Antiepileptics and suicidal thoughts and behaviour

Pharmacovigilance Working Party

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1.0 The Issue

Over the last few years concerns have arisen about the risk of suicidal thoughts and behaviour in association with the use of a number of antiepileptics. Upon review of the available data updates to the product information for some antiepileptics have occurred to reflect the available data and this potential risk – this includes updates to the product information for topiramate, levetiracetam, vigabatrin and zonisamide. Also the product information for many of the antiepileptics already contains information about the potential for the risk of depressed mood or depression - carbamazepine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide

However, the available data on the risk of suicidal ideation and behaviour has not been evaluated for all antiepileptic agents and on this basis, and in the context of an ongoing review of the issue by the US Food and Drug Administration (FDA), the Pharmacovigilance Working Party (PhVWP) of the Committee on Medicinal products for Human Use (CHMP) decided to initiate a review of suicidality associated with antiepileptic drugs.

This paper provides a summary of the findings of the data evaluated during the European review along with the findings of the FDA review and outlines the PhVWP discussion of these data.

2.0 PhVWP Review

In light of ongoing concerns about the risk of suicidal ideation and behaviour in association with antiepileptics and in the context of an ongoing review of the issue by the Food and Drug Administration the PhVWP decided to initiate a review of suicidality associated with antiepileptic drugs.

The Marketing Authorisation holders (MAHs) for the following antiepileptics were requested to submit a review of clinical trial data on the risk of suicidal ideation and behaviour in association with their antiepileptic agent(s):

- carbamazepine
- divalproex sodium
- felbamate
- gabapentin
- lamotrigine
- levetiracetam
- oxcarbazepine
- pregabalin
- tiagabine
- topiramate
- vigabatrin
- zonisamide

A summary of the available data considered for each drug in the context of the European review is provided below.

Carbamazepine

Clinical trial data - The MAH has not provided an analysis of all the available clinical trial data due to concerns that it would not be possible to obtain reliable information from this old dataset, which pre-dates the application of modern and current good clinical practices (cGCP) and is not readily searchable (available as hard copy only).

Therefore only 3 Novartis sponsored trials have been searched (two bioequivalence studies and 1 small (n=37 enrolled, 6 completed the study) – no reports of suicidal behaviour, self harm or hostility were reported in these trials. Due to their design or size are considered to be...
of little value in trying to evaluate the risk of suicidal thoughts and behaviour in association with carbamazepine.

**Post-marketing data** – the MAH used the MedDRA 9.1 SMQ Suicide/self-injury for this search. A total of 408 events from 362 reports were identified including 22 completed suicide, 194 intentional overdose, 137 suicide attempt and 29 suicidal ideation. The majority of report originated from spontaneous data (305, 74.8%), with the remaining from literature (96, 23.5%) or clinical trials (7, 1.7%). Most of the cases occurred in the adult population and where indication is provided occurred in patients being treated for epilepsy. The information in these cases is often limited with regards to past medical history, daily dosage, duration of treatment and concomitant medication. Therefore in many of these cases it is difficult to draw any conclusions on a possible association between the use of carbamazepine and the risk of suicidal thoughts and behaviour in the cases.

**Literature** – review of the published literature has not provided any evidence to suggest that there is an increased risk of suicidal behaviour, self harm or hostility in association with carbamazepine treatment. Some literature reports indicate that carbamazepine may have anti-suicidal properties.

**Divalproex sodium**

**Clinical trial data** – based on their review of the published clinical trial data the MAH did not identify any potential sign of increased risk of suicidality related with the use of the drug. However, it is important to note the paucity of the data and its poor quality. A great majority of the analysed studies had small numbers of patients, included patients with different clinical diagnosis (with a large preponderance of bipolar and other psychiatric disorders), with short follow-up and no adjustment for potential bias and confounders and, therefore, no conclusions can be drawn from these clinical studies.

**Post-marketing data** – the MAH ADR database has not revealed spontaneous reports of suicide, suicidal ideation, aggression or impulsivity with divalproex, across a range of different clinical patients (epilepsy, manic-depressive disorders, and migraine).

**Literature** – the published epidemiological studies are inconclusive. Two studies suggest that the use of sodium valproate is associated with a positive antidepressant effect and a reduction in suicide risk, comparing with other mood stabilizers. However, three other studies propose an increase in suicidality risk with valproate compared with other mood stabilizers. All these studies have methodological problems (retrospective, with small number of patients and short follow-up, not controlled by potential bias).

**Felbamate**

**Clinical trial data** – Data from a total of 10 trials were evaluated. These 10 trials in epilepsy included a total of 339 subjects who received felbamate and 337 subjects who received placebo. In many of these trials patients were excluded if they were considered to be at suicide risk (6 out of 10), had a history of suicide attempt (5 out of 10) or had a psychiatric disorder (7 out of 10; diagnosis of bipolar disorder, and/or psychotic symptoms, and/or first manic episode, and/or a personality disorder). Review of the data from these trials led to identification of 29 possibly suicide related adverse events – on further review, in 28 cases the events reported were not suicide related events (for example an injury was reported but it was related to a seizure), and in the remaining case there was not enough information. Therefore, no suicide related events have been identified from these trials.

**Post-marketing data** - The MAH searched their data base, from market launch in 01 October 1993 to 01 April 2007. The search retrieved 51 cases, including 9 cases of accidental overdoses and 1 case of prescribed overdose. Of the remaining 41 cases, 3 were consumer cases that had not been medically confirmed and therefore were excluded by the MAH from the assessment. This resulted in 38 cases – 5 completed, suicide, 25 suicide attempt, 1 suicidal behaviour and 7 suicidal ideation. 31% of the patients had a history of psychiatric disorders, including 13% of the patients who had a history of previous suicide attempt(s).
Literature – Felbamate has been reported to be linked to stimulant like psychiatric effects and also to insomnia, nervousness and depression.

Gabapentin

Clinical trial data - The MAH has searched the clinical trial data (all indications) for any signs related to suicidality – these trials included 5,194 patient receiving gabapentin and 4,337 patients receiving placebo or active control. This search identified 10 cases including: Gabapentin arm - 1 self-injurious behaviour, 2 suicidal ideation and 3 cases where there was not enough information; placebo arm – 1 suicidal ideation and 3 cases where there was not enough information. Overall, 0.06% (3 out of 5,194) of patients in the pregabalin group, 0.03% (1 out of 2,974) in the placebo group and none in the active control group experienced suicide-related events.

Post-marketing data – the MAH had not provided a review of the post-marketing data at the time of the review.

Lamotrigine

Clinical trial data – GSK have provided the results of a pooled analysis of suicidality events from 35 lamotrigine double-blind, placebo-controlled clinical trials with > 20 patients per arm. Data was available for 6467 patients and 52 healthy adult volunteers participating in studies across all indications. Examining the overall dataset the percentage of patients who experienced definitive suicidal behaviour and ideation in the lamotrigine group was 1.16% (43/3695) compared with 0.89% (25/2824) in the placebo group producing an Odds Ratio of 1.46 (95% CI 0.89–2.45, p=0.171). The highest number of events occurred in the bipolar disorder trials – lamotrigine (2.4% (29/1212)) compared with placebo (1.8% (19/1054)) but this difference did not reach statistical significance (OR 1.31 (95% CI0.73, 2.39, p=0.46)). Of note, is that the data on time to event and associated hazard ratios suggest that although there is no statistical difference overall between the treatment and placebo groups this is not the case during the early period of treatment where these is a statistically significant difference especially for the psychiatric indications where this is consistently seen in the first 6 weeks of treatment.

Post marketing data – Increased suicidality has not been evident using the MAH’s signal detection and evaluation processes, however spontaneous reports of suicidal behaviour and ideation have been received.

Levetiracetam

Clinical trial data – Twenty-three trials met the FDA’s criteria and were searched for possibly suicide-related adverse events - 8 epilepsy, 6 anxiety, 6 cognition and 3 "other" trials. A total of 19 total subjects (6.2%) in the levetiracetam and placebo arms experienced suicide-related events - 13 subjects in the levetiracetam treatment arm and 6 subjects in the placebo treatment arm. The reported events included 2 completed suicides (both on levetiracetam), 5 suicide attempts (3 levetiracetam, 2 placebo), 1 prepatory acts towards imminent suicidal behaviour (on levetiracetam), 8 self-injurious behaviour (4 levetiracetam, 4 placebo), 2 suicidal ideation (both on levetiracetam) and 1 report with no enough information (on levetiracetam).

The overall incidence rate (IR) over the 23 studies was higher for levetiracetam (25.8 per 1000 subject/years) than for placebo (19.0 per 1000 subject-years). Using Mantel-Haenszel methodology, the overall IR was estimated to be 1.55 times (95% CI: 0.54, 4.42) higher for levetiracetam.

Within the epilepsy indication (8 studies), for which levetiracetam is indicated, incidence rates were lower than in the overall population but still the IR was higher for levetiracetam than for placebo (IR of 18.5 and 10.1 per 1000 subject-years for levetiracetam and PBO, respectively).
For this indication the IR was estimated to be 1.85 times (95% CI: 0.36, 9.52) higher for levetiracetam.

**Post marketing data** – Based on data reviewed in the 8th Periodic Safety Update Report, there does not appear to be any signal of an increased frequency of suicidal behaviour with reference to the previously reported cases. Abnormal behaviour, aggression, anxiety, confusion, depression, hallucinations, irritability/ nervousness, psychotic reaction, suicide, suicide attempt and suicidal ideation are listed in the Summary of Product Characteristics.

**Epidemiological data** - the MAH conducted a study using a claims database of epileptic patients initiating levetiracetam or any of six other commonly prescribed antiepileptic drugs in order to identify patients with suicide attempt or injury diagnoses on their claims. Of note, data held in the claims database did not enable cases of suicide attempt to be classified separately from completed suicide (i.e. those leading to deaths) – the same was true for non-fatal or fatal injuries. In this study no difference was observed between levetiracetam and all other antiepileptics in terms of percentage of reports and the frequency per 1000 Patient-Years. The results were similar when comparing levetiracetam to each of the other antiepileptics.

**Oxcarbazepine**

**Clinical trial data** – A total of 16 double-blind randomized placebo (or low dose placebo-controlled) studies were included in the analysis involving 2,596 patients (1,569 in the oxcarbazepine group, 1,027 in the placebo group). A total of 237 patients with possibly suicide-related adverse events were identified. On further review only 5 patients were rated as having experienced suicidal-related adverse events. The remaining 232 patients were classified as either self-injurious behaviour with no suicidal intent or other: accident, psychiatric, medical.

On further review of the 5 cases, external experts classified 2 events as suicide attempt, one as suicidal ideation and 2 cases as self-injurious behaviour, intent unknown. Four patients (out of 1569, 0.26%) had been actively treated with oxcarbazepine and one patient (out of 1017, 0.10%) had received placebo. Two of the oxcarbazepine-treated patients and none in the placebo group attempted suicide.

**Post-marketing data** – the MAH had not provided a review of the post-marketing data at the time of the review.

**Pregabalin**

**Clinical trial data** - The MAH has searched the clinical trial data (all indications) for any signs related to suicidality – these trials included 7609 patient receiving pregabalin and 3,330 patients receiving placebo and 1,007 patients receiving active control. This search identified 31 cases including: Pregabalin arm - 1 completed suicide, 3 suicide attempts, 3 cases of suicidal ideation and 15 cases where there was not enough information; placebo arm – 1 self-injurious behaviour, 2 suicidal ideation and 4 cases where there was not enough information; active control – 1 suicide attempt and 1 suicidal ideation. Overall, 0.09% (7 out of 7,609) of patients in the pregabalin group, 0.09% (3 out of 3,330) in the placebo group and 0.2% (2 out of 1,007) in the active control group experienced suicide-related events.

**Post-marketing data** - During the reporting period of 07 January 2005 to 31 July 2005, a total of four suicide-related cases were received by the MAH. In three cases the indication for use was epilepsy and in the remaining case neuropathic pain. Patient exposure during this period was estimated to be 224,000 patients. During the reporting period 01 August 2005 to 31 January 2006, there were twelve suicide-related cases, of which ten were classified as serious. Patient exposure during this period was estimated to be 1,004,000 patients.

Ten cases mention suicidal ideation, single cases of intentional self-injury, self-injurious ideation and suicide attempt were received. There were five cases in which there seems to be relationship between pregabalin and the reaction and there was another case in which a positive rechallenge was reported.
Tiagabine

Clinical trial data – Data from a total of 12 placebo-controlled trials and 2 healthy volunteer studies were evaluated. These trials were in epilepsy (6), insomnia (4), generalised anxiety disorder (1) and post traumatic stress disorder (1) and included a total of 1,361 subjects who received tiagabine and 804 subjects who received placebo. In these trials patients were excluded if they were considered to be at suicide risk (3 out of 14) or had a history of bipolar disorder (2 out of 14). Clinically significant psychiatric disorders or psychological or behavioural problems were exclusion criteria for all trials. Review of the data from these trials led to identification of 2 suicide related events – these were both cases of suicidal ideation and they both occurred in tiagabine treated patients, one in an epilepsy trial and the other in the generalised anxiety disorder trial. This gives an incidence of 0.014 % for tiagabine treated patients versus 0 for placebo.

Post-marketing data - The MAH searched their data base, from market launch on 14 June 1996 to 28 February 2007. The search retrieved 81 cases – 5 completed, suicide, 30 suicide attempt, 14 suicidal ideation, 28 overdose (of which 10 were coded as intentional overdose) and 2 depression suicidal. A total of 51% of the patients had a history of psychiatric disorders, including 10% of the patients who had a history of previous suicide attempt(s). Based on cumulative exposure of tiagabine (565,889 patient treatment years), the reporting rate is 0.00014 per patient treatment years.

Topiramate

Clinical trial data - Suicide-related events were identified in 46 (0.5%) of 8,652 topiramate-treated subjects and in 8 (0.2%) of 4,045 placebo-treated subjects in the double-blind clinical studies. The corresponding event rates were 0.012 and 0.005, respectively. In the subset of subjects whose suicide-related events were characterized as suicide attempts, the event rate was 0.002 (9 events per 3,845 subject-years) on topiramate vs. 0 (0 event per 1,629 subject-years) on placebo. One completed suicide occurred during the open-label phase of a bipolar trial but was not included in the analyses. There was a consistent pattern of increased rate of suicide-related events in the topiramate group compared with placebo across the different indications studied. Overall the difference in incidence of suicide-related events for subjects given topiramate compared with those who received placebo is statistically significant (p=0.008 Fischer's exact test)

Post-marketing data – the MAH had not provided a review of the post-marketing data at the time of the review.

Vigabatrin

Clinical trial data – A total of 65 case reports were retrieved from the database. Among them, four cases were excluded from this safety review as considered “false positive”. Patients’ ages ranged from 5 to 60 years of age. Fourteen patients had experienced previous episodes of depression and/or suicidality. Three, who stopped vigabatrin before the onset of event (48 hours, 1 month and 3 months prior to onset). The outcome was recovery in forty-seven patients and unknown in six patients. Death was reported in eight patients.

Post-marketing data - The reporting rate for cases of suicidality ranged between 59 and 91 cases per million patients over the years 1992-1995. This reporting rate markedly decreased thereafter to 0-25 cases per million vigabatrin-treated patients during the last years. In total 60 cases of suicide-related reactions were received. Most of the patients (45/60) were adult (≥18 years) while 6 were less than 18 years old (unspecified age in 9 patients). Concomitant and/or past history of psychiatric disease such as psychiatric disorder (NOS), chronic psychosis, obsessional neurosis, depression, depressive disorders, suicidal ideation, mental retardation and/or concomitant antidepressant therapy, were noted in 42 cases. In two cases, chronic alcohol abuse was also reported.
Zonisamide

Clinical trial data – A total of 5 studies met the criteria for inclusion in the review and involved 961 individuals randomised to zonisamide treatment and 440 randomised to placebo treatment. Four of the trials were in the epilepsy indication and the remaining trial was in migraine prophylaxis. In these trials a total of 8 patients experienced possibly suicide-related adverse events - 6 in the zonisamide group and 2 in the placebo group. On further expert blinded review it was determined that 4 of the subjects experienced events that met the criteria for suicide attempt (3 zonisamide and 1 placebo), two subjects had events that met criteria for suicidal ideation (2 zonisamide, 0 placebo), one subject had an event that met criteria for self injurious behaviour, intent unknown (1 zonisamide, 0 placebo), and one subject experienced an event classified as "not enough information, non-fatal" (1 placebo). On the basis of the 3 zonisamide "suicide attempts", this provides an incidence of 0.3% (as compared to 0.2% for placebo). The 2 reports of suicidal ideation in the zonisamide group correspond to an incidence of 0.2% (as compared to 0% for placebo). Overall incidence of suicidal thoughts and behaviour is 0.5% in the zonisamide group compared with 0.2% in the placebo group.

Post-marketing data - Since the time of the MAA in Europe, seven reports have been received involving suicidal behaviour. These reports include 4 reports of suicide attempt and three reports of suicidal ideation. The age range in these reports was 17 to 34 years. In 4 of the reports the patients had a current or past psychiatric illness and in a further 2 reports they were also receiving other antiepileptic drugs.

Since a review of post-marketing data had not been provided for all the antiepileptics, in order to have an indication of whether they may be possible differences in terms of reporting for any of the anti-epileptics, the UK has examined the reports of suicide-related events that have been received through the Yellow Card. The table below provides the number of reports involving suicide-related events that have been received through the Yellow Card Scheme in association with each of the anti epileptics included in this review. With the exception of vigabatrin and zonisamide, a similar number of reports has been received for all the antiepileptics. The lower number seen with vigabatrin and zonisamide may reflect their relatively low usage in the UK.

Table 1: Reports of suicide-related events received through the Yellow Card Scheme in association with antiepileptic drugs

<table>
<thead>
<tr>
<th></th>
<th>Completed suicide</th>
<th>Suicide attempt</th>
<th>Suicidal ideation</th>
<th>Depression suicidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>1</td>
<td>7</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>1</td>
<td>2</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>5</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1</td>
<td>2</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>0</td>
<td>5</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Topiramate</td>
<td>3</td>
<td>2</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
3. FDA Review

As part of this review the FDA has considered data from 199 placebo-controlled trials across 11 antiepileptics used in epilepsy and psychiatric disorders (e.g. bipolar disorder, depression and anxiety). This analysis included 43,892 individuals (27,863 on antiepileptics and 16,029 on placebo) and the data were analysed for reports of suicidal thoughts and behaviour (completed suicides, suicide attempts and preparatory acts).

The key findings of the FDA review were as follows:

- Individuals receiving antiepileptics were at a small but significantly increased risk of suicidal thoughts and behaviour compared with those receiving placebo;
- Overall 0.43% in antiepileptic group compared with 0.22% in the placebo group experienced suicidal thoughts and/or behaviour, which corresponds to approximately 2 per 1,000 additional patients in antiepileptic group who experienced such events;
- The results were generally consistent among the 11 antiepileptics;
- No specific demographic to which increased risk could be attributed and in particular there was no clear pattern of risk across age groups.

### Relative Risk and Risk Difference for Suicidality According to Trial Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo Patients with Events Per 1000 Patients</th>
<th>Drug Patients with Events Per 1000 Patients</th>
<th>Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients</th>
<th>Risk Difference: Additional Drug Patients with Events Per 1000 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>1.0</td>
<td>3.5</td>
<td>3.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>5.2</td>
<td>8.3</td>
<td>1.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Other</td>
<td>0.8</td>
<td>2.0</td>
<td>2.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>2.2</td>
<td>4.3</td>
<td>2.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>

The FDA has entered into discussions with the MAHs for these antiepileptics over the findings of this review and the need for class wording. Furthermore, they have commented that although only certain drugs (carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate and zonisamide) were part of the analysis, they expect that all medications in the antiepileptic class share the increased risk of suicidality. This analysis is scheduled for consideration at a joint meeting on July 10th 2008 of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drugs Advisory Committee.
4.0 Overall conclusions

The available data for topiramate provide clear, consistent evidence of an increased risk of suicidal thoughts and behaviour across all indications studied. For both lamotrigine and levetiracetam there is a trend towards an increased risk and this appears to be seen across all indications studied in the trials. For many of the other antiepileptics it is recognised that the small number of events seen in the clinical trials mean that it is difficult to make meaningful comparisons between active and placebo and across the different indications studied. However, the small number of cases and the lack of a statistically significant increased risk of suicidal behaviour is likely due to this being a rare event, the sample size not being adequate to detect a significant difference between active and placebo treated subjects and that in many of trials patients who are considered to be at suicidal risk or may be particularly susceptible due to underlying psychiatric disorders were excluded from the trials. Furthermore, for some of the older products it is possible that the conduct of the trials pre-dates the application of modern and current Good Clinical Practice (GCP) and therefore recording of events may not have been so comprehensive or the data as searchable as that for the more modern antiepileptics agents. So whilst, for the majority of the antiepileptics, the available clinical trial data do not raise particular signals of an increased risk of suicidal behaviour, equally they cannot rule out an increased risk.

Where reviews of the post-marketing data have been completed, there is not clear evidence of a causal association. However, as the MAHs themselves state, in many of the cases there is a lack of important information such as past medical history, concomitant medication etc and therefore whilst it may not be possible to confirm a causal association between the event and the treatment, equally we are not able to exclude the possibility of an increased risk. Data on numbers of spontaneous reports received through the Yellow Card Scheme would also provide support for the potential increased risk of suicidal thoughts and behaviour being common to all antiepileptics.

The majority of these antiepileptics (9 out of 12- carbamazepine, gabapentin, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, vigabatrin, zonisamide) already contain warnings about the risk of depression and it therefore may be possible that in some individuals the depression experienced may be severe enough to result in suicidal ideation or even suicide attempt. Suicidal ideation and/or behaviour are also listed in the product information for four of the antiepileptics (levetiracetam (section 4.4 & 4.8) topiramate (section 4.4 & 4.8), vigabatrin (section 4.8) and zonisamide (section 4.8)). The current wordings contained in the product information for those products authorised through the centralised procedure is provided at Annex 1. Currently there appears to be some discrepancy between products with respect to existing warnings and in some cases products with similar levels of evidence do not have similar warnings, this includes centralised products – for example there are limited data available for zonisamide but the product information has already been updated to contain information about suicidal ideation whereas for pregabalin no such warning exists.

The FDA has completed a thorough meta-analysis of the available data from the clinical trials for these antiepileptics drugs and has examined patient level data. It is unlikely that further review of existing data would better inform this European review and to gather more definitive data about the link between antiepileptic treatment and suicidal thoughts/behaviour would require very large, controlled studies to be completed. The PhVWP considered the available data and concluded that where better quality clinical trial exist there is some evidence to suggest an increased risk of suicidal thoughts and behaviour and for the other products the limitations of the available data do not exclude the possibility of an increased risk. As it is unclear what the potential mechanism may be by which antiepileptics may increase the risk of suicidal thoughts or behaviour it is not possible to rule out certain products to which the potential for an increased risk could not apply. Unless clearly justified, based on the available data, it would be unwise to have very different wording in the summaries of product characteristics across the antiepileptics as this may lead to unnecessary and inappropriate switching of treatment, which is particularly inadvisable in this patient population.
Having considered all the available data, the PhVWP recommended that the summaries of product characteristics for all antiepileptic agents authorised in the EU should be updated to fully reflect the current evidence regarding the potential risk for suicidal thoughts and behaviour with antiepileptics. The agreed wording proposed for inclusion for the summaries of product characteristics and patient information leaflets is provided at Annex 2. The CHMP is asked to consider whether this proposed class labelling should also apply to those products that are authorised through the centralised procedure – levetiracetam (Keppra), Pregabalin (Lyrica) and zonisamide (Zonegran).
Annex 1

Warnings contained in the SPCs for the antiepileptics authorised through the centralised procedure

Levetiracetam

Section 4.4 Special warnings and precautions for use

Suicide, suicide attempt and suicidal ideation have been reported in patients treated with levetiracetam. Patients should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician.

Section 4.8 Undesirable effects

Psychiatric disorders
Common: agitation, depression, emotional lability/mood swings, hostility/aggression, insomnia, nervousness/irritability, personality disorders, thinking abnormal
Post-marketing experience: abnormal behaviour, anger, anxiety, confusion, hallucination, psychotic disorder, suicide, suicide attempt and suicidal ideation

Pregabalin

Section 4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
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<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Euphoric mood, confusion, irritability, libido decreased</td>
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<tr>
<td><strong>Uncommon</strong></td>
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<tr>
<td>Hallucination, panic attack, restlessness, agitation,</td>
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<tr>
<td>depression, depressed mood, mood swings,</td>
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<tr>
<td>depersonalisation, insomnia exacerbated, word finding</td>
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<tr>
<td>difficulty, abnormal dreams, libido increased, anorgasmia,</td>
</tr>
<tr>
<td>apathy</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
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<td>Disinhibition, elevated mood,</td>
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Zonisamide

Section 4.8 Undesirable effects

<table>
<thead>
<tr>
<th>Psychiatric Disorders</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
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<tbody>
<tr>
<td>Agitation</td>
<td></td>
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<td>Irritability</td>
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<td>Confusional state</td>
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<td>Depression</td>
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<td>Psychotic disorder</td>
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<td>Anger</td>
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<td>Aggression</td>
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<td>Suicidal ideation</td>
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<td>Suicidal attempt</td>
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<td>Hallucination</td>
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<td>Insomnia</td>
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(leicht geändert auf der Sitzung der PhVWP im Juli 08)

Summary of Product Characteristics

Section 4.4 - Special Warnings and Special Precautions for Use

Suicide/suicidal thoughts or clinical worsening

Depression and mood alterations have been reported in patients treated with anti-epileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic drugs has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for <drug substance>.

Therefore patients should be monitored for signs of depression or suicidal thoughts and behaviour and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation emerge.

Patient Information Leaflet

Section 2 Before you take X

Take special care with

During treatment with <drug substance> depression and mood alterations have been reported. If you feel depressed or have thoughts of killing your self at any time, contact your doctor. You may find it helpful to tell a relative or close friend that you are depressed or have an anxiety disorder, and ask them to read this leaflet.