavior, intent unknown	0 (0.000)	1 (0.030)	0 (0.000)	0 (0.000)
5: Suicidal ideation	3 (0.039)	2 (0.061)	1 (0.099)	0 (0.000)
6: Not enough information	15 (0.197)	4 (0.122)	0 (0.000)	0 (0.000)
6a: Fatal	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
6b: Non-fatal	15 (0.197)	4 (0.122)	0 (0.000)	0 (0.000)
Any event (1-5)	7 (0.092)	3 (0.091)	2 (0.199)	0 (0.000)
Any event (1-6b)	22 (0.289)	7 (0.213)	2 (0.199)	0 (0.000)

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 09JUN2006

Date of Table Generation: 13JUN2006 (09:59)

Table 6

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## PREGABALIN Placebo-Controlled Trials

Studies: 1008002, 1008007, 1008009, 1008011, 1008013, 1008014, 1008016, 1008017, 1008021, 1008022, 1008025, 1008026, 1008027, 1008029, 1008030, 1008031, 1008032, 1008034, 1008040, 1008045, 1008072, 1008080, 1008081, 1008083, 1008085, 1008087, 1008090, 1008091, 1008092, 1008094, A0081022, A0081038, 1008104, 1008105, A0081056, 1008112, 1008125, 1008127, 1008131, 1008132, 1008149, 1008155, 1008157, 1008173 and 1008196

## Summary of Events per Total Patient-Years

	Pregabablin (N=7609)	Placebo (N=3279)	Active Control (N=1007)	Low-Dose Placebo (N=51)
Total number of patient-years	1053.05	473.38	113.63	0.73
Category, n, n/patient-years				
1: Completed suicide	1 (0.001)	0 (0.000)	0 (0.000)	0 (0.000)
2: Suicide attempt	3 (0.003)	0 (0.000)	1 (0.009)	0 (0.000)
3: Preparatory acts toward imminent suicidal behavior	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
4: Self-injurious behavior, intent unknown	0 (0.000)	1 (0.002)	0 (0.000)	0 (0.000)
5: Suicidal ideation	3 (0.003)	2 (0.004)	1 (0.009)	0 (0.000)
6: Not enough information	15 (0.014)	4 (0.008)	0 (0.000)	0 (0.000)
6a: Fatal	0 (0.000)	0 (0.000)	0 (0.000)	0 (0.000)
6b: Non-fatal	15 (0.014)	4 (0.008)	0 (0.000)	0 (0.000)
Any event (1-5)	7 (0.007)	3 (0.006)	2 (0.018)	0 (0.000)
Any event (1-6b)	22 (0.021)	7 (0.015)	2 (0.018)	0 (0.000)

PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 09JUN2006

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Assessment of Suicidality with  $\alpha_2\delta$  Drugs

Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

**Appendix 3.**

**Listing of potential suicide-related adverse events from clinical studies completed subsequent to the 2006 dataset cut-off and prior to 01 January 2008.**

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## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
1	Joint sprain	SPRAIN OF RIGHT WRIST			ACCIDENTAL
2	Myocardial infarction	MYOCARDIAL INFARCTION	Y		HYPERCHOLESTEROLEMIA.
3	Headache	HEADACHE			HEAD TRAUMA/ACCIDENT
4	Suicidal ideation	SUICIDE THOUGHTS			
5	Joint sprain	SPRAINED ANKLE			ACCIDENT
6	Joint sprain	SPRAINED ANKLE			ACCIDENT
7	Fall	FALL			ACCIDENTAL
8	Bronchitis	ACUTE BRONCHITIS	Y		BACTERIAL INFECTION
8	Asthenia	ADYNAMIA	Y		
8	Somnolence	SOMNOLENCE	Y		
8	Oedema peripheral	WORSENING EDEMA INFERIOR LIMBS	Y		ACUTE, BRONCHITIS
9	Chest pain	CHEST PAIN	Y		LONG STANDING DIABETES
10	Papillitis	PAPILLITIS	Y		CHOLELITHIASIS
11	Ligament rupture	COLLATERAL LIGAMENT RUPTURE OF LEFT KNEE	Y		TRAFFIC ACCIDENT
11	Road traffic accident	TRAFFIC ACCIDENT	Y		TRAFFIC ACCIDENT
12	Typhoid fever	TYPHOID FEVER	Y		ACUTE INFECTION OF TYPHOID
13	Hyperglycaemia	HYPERGLYCAEMIA	Y		
14	Joint injury	BLUNT TRAUMA ON LEFT SHOULDER			
14	Chest injury	BLUNT TRAUMA ON RIGHT SIDE OF THORAX			
15	Gastric haemorrhage	GASTRIC BLEEDING	Y		CHRONIC GASTRITIS (DEACTIVATION)
15	Head injury	OCCIPITAL CRANIAL TRAUMA	Y		
16	Gastroenteritis	ACUTE GASTROENTERITIS			POSSIBLE FOOD POISONING
17	Pleural effusion	LEFT PLEURAL EFFUSION	Y		PREVIOUSLY DIAGNOSED NON HODGKIN'S LYMPHOMA - LAST TREATED 2002
18	Hyperglycaemia	HYPERGLYCEMIA	Y		UNKNOWN BUT NOT RELATED TO STUDY MEDICATION
19	Cataract	WORSENING OF CATARACT	Y		UNDERLYING DISEASE ; CATARACT
20	Pneumonia	PNEUMONIA	Y		UNKNOWN, NOT RELATED TO STUDY DRUG
21	Excoriation	SKIN ABRASION			INJURY - NOT-REALTED STUDY DRUG
22	Syncope	SYNCOPE	Y		
23	Fall	ACCIDENTAL FALL			POOR LIGHTING CONDITIONS - PATIENT HAD ACCIDENTAL FALL AT NIGHT
24	Nephrolithiasis	RENAL CALCULI	Y		
25	Angina pectoris	ANGINA	Y		
26	Coronary artery disease	CORONARY ARTERY DISEASE	Y		
27	Cholelithiasis	CHOLELITHIASIS	Y		

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
28	Gangrene	GANGRENE RIGHT SMALL PHALANGE	Y		
29	Back injury	LUMBAR STRAIN			
30	Skin ulcer	LEFT FOOT/TOE ULCER	Y		
31	Chest injury	TRAUMA TO CHEST WALL			
32	Limb injury	ACCIDENTAL INJURY LEFT LEG			
32	Limb injury	TIP RIGHT FINGER INJURED			
33	Syncope	SYNCOPE	Y		
34	Major depression	MAJOR DEPRESSION	Y		
34	Post-traumatic stress disorder	RECURRING POST TRAUMATIC STRESS DISORDER	Y		
35	Atrial fibrillation	ATRIAL FIBRILATION	Y		
36	Acute coronary syndrome	ACUTE CORONARY SYNDROME	Y		
37	Plantar fasciitis	BILATERAL PLANTAR FASCIITIS			PRIOR REPATIVE INJURY
38	Abdominal pain	ABDOMINAL PAIN	Y		CHOLECYSTITIS
39	Headache	HEADACHE	Y		ATHEROSCLEROTIC DISEASE
39	Muscular weakness	LEFT ARM WEAKNESS	Y		ATHEROSCLEROTIC DISEASE
39	Muscular weakness	RIGHT HAND WEAKNESS	Y		ATHEROSCLEROTIC DISEASE
40	Wound	RIGHT FOOT PUNCTURE WOUND			ACCIDENT
40	Cellulitis	RIGHT LEG CELLULITIS	Y		RIGHT FOOT PUNCTURE WOUND
41	Musculoskeletal pain	LEFT SHOULDER PAIN			MOTOR VEHICLE ACCIDENT
41	Muscle strain	RIGHT WRIST STRAIN			MOTOR VEHICLE ACCIDENT
42	Diplopia	DOUBLEVISION			CAR ACCIDENT - TRAUMA
42	Neck pain	NECK PAIN			CAR ACCIDENT - TRAUMA
43	Joint injury	TRAUMA LEFT KNEE			PATIENT FALL
44	Mouth injury	CUT HIS LIP			
45	Hypoglycaemia	HYPOGLYCEMIC EPISODE	Y		CONCOMITANT TREATMENT WITH INSULIN
46	Splenic rupture	RUPTURED SPLEEN	Y		UNKNOWN
47	Muscle strain	LEFT - SIDED LUMBOSACRAL MUSCLE STRAIN			INJURY.
48	Fall	FALL			INJURY
48	Skin graft	HEALING SKIN GRAFT UNDER RIGHT CLAVICLE			INJURY.
48	Arthralgia	RIGHT ELBOW PAIN			INJURY.
48	Arthralgia	RIGHT HIP PAIN			INJURY.
48	Arthralgia	RIGHT KNEE PAIN			INJURY.
48	Musculoskeletal pain	RIGHT SHOULDER PAIN			INJURY.
49	Angina pectoris	WORSENING OF ANGINA	Y		HISTORY OF CORONARY ARTERY DISEASE AND ISCHEMIA.

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
50	Skin laceration	LACERATION OF LEFT HAND BETWEEN THUMB + INDEX FINGER			INJURY
51	Myocardial infarction	SUBENDOCARDIAL MYOCARDIAL INFARCTION	Y		PREVIOUS MEDICAL HISTORY
51	Cardiac failure congestive	WORSENING CHF	Y		PREVIOUS MEDICAL HISTORY
52	Goitre	MULTINODAL GOITER	Y		THYROID DISEASE.
53	Limb injury	RT. LITTLE TOE INJURY			HIT LITTLE TOE AGAINST CORNER OF TABLE LEG.
54	Ligament injury	LIGAMENT INJURY TO RIGHT 3RD & 4TH FINGERS			SLIPPED AND FELL ON ICE
55	Wound infection	INFECTED CUT IN RIGHT LEG			UNTREATED CUT.
56	Chest pain	CHEST PAIN	Y		OCCLUDED STENT
56	Stent occlusion	OCCLUDED STENT	Y		OCCLUDED STENT
56	Angina unstable	UNSTABLE ANGINA	Y		OCCLUDED STENT
57	Chest pain	PAIN IN CHEST (LEFT SIDE)	Y		
57	Pain in extremity	PAIN IN LEFT HAND	Y		
57	Musculoskeletal pain	PAIN IN LEFT SHOULDER	Y		
58	Diplopia	DIPLOPIA	Y		
58	Syncope	SYNCOPE	Y		DIABETIC AUTONOMIC NEUROPATHY
59	Gastrointestinal haemorrhage	GASTRO INTESTINAL BLEED	Y		PEPTIC ULCER DISEASE, GASTRITIS.
59	Joint sprain	SPRAINED 4TH FINGER (LEFT)			INJURY.
60	Myocardial infarction	MYOCARDIAL INFARCTION	Y		CORONARY ARTERY DISEASE
61	Joint injury	INJURED KNEE			
62	Heat exhaustion	HEAT EXHAUSTION	Y		HE HAD NO AIR CONDITIONING IN APARTMENT.
63	Muscular weakness	BILATERAL LEG WEAKNESS	Y		
64	Cellulitis	CELLULITIS RIGHT FOOT	Y		
64	Gangrene	GANGRENE RIGHT GREAT TOE	Y		
65	Thermal burn	BURNS ON ABDOMEN			BURNS IN ABDOMEN FROM WELDING.
66	Cellulitis	CELLULITIS	Y		INTERCURRENT ILLNESS
66	Food poisoning	FOOD POISONING			INTERCURRENT ILLNESS
66	Staphylococcal infection	STAPH INFECTION	Y		INTERCURRENT ILLNESS
67	Dehydration	DEHYDRATION	Y		INTERCURRENT ILLNESS
67	Hypoventilation	HYPOVENTILATION	Y		SLEEP APNEA UNTREATED
67	Enteritis	INFLAMED BOWEL	Y		INTERCURRENT ILLNESS
67	Muscle spasms	LEG CRAMPS WORSENING	Y		PRIOR HISTORY LEG CRAMPS
67	Renal failure	RENAL FAILURE	Y		INTERCURRENT ILLNESS
67	Abdominal pain upper	STOMACH PAIN	Y		INTERCURRENT ILLNESS

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
67	Gait disturbance	UNEVEN GAIT	Y		INTERCURRENT ILLNESS
68	Arrhythmia	CARDIAC ARRHYTHMIA	Y		LOW MAGNESIUM & POTASSIUM
69	Contusion	BRUISED RIGHT FOOT (ARCH)			HIKING INJURY
70	Appendicitis	APPENDICITIS	Y		INFLAMMATION OF THE VERIFIRMAPPENDIX
71	Subclavian artery thrombosis	LEFT SUBCLAVIAN ARTERY THROMBOSIS	Y		STARTING PICC LINE PLACEMENT
71	Pneumonia	PNEUMONIA	Y		FULID IN LUNGS
71	Small intestinal obstruction	SMALL BOWEL OBSTRUCTION	Y		
72	Convulsion	SEIZURE	Y		UNKNOWN.NOT STUDY DRUG RELATED.
73	Chest pain	CHEST PAIN.	Y		CARDIOVASCULAR DISEASE
73	Renal failure	RENAL INSUFFICIENCY	Y		DIABETES MELLITUS
73	Diabetes mellitus inadequate control	UNCONTROLLED DIABETES	Y		
74	Intervertebral disc degeneration	DEGENERATIVE DISC DISEASE	Y		NEW MEDICAL CONDITION IS DEGENERATIVE DISC DISEASE
75	Hypertension	HYPERTENSION EXACERBATION	Y		STOPPED TAKING HYPERTENSION MED RANOUT, RESTARTED WHILE HOSPITALIZED
76	Muscle strain	BILATERAL GROIN MUSCLE STRAIN			INJURY
77	Ventricular tachycardia	CHEST PAIN SECONDARY TO VENTRICULAR TACHYCARDIA	Y		STRESSFUL LIFE EVENT.
78	Limb injury	RIGHT FOOT INJURY			PUNCTURE FROM A TACK.
79	Pregnancy test positive	POSITIVE PREGNANCY TEST	Y		
80	Limb injury	LEFT FOOT INJURY			
81	Anaemia	SYMPTOMATIC ANEMIA	Y		
82	Alcohol poisoning	DRUNKENNESS			
83	Alcohol poisoning	DRUNKENNESS			
84	Skin laceration	CUT LEFT 2ND FINGER			
85	Skin laceration	CUT FINGER			
86	Interstitial lung disease	INTERSTITIAL PNEUMONIA	Y		
87	Coronary artery disease	CORONARY ARTERY DISEASE	Y		
88	Injury	INJURED SHOULDER AND FOOT			
89	Joint injury	SORENESS LEFT SHOULDER, LEFT HIP AND LEFT WRIST DUE TO FALL			
90	Back pain	BACK PAIN BETWEEN SHOULDER BLADES	Y		
90	Chest pain	CHEST PAIN	Y		
90	Flushing	FLUSHED IN CHEEKS	Y		
90	Nausea	NAUSEA	Y		

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
90	Dyspnoea	SHORTNESS OF BREATH	Y		
91	Vertigo	VERTIGO	Y		
92	Thermal burn	INTERMITTENT BLANCHING OF FINGERTIPS			
93	Limb injury	LEFT INDEX FINGER INJURY			
94	Vertigo	VERTIGO	Y		
95	Whiplash injury	CERVICAL WHIPLASH			
96	Ovarian cyst	OVARIAN CYST	Y		
97	Skin laceration	CUT ON LEFT FIRST FINGER			ACCIDENT WHILE WORKING
97	Skin laceration	CUT ON LEFT THIRD FINGER			ACCIDENT WHILE WORKING
98	Angina pectoris	ANGINA PECTORIS SUSPECT	Y		IT IS THOUGHT TO BE AGE- APPROPRIATE FINDING
99	Back pain	LOW BACK PAIN WORSENED	Y		IT WAS THAT ROUTINE ACTIVITY TRIGGERED, NOT RELATED.
100	Cerebral infarction	RIGHT CEREBRAL INFARCTION	Y		FROM MODE OF ACTION OF STUDY DRUG, IT IS DIFFICULT TO THINK THAT THERE IS RELATI
101	Hypotension	HYPOTENSION	Y		
101	Loss of consciousness	TRANSIENT LOSS OF CONSCIOUSNESS	Y		
102	Subdural haematoma	LEFT SUBDURAL HAEMATOMA	Y		DUE TO FALL
103	Subdural haematoma	LEFT CHRONIC SUBDURAL HAEMATOMA	Y		BECAUSE OF HAEMATOMA DUE TO HEAD CONTUSION, THERE IS NO CAUSALITY WITH STUDY DRU
104	Small intestinal obstruction	SMALL INTESTINAL OBSTRUCTION	Y		IT WAS CAUSED BY ABDOMINAL OPERATION IN THE PAST.
105	Wound	WOUND (ANKLE)			BECAUSE BUMPED FOOT ACCIDENTALLY
106	Myocardial infarction	SUBACUTE MYOCARDIAL INFARCTION	Y		
107	Prostate cancer	PROSTATE CANCER SUSPECT	Y		
108	Completed suicide	SUICIDE	Y	Y	CAN THINK THAT STRONG PAIN AND WORRY ABOUT FAMILY MATTERS ARE THE CAUSE
109	Road traffic accident	AUTOMOBILE ACCIDENT			ACCIDENTAL EVENT
110	Loss of consciousness	LOSS OF CONSCIOUSNESS ATTACK	Y		
111	Food poisoning	FOOD POISONING			POSSIBILITY THAT COOKED INSUFFICIENTLY

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
112	Asthma	ASTHMA BRONCHIAL	Y		IT IS THOUGHT TO BE WORSENING OF COMPLICATION.
113	Chillblains	CHILLBLAINS (RIGHT AND LEFT SECOND, THIRD TOES)			ACCIDENT
113	Joint sprain	SPRAIN (RIGHT FOOT)			ACCIDENT
114	Fall	FALL			ACCIDENTAL EVENT
115	Accidental overdose	ACCIDENTAL OVERDOSE			
116	Foreign body trauma	INGESTION OF FOREIGN BODY (PIN)			ACCIDENTAL INGESTION
117	Food poisoning	FOOD POISONING			CONTAMINATED FOOD INGESTION
117	Grand mal convulsion	GENERALIZED TONIC CLONIC SEIZURE	Y		
118	Back pain	BACK PAIN			INJURY DUE TO LIFTING
119	Cholelithiasis	CHOLELITHIASIS	Y		PATIENT HAD GALLSTONES
120	Colon cancer metastatic	BIOPSY PROVEN RECURRENCE OF METASTATIC COLON CANCER	Y		RECURRENCE OF COLON CANCER
121	Back injury	STRAIN, RIGHT UPPER BACK			EXERCISE-INDUCED INJURY.
122	Colitis	COLITIS	Y		COLITIS
123	Abdominal pain	ABDOMINAL PAIN	Y		ADHESION/SCAR TISSUE
123	Diverticulitis	DIVERTICULITIS	Y		UNKNOWN CAUSE
124	Myocardial infarction	MYOCARDIAL INFARCTION	Y		HOSPITALIZED FOR CORONARY ARTERY DISEASE
125	Chest pain	CHEST PAIN	Y		NONOCCLUSIVE CORONARY ARTERY DISEASE & CHRONIC MILD OBSTRUCTIVE PULMONARY DISEAS
125	Pruritus	ITCHY SKIN	Y		DRUG REACTION AND NOT STUDY DRUG RELATED BUT AN INTERCURRENT ILLNESS
126	Chest pain	CHEST PAIN	Y		
127	Back injury	BACK STRAIN			PHYSICAL ACTIVITY, NOT RELATED TO STUDY DRUG
128	Accidental overdose	PREGABALIN OR PLACEBO ACCIDENTAL OVERDOSE			UNKNOWN
129	Cardiac failure congestive	CONGESTIVE HEART FAILURE	Y		PNEUMONIA
130	Constipation	CONSTIPATION AGGRAVATED	Y		BENIGN PROSTATE HYPERTROPHY WORSENERD; SUBJECT HAS HISTORY OF CONSTIPATION WITH O
130	Alcoholism	ETOH ABUSE	Y		NEW DIAGNOSIS UPON HOSPITAL ADMISSION
130	Obstructive uropathy	OBSTRUCTIVE UROPATHY	Y		BENIGN PROSTATE HYPERTROPHY

## LYRICA® NEURONTIN®

Assessment of Suicidality with  $\alpha_2\delta$  Drugs

## Appendix 3: Listing of Possibly Suicide-Related Adverse Events Sorted by Preferred Term

No.	AE preferred term	AE investigator term	SAE	Death	Comments
130	Benign prostatic hyperplasia	WORSENING BENIGN PROSTATE HYPERTROPHY	Y		HISTORY OF BPH, WORSENERD DUE TO AGE
130	Hyponatraemia	WORSENING OF HYPONATREMIA	Y		SUBJECT HAS A HISTORY OF CHRONIC HYPONATREMIA WITH ONSET DATE 15JAN2003
130	Urinary retention	WORSENING OF URINARY RETENTION	Y		WORSENERD BENIGN PROSTATE HYPERTROPHY
131	Meningioma	MENINGIOMA IN THE PERIPHERY OF THE LEFT SUPERIOR PARIETAL REGION	Y		NEW DIAGNOSIS, NOT IN CURRENT INVESTIGATOR BROCHURE AS POTENTIAL AE.
132	Joint injury	INJURY TO WRIST			SLIPPED IN GARDEN. FELL AND PUT HAND OUT TO PREVENT INJURY. WRIST TOOK STRAIN OF
133	Head injury	TRAUMATIC HEAD INJURY			ACCIDENTAL HEAD TRAUMA
134	Head injury	TRAUMATIC HEAD INJURY			ACCIDENTAL HEAD TRAUMA
135	Limb injury	INJURY LEFT FOOT			DROPPED HEAVY OBJECT ON FOOT