London, 20 March 2005
Product name: LYRICA
Product no: EMEA/H/C/000546/II/0004

SCIENTIFIC DISCUSSION

1. Introduction

The active substance, pregabalin is an analogue of the mammalian neurotransmitter gamma-aminobutyric acid (GABA). However, pregabalin does not mediate its effects specifically though an effect upon GABA-ergic transmission. It is claimed that the mechanism of action of pregabalin is binding to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin.
On 6 July 2004, a Commission Decision was granted for Lyrica (pregabalin) for the treatment of peripheral neuropathic pain and for partial seizures (as adjunctive therapy) in adults. The Marketing Authorisation Holder (MAH) (Pfizer Ltd.) submitted on 15 July 2005 an application for the following extension of indication: "*treatment of Generalised Anxiety Disorder (GAD) in adults."* The rationale for the proposed addition of the GAD indication is based on both preclinical and clinical evidence obtained with pregabalin.

2. Non clinical aspects

2.1 - Primary pharmacology

Pregabalin has anxiolytic-like activity in animals. In particular, pregabalin is effective in anxiety models like punished responding conflict tests in rodent and monkey (Geller and Vogel Water-Lick Conflict tests; ED50-value of 3-10 mg/kg p.o.) that are sensitive also to benzodiazepine and other clinically useful anxiolytic drugs.

In the Geller Conflict test in rats the maximum effect was observed with a 30 mg/kg dose. Higher doses decreased the response due to sedation/ataxia. In the rhesus monkey this dose was the minimal effective dose.
It should be noted that in previously reported CNS safety pharmacology studies submitted as part of the original application for Marketing Authorisation, rats given oral doses of >25 mg/kg showed reduced spontaneous locomotor activity, keep balance in walking on a narrow rod and ataxia. In the Sidman avoidance test in squirrel monkeys, pregabalin dose-dependently reduced activity and motor coordination at 30 and 100 mg/kg indicating sedative-like activity and reduction of motor coordination.
These data suggest that similar side-effects in humans may occur at therapeutic doses, which should be weighed in the risk-benefit assessment for this indication.

2.2 - Safety pharmacology

One additional piece of pharmacological data is in vitro hERG potassium channel pharmacology.

Pregabalin was tested at 60 and 600 μM concentrations with single cell voltage-clamp electrophysiology in a stable mammalian fibroblast cell line expressing recombinant hERG channels. Pregabalin did not alter the function of hERG channel in a manner that was different from 5 min incubation without drug addition (Pfizer Study Report PD144723/IC/001/05). These results suggest that pregabalin is unlikely to alter cardiac function via interaction with hERG channels in the heart.

The maximum concentration chosen in this study exceeded the human therapeutic free plasma concentration by a factor of 10. Therefore the margin of safety that can be derived from this study is limited. Yet, in view of the minimal effect observed at 600 μM (~11% inhibition), it may be concluded that the results do not raise a concern with respect cardiac safety.

3. Clinical aspects

GCP statement on application of ethical standards in clinical trials

The CHMP requested the MAH to provide a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC (Articles 8 (ia) of the amended Directive, 9.4(c) and 127 (a) of the new Regulation).

The MAH provided a statement that Lyrica (pregabalin) clinical trials conducted outside of the Community were carried out in accordance with ethical standards of ICH GCP and therefore in accordance with the ethical standards of Directive 2001/20/EC. The CHMP considers the MAH's response acceptable.

3.1 Clinical efficacy

3.1.a Introduction

Treatment of Generalised Anxiety Disorder (GAD)

GAD was introduced into the psychiatric nomenclature in 1980 with the publication of DSM-III (Diagnostic and Statistical Manual of Mental Disorders). The diagnostic changes applied to GAD between DSM-III and DSM-IV have made it difficult to develop a consistent understanding of its course. The Epidemiologic Catchment Area (ECA) study found that the duration of DSM-III GAD was longer than five years in 40% of patients. The reported lifetime prevalence rates for DSM IV GAD in the general population is approximately 5-6% with rates as high as 10% among women aged 40 years and above and in elderly (aged 55-85 years) of about 7%.
Cross-sectional rates among primary care attendees are about 8%, making GAD the most prevalent anxiety disorder in primary care.
GAD seems to be a disorder not occurring in children, as a condition on its own. Prevalence rates of GAD in adolescents seem to be low.
As GAD is a more chronic disorder, treatment needs to be prolonged beyond short-term usage.

Diagnosis
The defining features of GAD are excessive anxiety and worry, and the diagnosis can only be made when there is significant social, occupational, and functional impairment that has persisted for at least 6 months (according to DSM IV functional impairment is not necessary for the diagnosis if clinically significant distress is evident)

Clinical manifestation
Patients with GAD may have many somatic complaints. This may account for the high use of medical resources among patients with GAD. In addition, patients with GAD have higher risk of negative outcome (e.g. increased burden on the health care system, increased morbidity and mortality rates).
GAD is associated with diminished overall emotional health and identified evidence of decreased employment and corresponding increased reliance on public assistance, impaired social life, and low ratings of life satisfaction.
In conclusion GAD is associated with significant psychosocial impairment and significant negative effect on quality of life.

Co-morbidity
GAD is frequently associated with a wide spectrum of other mental disorders, with a lifetime comorbidity among 90.4% of the people who had a history of GAD (about 17% of the GAD patients report a lifetime major depression; also other anxiety disorders are very common in patients with GAD).

Scales
In the GAD studies the Hamilton Anxiety Rating Scale (HAM-A) is the primary outcome measure. This scale is not ideal to measure GAD but is "routinely used in GAD studies for registration purposes". The HAM-A provides an overall measure of global anxiety, including psychic and somatic symptoms. The HAM-A is a clinician-rated scale that measures the severity of anxiety-related symptoms in 14 areas, with total scores ranging from 0 to 56.

In this application, some secondary efficacy parameters were used to support the primary efficacy parameter of HAM-A change from baseline. Secondary efficacy parameters that were assessed in one or more of the controlled GAD studies (adult and elderly) included:
- change in HAM-A total score at each week of treatment;
- HAM-A responder rate (the proportion of patients having a ≥50% reduction from baseline to endpoint in total HAM-A);
- Clinical Global Impression of Improvement (CGI-I) responder rate [the proportion of patients with a CGI-I score of 1 (very much improved) or 2 (much improved)];
- onset of effect assessments;
- change in Hamilton Depression Rating Scale (HAM-D) score. In some studies also other secondary measures were used.

Physician Withdrawal Checklist (PWC): The PWC is a clinician-rated instrument that measures 20 common symptoms of withdrawal on a scale ranging from 0 (not present) to 3 (severe); scores on the 20 individual items are summed to obtain a PWC total score 23. The PWC was used to determine whether patients experienced withdrawal symptoms during taper.

3.1.b Efficacy results

The efficacy results are based on 6 short-term placebo controlled trials (4-6 weeks), 1 short-term placebo controlled elderly study (8 weeks) and 1 long-term study (6 months).

1. Short-term efficacy: HAM-A and HAM-D

To substantiate short-term efficacy six placebo-controlled, fixed dose studies were conducted (Studies 021, 025, 026 083, 085, and 087). The methodology of these studies was in most respects in line with the CHMP GAD guideline.

The double-blind treatment period in the controlled adult studies was 4 to 6 weeks:
- 4 weeks in four studies (Studies 021, 025, 026 and 083);
- and 6 weeks in the remaining two (Studies 085 and 087).

Although the recently issued CHMP guideline (Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Generalised Anxiety Disorder CPMP/EWP/4284/02) recommends that the duration of short-term trials for GAD should be at least 8 weeks, these studies were planned and designed during the period (1998-1999) prior to the draft CHMP guideline (September 2003) and in line with the 4 to 6 weeks duration requirements for short-term GAD studies at the time. All but one of the six controlled adult GAD studies included a benzodiazepine or serotonin noradrenaline reuptake inhibitor (SNRI) active validator: lorazepam in Studies 021, 025, 026, alprazolam in Study 083 and venlafaxine in Study 087.
The controlled elderly GAD study (study 090/152) had a double-blind treatment period of 8 weeks but no third arm.

1.a Mean HAM-A improvement (see table 1 below):

In all studies the mean HAM-A score was at baseline between 23 and 25 points indicating a moderate severity of GAD symptoms:

- **study 21** is presenting that lorazepam 6 mg given by TID (total daily dose, administered) is a very effective in the treatment of GAD with a rather large magnitude of effect. Pregabalin 150 mg given by TID and pregabalin 600 mg given by TID were also superior to placebo but the magnitude of effect was modest.
- **study 25** was a study with no assay sensitivity. All active treatments including lorazepam 6 mg were not superior to placebo. This study should be considered as a failure.
- In **study 26** pregabalin 150 mg given by TID was not superior to placebo but pregabalin 600 mg given by TID and lorazepam 6 mg were significant superior to placebo with modest magnitudes of effect.
- All active treatments in **study 83** were superior to placebo with modest magnitudes of effect. The same applies for studies **85, 87** and **090/152.**

1.b HAM-A Responder results(see table 1 below):

In **study 21** lorazepam 6mg and pregabalin 600 mg given by TID were superior to placebo but pregabalin 150 mg was not superior to placebo.
Study 25 was a study with no assay sensitivity. More placebo responders than lorazepam 6 mg responders.
In **study 26** pregabalin 600 mg given by TID was superior to placebo but pregabalin 150 mg given by TID and lorazepam 6mg were not significantly superior to placebo.
Study 83 presented confusing results: pregabalin 300 mg given by TID and pregabalin 600 mg were superior to placebo, while pregabalin 450 mg given by TID and alprazolam were not better than placebo. Moreover the magnitude of effect of pregabalin 300 mg was the largest.
All active treatments except pregabalin 600 mg in **studies 85, 87** were showing a statistically significant difference superior to placebo, while the elderly study **090/152** was negative for responders.

All other (secondary) efficacy outcome measures were more or less in line with the primary outcome measures.

Although not all results are convincing, it can be that short-term efficacy for pregabalin is demonstrated, with a modest magnitude of effect. This magnitude is comparable to other medicinal products that have already been granted a Marketing Authorisation for the indication GAD.

The MAH states that in the adult studies, patients with current diagnoses of any of the Axis I disorders of major depressive disorder (MDD), social phobia, panic disorder with or without agoraphobia, acute stress disorder, obsessive compulsive disorder, posttraumatic stress disorder, anorexia, bulimia, and/or delirium, dementia, amnesic, and other clinically significant cognitive disorders, were excluded.

Although patients with an MDD diagnosis (as well as other axis I disorders) were presumably excluded, baseline HAM-D scores are high (baseline HAM-D scores in the studies, indicate that the patients were having at least mild depressive symptoms on average). In addition, during the course of the trials considerable improvements in HAM-D were observed. In most studies there was a statistically significant and clinical relevant improvement on the HAM- D that seem to be parallel with the improvement on the HAM-A. Therefore the CHMP requested the MAH to disentangle effect on anxiety from effect on depression i.e. to demonstrate that improvements in HAM-A scores are not due to improvement in HAM-D scores, request to be responded by examining the improvement in HAM-A while controlling for improvements in HAM-D; the question was whether improvements in HAM-A are statistically significant and clinically relevant once changes in depression scores are controlled for (whether pregabalin is an effective compound in the treatment of GAD and improving depressive symptoms is secondary or that it is mainly effective as an antidepressant and improving GAD symptoms is secondary.)

The CHMP also requested the MAH to provided further information about:

- the inclusion/exclusion criteria with respect to maximum total HAM-D scores and/or HAM-D item 1 scores.
- the mean and spread of HAM-D total scores and HAM-D item 1 scores at baseline in each study.

The MAH explained that the effect of pregabalin seen on reduction of anxiety in patients diagnosed with GAD was not due to improvement in depression:

- Analysis of the data and published literature show that HAM-A and HAM-D total scores are highly correlated due to a substantial overlap in items on the scales. These scales are instruments that have been separately validated in patients who have either been diagnosed with anxiety (HAM-A) or depression (HAM-D).
- Improvement in HAM-A is not consistently related to the HAM-D score at baseline.
- Even when adjusting for the changes seen in HAM-D scores changes in HAM-A still favour pregabalin over placebo.
- The Mini-International Neuropsychiatric Interview (MINI) a validated structured psychiatric interview, was used to diagnose patients for the studies, therefore no patients with major depression were included in the study (only patients with GAD were included). There were no inclusion/exclusion criteria for HAM-D scores specified in the protocols; however, the Raskin Depression Scale total score had to be ≤ 7 and the Covi Anxiety Scale total score ≥ 9 to insure predominance of anxiety symptoms over depression symptoms.
- The mean and spread of HAM-D total scores at baseline were similar across treatment groups within each study and were also comparable across studies. The majority of patients had baseline HAM-D Item 1 scores of 0 or 1.

There is a high comorbidity between GAD and MDD and analysis of the data and published literature show that HAM-A and HAM-D total scores are highly correlated. The GAD CHMP guideline recommends to include only patients with a low HAM-D score. Nevertheless in the pivotal studies the MAH allowed patients with at least mild depressive score leading. Moreover because the HAM-D scores are treatment-dependent it cannot be properly used as a covariate in a model.

Moreover the MAH presented data showing that there is no consistent pattern of lower or higher HAM-D baseline having greater HAM-A response. The MAH also presented the HAM-D Item 1 (depressed mood) at baseline (most patients had 0's and 1 on this item (> 70%)).

In view of the above it can be concluded that the comorbidity is an important issue in GAD, especially comorbidity with MDD. From the data submitted by the MAH the CHMP is of the opinion that the effect seen on the HAM-A is not driven by an antidepressant effect. This question has therefore been resolved.

Table 1: Efficacy results in the short-term pregabalin studies

Studies	*Treatments**: n (ITT)*	*Withdrawals Total*	*adv ev.*	*inefficacy*	*Mean Baseline HAMA*	*Mean improvement on the HAMA*	*Mean psychic factor improvement of the HAMA,*	*% HAMA/responder/ % CGI responders*		*Remission HAMA ≤ 7*	*HAM-D score Baseline*	*Endpoint*
021	*Placebo: 64*	*28%*	*10%*	*1%*	*22.9*	*- 6.82*	*-4.0*	*27%*	*28%*	*11%*	*13.3*	*-2.5*
	PGB 150 mg TID: 68	*10%*	*3%*	*3%*	*23.4*	*-9.24**	*-5.1*	*29%*	*37%*	*19%*	*14.2*	*-4.2**
	PGB 600 mg TID: 68	*30%*	*20%*	*3%*	*23.2*	*-10.25**	*-5.7**	*46%**	*47%**	*25%**	*13.6*	*-5.3**
	LO 6 mg TID: 62	*41%*	*30%*	*2%*	*23.6*	*-11.96**	*-6.2**	*61%**	*57%**	*32%**	*13.9*	*-4.9**
025	*Placebo: 67*	*24%*	*11%*	*3%*	*23.9*	*-7.86*	*-3.9*	*36%*	*37%*	*21%*	*15.9*	*-3.1*
	PGB 150 mg TID: 66	*21%*	*9%*	*6%*	*25.5*	*-9.19*	*-5.0*	*39%*	*42%*	*11%*	*15.9*	*-4.7*
	PGB 600 mg TID: 69	*34%*	*27%*	*1%*	*24.4*	*-9.25*	*-4.9*	*42%*	*45%*	*20%*	*15.6*	*-5.2**
	LO 6 mg TID: 64	*54%*	*41%*	*3%*	*24.3*	*-7.63*	*-4.0*	*30%*	*41%*	*19%*	*15.5*	*-3.6*
026	*Placebo: 66*	*28%*	*6%*	*5%*	*24.8*	*-9.27*	*-5.1*	*44%*	*42%*	*17%*	*13.0*	*-4.2*
	PGB 150 mg TID: 69	*24%*	*7%*	*0%*	*24.9*	*-10.89*	*-6.0*	*52%*	*48%*	*22%*	*12.8*	*-5.5*
	PGB 600 mg TID: 61	*30%*	*19%*	*2%*	*25.4*	*-13.17**	*-7.4**	*59%*	*49%*	*31%**	*13.8*	*-6.2**
	LO 6 mg TID: 64	*47%*	*35%*	*2%*	*24.7*	*-11.62**	*-6.2*	*55%*	*56%*	*27%**	*14.0*	*-5.6*
083	*Placebo: 85*	*29%*	*11%*	*33%*	*24*	*-8.35*	*-4.3*	*34%*	*31%*	*18%*	*13.1*	*-2.7*
	PGB 300 mg TID: 89	*11%*	*3%*	*0%*	*25*	*-12.25**	*-6.6**	*61%**	*61%**	*27%*	*12.8*	*-5.6**
	PGB 450 mg TID: 87	*20%*	*8%*	*1%*	*25*	*-11.00**	*-6.3**	*47%*	*44%*	*24%*	*13.3*	*-4.4**
	PBG 600 mg TID: 85	*26%*	*14%*	*1%*	*25*	*-11.79**	*-6.3**	*53%**	*51%**	*26%*	*13.1*	*-4.3**
	LO 6 mg TID: 88	*27%*	*13%*	*0%*	*25*	*-10.91**	*-6.0**	*43%*	*45% **	*27%*	*13.4*	*-4.9**
085	*Placebo: 83*	*29%*	*8%*	*2%*	*25*	*-9.29*	*-4.9*	*34%*	*34%*	*15%*	*14*	*-3.1*
	PGB 200 mg BID: 75	*30%*	*9%*	*0%*	*26*	*-12.42**	*-6.6**	*56%**	*56%**	*21%*	*14*	*-5.8**
	PGB 400 mg BID: 85	*28%*	*11%*	*2%*	*26*	*-12.94**	*-6.7**	*55%**	*55%**	*28%**	*14*	*-5.5**
	PBG 450 mg TID: 85	*25%*	*13%*	*2%*	*25*	*12.43**	*-6.3**	*53%**	*59%**	*22%*	*14*	*-4.8**
087	*Placebo: 100*	*19%*	*11%*	*2%*	*27.4*	*-11.6*	*-5.9*	*45%*	*42%*	*23%*	*no*	*-3.0*
	PGB 400 mg BID: 94	*17%*	*7%*	*2%*	*26.3*	*-14.68**	*-7.7**	*61%**	*56%**	*34%*	*data*	*-3.4**
	PGB 600 mg BID: 104	*26%*	*14%*	*2%*	*26.5*	*-14.12**	*-7.7**	*58%*	*58%**	*38%*		*-4.9**
	Venla 75 mg BID: 110	*30%*	*20%*	*4%*	*26.0*	*-14.08**	*-7.8**	*62%**	*61%**	*36%*		*-5.1*
												*-4.0**
O90-152	*PLA: 95*	*28%*	*9%*	*7%*	*26.2*	*-10.65*	*-5.6*	*39%*	*48%*	*No data*	*no*	*-4.0*
ELDERLY	*ALL PGB: 171*	*25%*	*11%*	*4%*	*26.7*	*-12.84**	*-7.0**	*53%*	*58%*		*data*	*-5.5**

HAMA responder: ;patient who had at least a 50% improvement in HAM-A from baseline

PBG = pregabalin, Venla = Venlafaxine,
Pa = psychic anxiety
** statistically significant difference between active and placebo groups: p-value ≤ 0.05*
*** the dosage stated is the total daily dose followed by the number of gifts*

1.c Dose

The MAH initially proposed the following wording for section 4.2 of the SPC (Posology and Method of Administration):

"The dose range is 150 to 600 mg per day given as two divided doses.
Pregabalin treatment can be started with a dose of 150mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300mg per day after 1 week. Following an additional week the dosage may be increased to 450mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week."

To substantiate the BID (twice daily) dosage regimen the MAH stated that in Study 085, BID dosing with 200 and 400 mg/day achieved significant improvement of anxiety symptoms as measured by the change from baseline in HAM-A total scores compared with placebo. Both doses of pregabalin were also significantly better than placebo as measured by HAM-A responder rate changes from baseline in the HAM-A Psychic Anxiety and Somatic Anxiety subscales at endpoint and Clinical Global Impression of Change (CGIC) responder rate (see table 1).

Effects of pregabalin administered BID versus TID were compared by looking at the primary and secondary efficacy results for 400 mg/day taken BID versus 450 mg/day taken three times daily (TID), and for 600 mg/day BID versus 600 mg/day TID. In general, pregabalin given BID produced comparable effects to equivalent TID doses. Based on the primary efficacy analysis (see table 1), HAM-A improvements were similar for both 400 mg/day BID and 450 mg/day TID. For the 600 mg/day dose, HAM-A improvements were similar for both regimes. In general, as with the HAM-A change scores, 400 mg/day BID had slightly better effects on the secondary parameters than 450 mg/day TID. For 600 mg/day, TID dosing produced slightly better effects on some secondary parameters in some studies compared with 600 mg/day BID.

In most studies pregabalin 450 mg/day taken TID does not seem to be an effective dose and also 600 mg/day given by TID is not always better than placebo. A TID regimen does not seem to differ from a BID regimen concerning efficacy (see table1). Therefore the CHMP is the opinion that the proposed text by the MAH is acceptable. However, the general sentence in section 4.2 of the SPC stating that the product can be given BID or TID is also relevant for this indication. Therefore the following wording in the section 4.2 of the SPC is endorsed by the CHMP:

"The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.
Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week."

1.d Early onset of action

The MAH claimed that the effect of pregabalin is observed starting from week 1:
"Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1."

To substantiate this claim the MAH investigated the following:
1. The time to Onset of Sustained HAM-A Improvement at 30%
Time to onset of sustained HAM-A improvement was examined in several short-term studies. Sustained HAM-A improvement, defined as a $\geq$ 30% reduction from baseline in HAM-A total score that is sustained for the remainder of the study, was compared between treatment groups. Comparisons were done using log-rank statistics in all studies except for Study 087, which used the Cox proportional hazards model. Every pregabalin treatment group, except for pregabalin 400 mg/day in Study 087, demonstrated a significantly shorter time to onset of sustained improvement than the placebo group at the 0.05 significance level.

2. The Early Onset of Effect

Analyses were planned to examine early onset of effectiveness. The objective was to investigate if pregabalin is effective in providing sustained improvement as early as Week 1. This was done by comparing rates of sustained response (defined as a 30% or a 50% improvement in HAM-A at Week 1 which was sustained to the end of treatment) between placebo and each active treatment. In most cases, for both the 30% and the 50% criteria, pregabalin treatment groups achieved statistical significance indicating that pregabalin is effective as early as Week 1 in treating GAD.

For those comparisons that did not reach statistical significance, the responder rates for pregabalin were higher than placebo for all but 1 comparison (study 026, 150 mg/day). The elderly study 090/152did not achieve statistical significance. However it should be noted that at week 1, patients were on 150 mg/day only for 3 days.

The MAH did the analysis on the Intention to Treat (ITT) population. To demonstrate sustained response the completers should be analysed and secondary the ITT population. Moreover studies with a duration of 8 weeks are really necessary to substantiate this claim. Therefore, the CHMP considered that the early onset of action could not be granted upon this analysis and this question was addressed to the MAH.

Two types of evaluations were performed: 'Time to Onset' and 'Early Onset of Effect':

- The first evaluation, time to onset of sustained HAM-A improvement, supported the primary hypothesis that pregabalin is an effective treatment and consistently leads to improvement earlier than placebo.
- The latter analyses showed that pregabalin is effective in providing sustained improvement in the HAM-A total score as early as Week 1 of treatment.

In response to the CHMP's request to better substantiate sustained response of pregabalin by performing analyses on the completers, the MAH has evaluated the 'Early Onset of Effect' on this group in the short-term controlled GAD studies. These new analyses provided further evidence that pregabalin provides sustained improvement in GAD as early as Week 1 of treatment.

Regarding the duration of short-term trials in the GAD programme, although the recently issued CHMP guideline CHMP/EWP/4284/02 recommends that the duration of short-term trials for GAD should be at least 8 weeks, the short-term studies in the clinical development programme were planned and designed during the period 1998-1999, prior to the issuance of the draft CHMP guidelines (September 2003) and in line with the 4 to 6 weeks duration requirements for short-term GAD studies at the time. However to demonstrate sustained response in the absence of short-term studies of 8 weeks duration the MAH has analysed the sustained nature of the anti-anxiety response to pregabalin between 4 and 6 weeks in the three short-term controlled trials of greater than 4 weeks duration (Studies 085, 087 & 090/152). By exploring the temporal relationship of the response it can determined if there is any evidence that the effect seen in these studies would be compromised in longer studies. This was accomplished by plotting the change at Week 4 versus the change at Week 6 for patients with both a Week 4 and Week 6 change score. The sustained response data between 6 and 8 weeks in the controlled elderly study, Study 90/152 was investigated in a similar manner.

Studies 085, 087 and 090/152 demonstrate that the Week 4 HAM-A change scores of patients on pregabalin are highly predictive of their Week 6 HAM-A change scores in all of the three studies. These figures demonstrate that the effect seen at Week 6 is very similar to that seen at Week 4 for most patients.

The MAH presented the completers analysis (see table 2) as an addition to the ITT analysis and demonstrated that early onset of effect globally occurred more in the active compound groups than in the placebo-groups. Moreover in the study where venlafaxine - 75 mg BID (Study 087) was used as an active comparator pregabalin 600 mg/ day (BID) showed early onset of effect in contrast to venlafaxine 75 mg.

Although the answer from the MAH concerning the duration of the short-term studies (< 8 weeks may be too short to demonstrate early onset of effect) did not seem very relevant (no reduction of effect between 4 weeks and 6 weeks) the CHMP considers that the above-mentioned objection is resolved. The claim in section 5.1: "*Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1*" is acceptable to the CHMP.

Table 2. Results of Early Onset of Effect Analyses by Study - Completers

Study (Pregabalin Dose and [Regimen])	Statistical Outcome – 30% Sustained Efficacy Starting at Week1[a]		Statistical Outcome – 50% Sustained Efficacy Starting at Week1[a]	
	p-value	N (%)	p-value	N (%)
Study 021				
placebo		6 (12.2%)		1 (2.0%)
PGB 150 mg/day [TID]	ND[c]	16 (25.8%)	ND[c]	3 (4.8%)
PGB 600 mg/day [TID]	0.0001*	25 (50.0%)	0.0594	7 (14.0%)
Lorazepam	<0.0001*	28 (70.0%)	0.0044*	9 (22.5%)
Study 026				
placebo		22 (47.8%)		2 (4.4%)
PGB 150 mg/day [TID]	ND[b]	20 (38.5%)	ND[b]	8 (15.4%)
PGB 600 mg/day [TID]	0.7896	23 (50.0%)	0.0072*	12 (26.1%)
Lorazepam	0.2913	23 (63.9%)	0.0001*	14 (38.9%)
Study 083				
placebo		16 (24.6%)		1 (1.5%)
PGB 300 mg/day [TID]	0.0008*	41 (51.3%)	0.0002*	17 (21.3%)
PGB 450 mg/day [TID]	0.0565	28 (40.0%)	0.0047*	11 (15.7%)
PGB 600 mg/day [TID]	0.0014*	34 (51.5%)	0.0001*	16 (24.2%)
Alprazolam	0.1223	21 (33.9%)	0.0077*	9 (14.5%)
Study 085				
placebo		4 (6.7%)		1 (1.7%)
PGB 200 mg/day [TID]	<0.0001*	27 (51.9%)	0.0002*	13 (25.0%)
PGB 400 mg/day [TID]	<0.0001*	32 (53.3%)	0.0165*	9 (15.0%)
PGB 450 mg/day [TID]	<0.0001*	31 (48.4%)	0.0089*	10 (15.6%)
Study 087				
placebo		16 (19.8%)		3 (3.7%)
PGB 400 mg/day [BID]	0.3348	23 (28.4%)	0.3281	7 (8.6%)
PGB 600 mg/day [BID]	0.0167*	31 (38.3%)	0.0086*	14 (17.3%)
Venlafaxine	ND[c]	17 (21.5%)	ND[c]	3 (3.8%)
Study 090/152				
placebo		17 (24.6%)		1 (1.5%)
PGB [BID or TID]	ND[c]	36 (27.3%)	ND[c]	3 (2.3%)

PGB = Pregabalin; * Statistically significant difference from placebo ($p < 0.05$).
[a] Study 025 is not included as the comparator in this study failed to demonstrate improvement in HAM-A total score
[b] Evaluation of Early Onset of Effect failed as endpoint was not significant.
[c] Evaluation of Early Onset of Effect failed as Week 1 mean was not significant.
ND - Sustained responder analysis was not done since HAM-A change score analysis (endpoint or week 1) was not significant.

2. Long-term efficacy

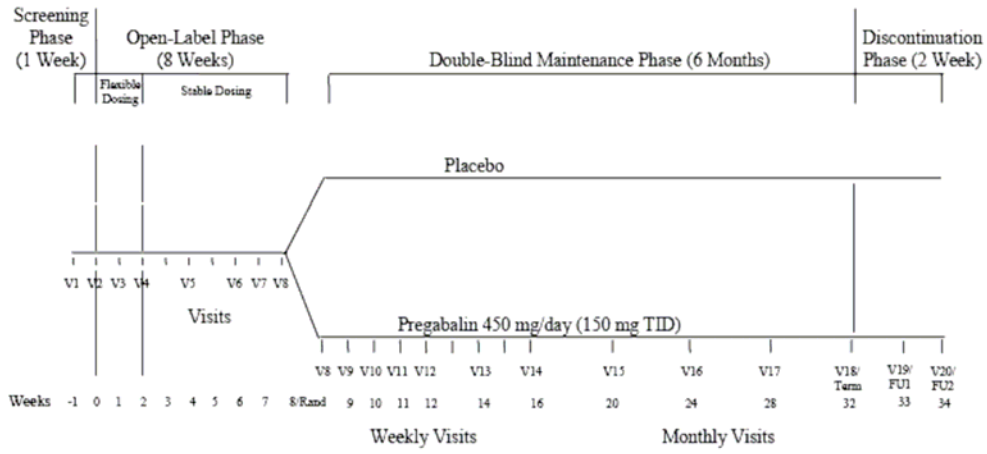
Pregabalin's maintenance of efficacy was evaluated in a randomized, double-blind, fixed-dose, placebo-controlled, parallel-group, multicenter study that followed a standard relapse prevention design.

2.a Study design

The study consisted of 4 phases (see figure 10 below):

- a 1-week screening phase,
- a 8-week open-label acute phase in which all patients received pregabalin,
- a 6-month double-blind maintenance phase in which patients received either placebo or pregabalin 450 mg/day, and
- a 2-week discontinuation assessment phase.

Figure 10. Study Design (Study 088)



At the start of the open-label phase, patients received 300 mg/day (total daily dose, administered TID) for the first 3 days and 450 mg/day (TID) for 4 days. Dosage adjustments for intolerance could be made during the second week of treatment only. Any patient who could not tolerate the 450 mg/day dose by the end of Week 2 was discontinued from the study.

For the remainder of the open-label phase, all patients received the fixed dose of 450 mg/day pregabalin. If patients met the entry criteria (HAM-A total score ≤ 11 and ≥ 50% reduction from open-label baseline in HAM-A total score at 2 of the last 3 open-label visits) for the double-blind maintenance phase, they were then randomly assigned to placebo or pregabalin.

The initial double-blind treatment for patients randomized to placebo was a taper from pregabalin (300 mg/day for 3 days). Double-blind treatment continued for up to 6 months or until patients met study exit criteria.

In the discontinuation phase, study medication was reduced to 300 mg/day (TID) for 3 days before it was discontinued. Patients who discontinued or completed the double-blind phase were eligible to enroll in the open-label Study 084.

2.b Patient population

Eligible patients were men or nonpregnant women, ≥ 18 years of age with the diagnosis of GAD who were recruited from the general outpatient population. The primary parameter was time to relapse. Relapse was defined as removal of the patient from the double-blind maintenance phase for any of the following 3 reasons:

1. fulfillment of the study entry criteria of observer-rated HAM-A (≥ 20) and Mini-International Neuropsychiatric Interview (MINI) diagnostic criteria of GAD (excluding duration) at 2 successive visits 1 week apart;
2. a score of "much worse" (score of 6) or "very much worse" (score of 7) on the CGI-I scale and meeting the criteria (excluding duration) for GAD assessed by the MINI at 2 successive visits 1 week apart; or
3. worsening anxiety symptoms such that immediate intervention was needed per the clinical judgment of the principal investigator.

Patients who completed 6 months of treatment, patients who were withdrawn for other reasons (adverse events, noncompliance, withdrew consent, other/administrative reasons), and patients who were lost to follow up were categorized as "not relapsed".

2.c Analysis

For the primary analysis, Kaplan-Meier estimates of time to relapse of GAD were calculated separately for the placebo and pregabalin treatment groups. The treatment groups were compared using the log-rank statistic. Observations were treated as right-censored for patients who completed the 6-month double-blind maintenance phase or who withdrew early due to non-compliance, adverse events, withdrawal of consent, other/administrative reasons, or who were lost to follow-up.

A total of 859 patients were screened, 624 entered the open-label phase, 339 entered the double-blind phase and 239 completed the double-blind phase (see table 23 below). Two hundred thirty five patients entered and 205 completed the discontinuation phase. The ITT population comprised 338 patients since one of the 339 randomized patients did not take study medication.

Table 23. Summary of Patient Disposition for Study 088

	Treatment Group		
	Placebo	Pregabalin	All Patients
Entered Screening			859
Withdrawn During Screening			233
Entered Open-Label Phase			624[a]
Withdrawn During Open-Label			285
Completed Open Label			339
Entered Double-Blind Phase	170	169	339
ITT	170	168[b]	338
Withdrawn During Double-Blind	38 (22.4)	61 (36.3)	99 (29.3)
Lack of Compliance	1 (0.6)	4 (2.4)	5 (1.5)
Adverse Event	4 (2.4)	10 (6.0)	14 (4.1)
Other	16 (9.4)	27 (16.1)	43[c] (12.7)
Lost to Follow-Up	10 (5.9)	13 (7.7)	23 (6.8)
Patient Withdrew Consent	7 (4.1)	7 (4.2)	14 (4.1)
Completed Double-Blind	132 (77.6)	107 (63.7)	239 (70.7)
Lack of Efficacy (Relapse)	111 (65.3)	71 (42.3)	182 (53.8)
HAM-A /MINI criteria	33 (19.4)	23 (13.7)	56 (16.6)
CGI-I/MINI criteria	32 (18.8)	20 (11.9)	52 (15.4)
Investigator's judgment	46 (27.1)	28 (16.7)	74 (21.9)
Completed 6 Months Treatment	21 (12.4)	36 (21.4)	57 (16.9)
Entered Discontinuation Phase	126	109	235
Completed Discontinuation Phase	112 (65.9)	93 (55.4)	205 (60.7)

Source: CSR 088, In-Text Table 4.
ITT = Intent-to-treat; HAM-A = Hamilton Anxiety Rating Scale;
MINI = MINI International Psychiatric Interview; CGI-I = Clinical global impression of improvement.

[a] All patients who received at least 1 dose of study medication during this phase; 2 patients completed screening but did not take a dose of open-label study medication.

[b] One patient was randomized to the pregabalin treatment group but didn't take study medication.

[c] Includes 37 patients (12 placebo, 25 pregabalin) required to withdraw due to study closure in Feb 2001.

During the 6-month double-blind maintenance phase, time to relapse of GAD was significantly longer for patients treated with pregabalin than placebo ($p = 0.0001$). A total of 111 (65%) of placebo-treated patients relapsed compared with 71 (42%) of pregabalin-treated patients (see figure 11 below).

Based on Kaplan-Meier estimates of time-to-event, 25% of placebo-treated patients had relapsed by Day 14 whereas 25% of the pregabalin patients had relapsed by Day 25 and 50% of the placebo patients had relapsed by Day 23 whereas, by Day 116, 50% of pregabalin group still had not relapsed.

For the placebo group, the last relapse was on Day 153, at this time there were 23 patients left of whom 21 completed 6 months of treatment. In the pregabalin group the last relapse was on Day 116, at this time there were 50 patients left of whom 36 completed 6 months of treatment. A secondary analysis expanding the definition of relapse was carried out. In addition to the patients defined as relapsers in the primary analysis, patients who withdrew due to an adverse event (AE) or noncompliance were categorized as relapsers. Using these criteria, time to relapse was significantly longer in the pregabalin treatment group compared with placebo. Results are presented in the table 24 below.

Figure 11. Kaplan Meier Plot of Time to Relapse

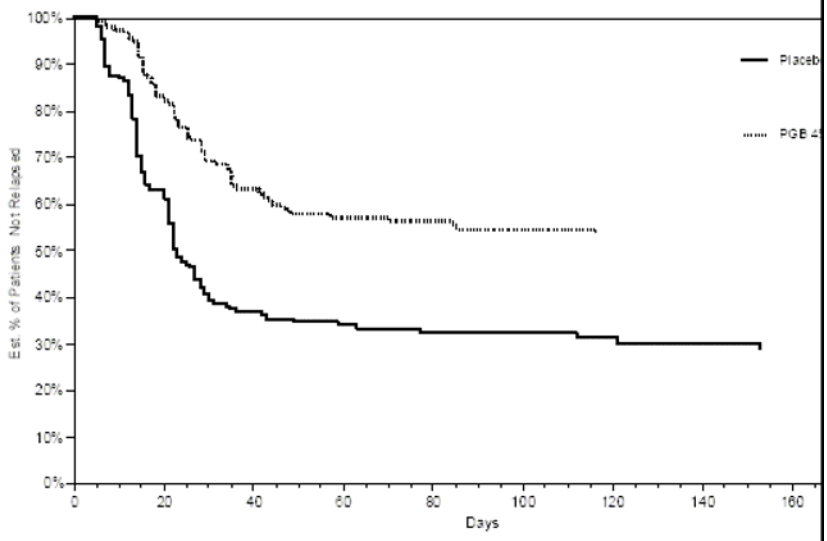


Table 24. Summary of Kaplan-Meier Estimates of Time-to-Relapse of GAD (Days)

Treatment	N	1st Quartile (Days)	95% CI (Days)	Median	95% CI
Primary Analysis					
Placebo	170	14	13 to 15	23	21 to 28
Pregabalin	168	25	22 to 34	NA	NA
Secondary Analyses[a]					
Placebo	170	14	13 to 15	22	21 to 28
Pregabalin	168	23	21 to 29	79	44 to NA

Source: CSR 088, In-Text Table 12
GAD = generalized anxiety disorder; CI = Confidence interval;
NA = Not applicable as 50% of patients had not yet relapsed;
AE = Adverse event.
[a] For this analysis, the 'relapse' population included patients who withdrew for any reason listed for the primary analysis or withdrew due to an AE or noncompliance.

In Study 088, the secondary endpoints of HAM-A change score, HAM-D change score and Clinical Global Impression of Severity (CGI-S) were analyzed using an ANCOVA statistical model; CGI-I responder analysis was assessed by logistic regression. At endpoint, treatment differences from placebo were –4.64, -2.68, -0.63 for the HAM-A change score, HAM-D change score and CGI-S, respectively. Each result was statistically different from placebo ($p < 0.0002$).

At endpoint, 64% of the placebo patients were CGI-I non responders versus 43% of the pregabalin group. A post hoc analysis of time to relapse was performed using a definition of relapse, which takes into consideration the possible confounding of medication discontinuation effects, and relapse during the first 2 weeks of the double-blind phase. Relapse was defined as in the primary analysis with the following exceptions:

- all patients removed from the double-blind phase for any reason during the first week were considered non-relapsers;
- patients removed from the double-blind phase during the second week were considered to have relapsed only if the reason for withdrawal was “investigator judgment.”

Using this definition, time to relapse continued to be significantly longer for patients treated with pregabalin 450 mg/day compared with placebo (p=0.0008). Based on Kaplan-Meier estimates of time-to-event, 25% of placebo-treated patients relapsed by Day 22 compared with Day 35 for the pregabalin group.

Based on the above data the long-term efficacy was not shown unequivocally. The MAH claimed that relapse prevention was demonstrated by means of a well-conducted placebo controlled relapse prevention study with duration of the double blind period of 6 months. The CHMP is of the opinion that this study was positive for the relapse criteria as defined in the study. However, the third reason for relapse was: *worsening anxiety symptoms such that immediate intervention was needed per the clinical judgment of the principal investigator*. This criterion seemed to be the largest contribution to the positive result of this study. The CHMP guideline, however, states that "worsening or relapse has to be defined in the protocol and should be a clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits."

Reason 1 (HAMA/MINI criteria) seemed to comply with the CHMP guideline criterion. 19 % of the placebo treated patients relapsed according to this criterion, while 14% of the pregabalin patients relapsed. To overcome this result the CHMP requested the MAH to submit the HAM-A data of all patients at relapse and use that for a new relapse analysis: the MAH was requested to find out, analyse and submit the data related to what the HAM-A/ CGI-I score was at the moment the investigator judged that the patient was taken out of the study, in order to conclude on the concerning relapse prevention. In addition, an analysis in which all patients removed from the study during the first 2 weeks of the double blind period would not be considered as relapsers was requested by the CHMP.

i) *Analysis of the HAM-A data of all patients at relapse (new relapse analysis):*

The MAH responded that in the long-term relapse prevention study (Study 088), relapse was defined as patient discontinuation from the double-blind maintenance phase for any of the following 3 reasons:

1. Fulfilling study entry criteria of observer-rated HAM-A (≥ 20) and Mini-International Neuropsychiatric Interview (MINI) diagnostic criteria of GAD (excluding duration) at 2 successive visits 1 week apart;
2. Score of “much worse” (score of 6) or “very much worse” (score of 7) from double-blind baseline on the CGI-I and meeting diagnostic criteria (excluding duration) for GAD as assessed by the MINI at 2 successive visits 1 week apart;
3. Worsening anxiety symptoms that necessitated immediate intervention per the clinical judgment of the principal investigator.

In view of the concern raised by the CHMP regarding investigator judgement as a method for diagnosis of relapse, the MAH has performed analyses using the HAM-A score as a sole measure for determining relapse. Relapse was defined as the first occurrence of HAM-A total score ≥ 20 excluding baseline and follow-up as per the CHMP guidelines. Investigator judgment and CGI-C scores were not considered reasons for relapse. This definition is the same as the first criteria specified above with the exception that there is not the requirement of confirmation at 2 successive visits.

Results of this analysis demonstrate that there was a statistically significant difference in time–to-relapse for pregabalin compared to placebo (p<0.0001). Overall relapse occurred earlier and more frequently in the placebo group (see figure a and table b below).

Using HAM–A scores ≥ 20 as the sole criteria for relapse in Study 088, 58% of the placebo group relapsed (99/170 patients) compared to only 40% in the pregabalin group (67/168 patients). Table b below provides a summary of the Kaplan Meier estimates of time to relapse of GAD, where relapse is defined as a HAM-A score ≥ 20.

Figure a - Kaplan - Meier plot for Time to Relapse in Study 088.

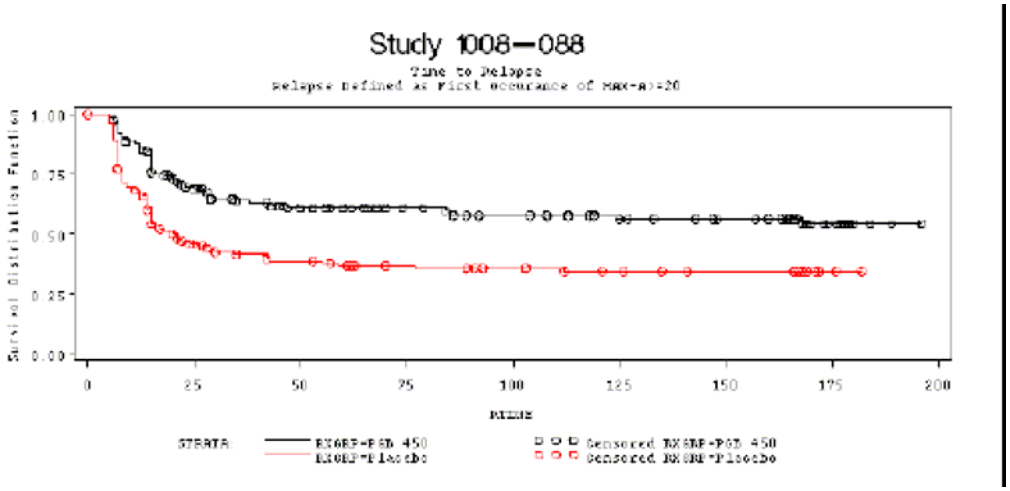


Table b - Summary of Kaplan-Meier Estimates of Time-to-Relapse of GAD. Relapse Defined as First Occurrence of HAM- ≥ 20 in Study 088

Treatment	N	Time To Relapse (Days)			
		1st Quartile	95% CI	Median	95% CI
Placebo	170	8	(7, 12)	20	(15, 34)
Pregabalin 450 mg/day	168	18	(15, 28)	NA	NA
log-rank test: p<0.0001					

For patients who were determined to be relapsed by investigator judgment, the majority had HAM-A scores ≥ 20. This data, summarised in table c below, describes the frequency and percentage of patients having HAM-A≥ 20 or CGI-C scores ≥ 6 at time of relapse for each protocol-defined relapse status/reason. The "investigator judgment" relapse decision is very strongly linked to a relevant increase of symptoms, scored on a validated rating scale, as indicated by the large proportion of patients with HAM-A scores > 20. These summaries demonstrate that for all reasons the relapse were consistently based on clinical relevant increase of symptoms, scored on a validated rating scale at one or more visits.

Table c - Frequency and percentage of patients having HAM-A ≥ 20 or CGI-C score ≥ 6 for each protocol-defined relapse status/reason in Study 088

Relapse Status/Reason	N	HAM-A≥20 n(%)	CGIC≥6 (worse, very much worse) n(%)
HAM-A/MINI	56	56 (100%)	52 (93%)
CGIC/MINI	52	30 (58%)	52 (100%)
Investigator Judgment	74	56 (76%)	63 (85%)
Non-Relapsers	156	6 (4%)	11 (7%)

ii) *Analysis in which patients removed from the study during the first 2 weeks of the double blind period would not be considered as relapsers:*

An analysis that did not consider patients as relapsers during the first two weeks was conducted as requested by the CHMP. This analysis censored patients who either dropped out of the study or relapsed during the first two weeks and demonstrates that there was a statistically significant difference in time to relapse for pregabalin compared to placebo ($p<0.0142$).

Using HAM-A scores ≥ 20 as the sole criteria for relapse and removing all patients who were withdrawn during the first two weeks of double-blind, 41% of the placebo group relapsed (41/101 patients) compared to only 28% of the pregabalin group (39/138 patients). Overall relapse occurred earlier and more frequently in the placebo group (see table d and figure 2 below). This analysis shows that the long-term efficacy seen on pregabalin is evident even when the early relapsers are excluded.

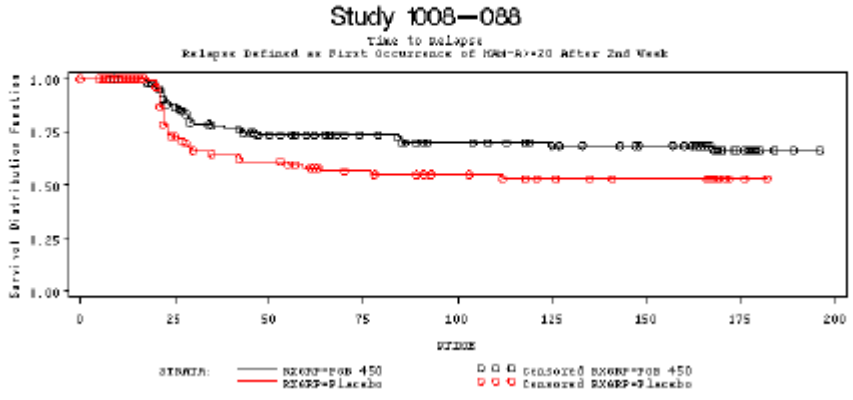
Table d - Relapse Defined as First Occurrence of HAM ≥ 20 After Second Week of Double Blind in Study 088

Summary of Kaplan-Meier Estimates of Time-to-Relapse of GAD Relapse Defined as First Occurrence of HAM-A≥20 After Second Week of Double-blind

Treatment	N	Time To Relapse (Days)			
		1st Quartile	95% CI	Median	95% CI
Placebo	170	23	(22, 34)	NA	NA
Pregabalin 450	168	43	(29, NA)	NA	NA

log-rank test: p<0.0142

Fig 2 Kaplan - Meier plot for Time to Relapse in Study 088 with Relapse Defined as First Occurrence of HAM ≥ 20 After Second Week



The MAH concluded that these additional analyses of relapse prevention data in Study 088 using HAM-A scores ≥ 20 as the sole criterion for relapse, further demonstrate that pregabalin is effective in preventing relapse of GAD, and maintaining both symptom reduction and improved functioning when given for up to 6 months. In addition, the MAH stated that most patients who relapsed based on investigator judgment indicated clinical relevant increases of symptoms.

By means of the above-mentioned analyses that complete the original analysis, the CHMP is of the opinion that the relapse prevention was sufficiently demonstrated for pregabalin in GAD.

3.2 Clinical safety

The safety profile of the product is based on the AEs reported in the previous mentioned clinical studies:

3.2.a AEs in the short-term studies

The table 17 below presents the adverse events for the adult GAD studies.

The most frequently reported treatment-related adverse events in pregabalin treated subjects during the short-term controlled adult GAD studies were CNS events: mainly dizziness and somnolence. These two adverse events were the two most frequent severe events reported and were the most frequent adverse events associated with discontinuation (see table 17). Somnolence was also the most frequently reported treatment-related adverse event reported for lorazepam (53.4%) and alprazolam (41.9%), although nausea was the most frequently reported event for venlafaxine (27.4%). The pattern of frequently reported adverse events in pregabalin treated subjects with GAD was similar to that seen in the overall safety database for the randomised controlled pregabalin studies for all indications (reported in the original MAA) i.e. the adverse reactions summarised in Section 4.8 of the currently approved SPC.

Adverse events, whether treatment related or not, that were reported with an incidence of at least 5% and with a higher incidence than placebo in the controlled adult GAD studies are dizziness, somnolence, dry mouth, asthenia, amblyopia, peripheral oedema, thinking abnormal and weight gain. This was similar for both the controlled studies for all indications (original MAA) and the controlled adult GAD studies. Few adverse events were considered to be severe in intensity in either study populations. Therefore the adverse event profile in controlled adult GAD studies as stated above is similar to that of the controlled studies in all indications that was presented in the original MAA.

Table 17. Summary of Adverse Events (>5%) for Controlled Adult GAD Studies

	Placebo (N=484)				Pregabalin (N=1149)			
	AC		TR	Discont	AC		TR	Discont
	Incidence (%)	Severe (%)	Incidence (%)	%	Incidence (%)	Severe (%)	Incidence (%)	%
Overall incid	**70.5**	**9.5**	**53.1**	**9.3***	**82.2**	**11.8**	**73.3**	**11.3***
Dizziness	8.9	0.2	7.9	0.6	31.1	2.3	30.2	2.5
Somnolence	11.6	0.4	11.4	1.2	29.2	2.6	28.6	4.0
Headache	16.7	1.9	12.8	0.6	16.6	1.7	13.3	1.0
Dry mouth	6.4	0.2	5.8	0	15.1	0.4	14.5	0.3
Infection	8.1	0.2	0	0.2	10.2	0.3	0.4	0
Nausea	9.3	0.4	7.2	0.6	9.8	0.6	8.3	1.0
Amblyopia	2.1	0	1.9	0	7.5	0.3	7.0	0.9
Incoordination	1.0	0	1.0	0	7.1	0.3	7.0	1.0
Asthenia	7.0	0.2	6.2	0.6	6.7	0.6	6.4	0.5
Constipation	3.1	0.4	2.9	0.2	6.2	0.8	5.6	0.2
Thinking abnormal	2.3	0.6	2.3	0.2	6.1	0.8	6.0	1.1
Diarrhoea	8.5	1.0	6.2	0.4	5.1	0.1	3.7	0.3

Key: AC = All causality; TR = treatment-related; Incid = incidence; Discont = discontinued
* discontinuation from double blind phase of studies.

As in the overall database of controlled pregabalin studies in all indications (original MAA), the incidence of treatment related adverse events in the 150 mg/day pregabalin treatment group in the controlled adult GAD studies was similar to that seen with placebo. Although dizziness and somnolence were the most common adverse events, the incidence was varied with no clear relationship to dose or regimen. The profile of treatment related adverse events in the controlled adult GAD studies was very similar to the treatment related adverse event profile of pregabalin in the controlled pregabalin studies in all indications presented in the original MAA. Dry mouth occurred more frequently in the GAD patient population than in the other study populations (neuropathic pain and epilepsy), whereas peripheral oedema, unlike in the neuropathic pain population, was not a common adverse event in the GAD population.

The CHMP considered that the adverse events in the short-term studies are well-known pregabalin adverse events. However symptoms like depersonalistion, euphoria, nervousness, abnormal thinking and amnesia may reflect benzodiazepine -like adverse events. The MAH was requested to explain these symptoms more extensively and explain why pregablin should not be considered as a benzodiazephine-like compound. This question was addressed by the CHMP to the MAH along with additional questions on the rebound effect (see below item vi, paragraph 5 of section 3.3.2.b)

1. Controlled study in elderly GAD (Study 090/152)

Although the adverse event profile for the short-term controlled elderly GAD study (Study 090/152) was similar to short-term controlled adult GAD studies, the incidence of the common adverse events were lower in Study 090/152. The flexible dosing regime used in the controlled elderly GAD study may explain this reduced incidence. The most common treatment-related adverse events reported during Study 090/152 were CNS events: mainly dizziness and somnolence, the incidences of which were much less in the elderly study. The incidence of dizziness in Study 090/152 was 16.4% compared with 30.2% in the controlled pregabalin adult GAD studies. Like wise the incidence of somnolence in Study 090/152 was 13.0% compared with 28.6% in the controlled adult GAD studies.

2. Controlled study in elderly GAD vs Elderly patients in Controlled studies in all Indications

The safety profile of Study 090/152 was also very similar to that seen in the patients who were ≥65 yrs of age in the controlled pregabalin studies in all indications, most of whom were patients with neuropathic pain (original MAA). The majority of all causality events were reported at a lower frequency in pregabalin patients in controlled elderly GAD (Study 090/152) compared with elderly patients in controlled pregabalin studies in all indications (original MAA).

3. Discontinuations due to Adverse Events

Similar percentages of placebo- and pregabalin-treated patients completed the controlled adult GAD studies (74% and 77%, respectively). The proportion of subjects withdrawing early from the controlled adult GAD studies due to adverse events in the placebo and pregabalin groups was also similar (9.3% and 11.3%, respectively).

The most frequent adverse events leading to withdrawal in all pregabalin-treated patients in the controlled adult GAD studies were somnolence (4%) and dizziness (2.5%); in these studies all other adverse events that led to discontinuation occurred with a frequency of ≥ 1% in all pregabalin-treated patients. There did not appear to be any clear pregabalin dose-response on the frequency of discontinuations; however, the withdrawal rate in patients treated with pregabalin 600 mg/day was almost twice that in patients treated with any other dose of pregabalin.
Similar percentages of placebo and pregabalin-treated patients completed the controlled elderly GAD study (72% and 75%, respectively). The proportion of subjects withdrawing early from the controlled elderly GAD study due to adverse events in the placebo and pregabalin groups was also similar (9.4% and 10.7%, respectively), and overall this was similar to that seen in the controlled adult GAD studies. Pregabalin is tolerated as well in the elderly population as it is in the younger population.

As in the controlled adult studies, the most frequent adverse events leading to withdrawal in all pregabalin-treated patients in the controlled elderly GAD study (Study 090/152) were dizziness (8 patients, 4.5%) and somnolence (2 patients, 1%).

4. Discontinuation Emergent Adverse Events and PWC data

The potential discontinuation effects of pregabalin were investigated in the GAD studies using discontinuation emergent signs and symptoms (DESS) and the Physician's Withdrawal Checklist (PWC).
Adverse events appearing during taper of study drug and up to 2 weeks after this were termed discontinuation emergent and assessed in the DESS evaluation. If an adverse event occurred with greater severity during the 2 week follow-up period, this was also termed discontinuation emergent and was counted in the DESS assessment. In the short-term controlled adult GAD studies, the

percentage of pregabalin-treated patients with at least one DESS adverse event (16.3%) was low and similar to that of placebo-treated patients (12.6%).
PWC data were evaluated prospectively in the controlled adult GAD studies. The PWC, which was developed specifically to measure symptoms of benzodiazepine withdrawal, rates 20 common symptoms of withdrawal and was used to determine whether patients experienced withdrawal symptoms after cessation of study medication. The symptoms measured are based on those that are potentially related to benzodiazepine withdrawal: gastrointestinal, mood, sleep, motor, somatic, perception and cognition.

In the table below (table 2) the most relevant results of the PWC in the short-term studies are presented. The CHMP is of the opinion that the below results indicate that pregabalin causes withdrawal symptoms.

Table 2: PWC score in the short-term placebo controlled studies

Studies	*Treatments: n (ITT)*	*N* *Begin of the taper phase / end of the taper phase*	*PWC* *Begin of the taper phase*	*PWC* *End of the taper phase*
021	*Placebo: 64*	*58/51*	*11.6*	*11.9*
	PGB 150 mg TID: 68	*63/63*	*11.5*	*13.4*
	PGB 600 mg TID: 68	*60/57*	*11.0*	*13.9*
	LO 6 mg TID: 62	*58/44*	*11.7*	*15.4**
025	*Placebo: 67*	*58/53*	*10.0*	*10,2*
	PGB 150 mg TID: 66	*61/56*	*9.8*	*10.3*
	PGB 600 mg TID: 69	*61/55*	*9.6*	*12.1*
	LO 6 mg TID: 64	*58/45*	*10.9*	*12.7*
026	*Placebo: 66*	*54/44*	*9.9*	*8.7*
	PGB 150 mg TID: 69	*61/55*	*8.6*	*10.5**
	PGB 600 mg TID: 61	*56/44*	*7.0*	*10.1**
	LO 6 mg TID: 64	*54/42*	*10.5*	*11.3**
083	*Placebo: 85*	*65/66?*	*14.2*	*15.8*
	PGB 300 mg TID: 89	*74/70*	*15.2*	*14.8*
	PGB 450 mg TID: 87	*62/68?*	*15.7*	*15.2*
	PBG 600 mg TID: 85	*67/57*	*15.1*	*19.4**
	LO 6 mg TID: 88	*68/65*	*15.3*	*15.7*
085	*Placebo: 83*	*65/64*	*11.3*	*12.1*
	PGB 200 mg BID: 75	*53/50*	*11.4*	*14.0*
	PGB 400 mg BID: 85	*64/64*	*11.6*	*14.6**
	PBG 450 mg TID: 85	*65/65*	*13.2*	*17.8**
087	*Placebo: 100*	*96/88*	*10.1*	*8.9*
	PGB 400 mg BID: 94	*92/86*	*7.8*	*9.5**
	PGB 600 mg BID: 104	*101/95*	*8.7*	*10.1**
	Venla 75 mg BID: 110	*107/96*	*7.9*	*8.3*

* statistically significant difference from placebo

5. Serious Adverse Events (Controlled GAD Studies (Adults & Elderly):

The frequency of serious adverse events in the pregabalin treatment groups in the controlled adult GAD studies was low (0% to 1.8%; overall 0.6%), and comparable to the placebo group (1.2%). Serious adverse events frequency did not increase with increased pregabalin dose. One serious adverse event, accidental injury, was reported by 2 pregabalin-treated patients. The other serious adverse events reported by pregabalin-treated patients were anxiety, bone pain, cardiomyopathy, dizziness, gastrointestinal disorder, and myocardial infarction. There were no deaths in any of the controlled adult GAD studies. The frequency of treatment-related serious adverse events in the controlled adult GAD studies was similar between placebo and pregabalin.
The overall incidence of serious adverse events in the controlled elderly GAD study was similar between the pregabalin treated patients (4%) compared with the placebo treated patients (3%). The serious adverse events reported by the pregabalin treated patients were accidental injury, chest pain, cerebral haemorrhage, palpitation, vascular disorder, ventricular tachycardia, anxiety, dizziness, somnolence and skin ulcer. The patient who suffered from a cerebral haemorrhage died but the investigator did not consider the event to be related to pregabalin treatment.

3.2.b Adverse events in Long-Term GAD Studies (Studies 088, 084 &100):

1. GAD - long-term safety

i) Study 088

The long-term safety of GAD has been assessed in Study 088, in which up to 8 months pregabalin treatment was administered: 8 weeks open-label, before randomisation to either pregabalin or placebo for up to 6 months.

The incidence of CNS adverse events in the open-label phase of Study 088 was similar to that of the six controlled adult GAD studies, with the most common adverse events (>10%) of: somnolence, dizziness, dry mouth, euphoria, weight gain, headache, incoordination, infection and thinking abnormal.

For most adverse events, there did not seem to be an increase in risk with continued pregabalin treatment, as the incidence of all adverse events was lower in the double-blind phase compared with open-label phase. Adverse events that started during the double-blind phase and had a higher incidence among pregabalin-treated patients than in open-label included infection, sinusitis and somnolence. In addition, some events that occurred in <5% of patients, were reported with higher frequency in the pregabalin treatment group: weight gain, back pain, depression, amblyopia and paraesthesia. The incidence of dizziness in this phase of the study was markedly reduced in comparison with the open-label phase, being reported in 4.2% of pregabalin-treated patients compared with 2.9% of placebo-treated patients.

DESS were also assessed in Study 088 and were assessed in the double-blind phase of the study (including the 3-day taper off medication for subjects switching from pregabalin to placebo). These DESS were measured in patients not relapsing, therefore with long exposure to pregabalin (8 months). The incidence of DESS was similar between placebo (18.8%) and pregabalin (17.9%) and was similar to that observed in the short-term studies.

PWC change scores were also assessed in Study 088, and scores of 2.05 and 1.87 were observed at the first and second follow-up visits, respectively after long-term treatment with pregabalin at 450 mg/day. This was statistically significantly different from placebo, the difference at both follow-up visits was comparable to the scores noted after short-term treatment.

The CHMP is of the opinion that the long-term PWC results, like the short-term results indicate that pregabalin may cause withdrawal symptoms after stopping.

ii) Other Studies – 084 and 100

Seven hundred and ninety seven patients from the controlled adult and elderly studies entered the open-label studies (084 & 100), which make up the uncontrolled GAD studies. Within this uncontrolled GAD studies the patient population was split according to age for the safety assessment. In patients ≥ 65 yrs of age, 157/683 patients (23%) had not been previously exposed to pregabalin. Overall, the adverse event profile in the patients ≥ 65 yrs of age in these studies was similar to that of the controlled adult GAD studies. Although dizziness and somnolence were again the two most common adverse events, the incidences were lower in these studies than the controlled adult studies. As patients were dosed flexibly in the open-label studies, guided by the physician's clinical assessment of efficacy and tolerability, this might have contributed to the apparent improved tolerability. The adverse event profile in the patients ≥ 65 yrs of age was similar to that of the controlled adult GAD studies. Dizziness and somnolence had similar incidences to the younger age group and lower than that of the controlled adult studies.

2. Serious Adverse Events

In Study 088, 2 patients (0.3%) experienced serious adverse events during open-label treatment and 3 patients (1.8%), all pregabalin-treated, experienced serious adverse events during the double-blind phase. The serious adverse events (preferred terms) that occurred during pregabalin treatment were cardiovascular disorder, ovarian cancer, grand mal convulsion, breast carcinoma, and hernia (one each). One patient, who later entered treatment and received placebo during double-blind, experienced a serious adverse event (pancreatitis) during screening. None of these adverse events were considered related to treatment.

The overall frequency of serious adverse events in uncontrolled Adult GAD (Studies 084 & 100) patients was 3.5%, (24/683 patients). Overdose was the only SAE reported in more than one pregabalin patient. The pattern of these SAEs was generally reflective of the pattern in the overall combined controlled and uncontrolled GAD studies (mainly cardiac, vascular, or CNS events and carcinomas). Three SAEs (0.4%) were considered related to pregabalin treatment in uncontrolled adult GAD patients (neoplasm, rectal disorder and convulsion).

3. Deaths

In the pregabalin GAD clinical program there were 3 deaths in total. One patient each died in Study 090/152, Study 181 and in Study 100. None of these deaths were considered to be related to pregabalin treatment. However no details about these deaths were available for assessment. The overall incidence of death was 0.14% or 4.2 deaths per 1000 patient years.

4. GAD Studies – Other Safety Parameters

The results of the clinical laboratory analyses for controlled GAD studies were comparable to those for the overall profile of pregabalin presented in the original MAA. Overall, few GAD patients met the MAH-defined very high or very low laboratory criteria during the controlled or open-label studies.
As with the overall vital sign profile observed with pregabalin, there were no clinically significant changes observed specifically in the GAD population. The results of the analyses of change in body weight are consistent with the overall safety profile of pregabalin presented previously in the original MAA.

In general, there were no clinically significant ECG findings in any of the GAD studies, similar to the overall product safety profile noted across all indications.

3.2.c Special safety topics

The CHMP guidance on generalised anxiety disorder identifies a number of adverse reactions of particular interest for medicinal products intended for the treatment of generalized anxiety disorder, such as rebound/withdrawal/dependence, key central nervous system adverse reactions and those of other body systems. These events were considered within the initial MAA for pregabalin in the treatment of neuropathic pain and partial seizures.

Review of the current safety data from the overall GAD development programme has not identified any clinically significant differences in the profile of these events within the GAD patient population compared with the neuropathic pain and partial seizure patient populations. The additional events reviewed below are those, which are considered most pertinent to this application and the intended patient population.

1. Oedema

Oedema, which is mainly peripheral oedema, is associated with the use of pregabalin. Importantly, it is not clearly indicative of any underlying changes in renal or cardiac function, and does appear to be responsive to diuretic therapy. GAD patients do not seem to have an increased incidence of oedema compared with some other patient populations e.g. neuropathic pain.

2. Weight gain

As presented in the original Marketing Authorisation application, pregabalin associated weight gain is time and dose dependent. It is more likely with the higher doses of pregabalin, it remains with chronic therapy and ceases, or reverses, on discontinuing therapy. Weight gain in pregabalin treated GAD patients was similar to that seen in pregabalin treated patients in all indications (original MAA). In the integrated safety database, there was no evidence of sustained changes in blood pressure or glucose dysregulation, no evidence of any drug-drug or drug-disease interaction and 1% of patients discontinued treatment because of weight gain. Most patients did not gain more than 10% of their baseline weight whilst on therapy; however, weight gain of greater than 25% occurred in approximately 1% of patients. Patients experiencing weight gain may be at greater risk for obesity related morbidities.

3. Dependence potential, tolerance and withdrawal

Drugs that are active in the central nervous system are sometimes associated with withdrawal symptoms after discontinuation of treatment. In some cases, withdrawal symptoms can lead to potential for dependence as patients attempt to avert the unpleasant discontinuation symptoms. The presence of discontinuation symptoms is not always a precursor to dependence. As an analgesic and anxiolytic agent, pregabalin has been investigated extensively for any dependence or abuse potential in a specific clinical study and in preclinical models. In addition, withdrawal and discontinuation symptoms have been examined in the clinical studies, as well as tolerance, to ensure a comprehensive review of any potential signals for dependence.

In animal studies, pregabalin did not produce the subjective and reinforcing effects associated with drugs of abuse. Specifically with regard to subjective effects, pregabalin did not produce benzodiazepine-like discriminative stimulus effects in rhesus monkeys trained to discriminate midazolam from vehicle, nor did it maintain IV self-administration in rhesus monkeys. Unlike morphine, pregabalin did not induce conditioned place preference or drug discrimination in rats, suggesting low reinforcing effects.

The subjective effects of pregabalin were evaluated in a study conducted in 15 recreational alcohol/sedative users. This was a single dose crossover study with 5 treatment arms – placebo, diazepam 15 mg, diazepam 30 mg, pregabalin 200 mg, and pregabalin 450 mg. Pregabalin did produce subjective effects on a wide variety of measures that were different than placebo as would be expected from any psychotherapeutic agent. However, the pregabalin responses were divergent from
those seen with diazepam and indicate that pregabalin does not share a profile of abuse liability similar to benzodiazepines.

The lack of any dependence or abuse signal from the gabapentin post-marketing database provides confidence that pregabalin would similarly not be associated with abuse or dependence. For thoroughness, the pregabalin database has been examined extensively for any signs of dependence potential in accordance with established indicators.

4. Tolerance

Tolerance is defined as loss of pharmacological effect despite constant dosing of a drug. Tolerance to the therapeutic effect of a compound may contribute to the potential for misuse of the compound when it is marketed. Patients who experience tolerance may inappropriately, and perhaps without medical supervision, escalate their medication dose in an attempt to re-establish the drug effect.

The possible development of tolerance was analysed in the neuropathic pain studies because they provided the most extensive open-label long-term treatment data.

Although open-label data are available for GAD and provide some data for interpretation on tolerance, the neuropathic pain population was considered more likely to develop measurable tolerance and possibly abuse.
No evidence of significant dose escalation was detected in these patients, suggesting that tolerance does not develop to the analgesic effects of pregabalin. Similarly, in the open-label psychiatric Studies 084 and 100, subjects did not escalate their doses, which can be interpreted as a lack of tolerance to the anxiolytic effects of pregabalin.

5. Discontinuation Phenomena

The two specific measures previously defined (DESS and PWC) prospectively allow to investigate potential withdrawal symptoms. DESS data were analysed prospectively in the controlled GAD studies and in DPN Study 040. PWC data were evaluated prospectively in the controlled adult GAD studies.
Adverse events appearing during taper of study drug and up to 2 weeks after this were termed discontinuation emergent and assessed in the DESS analysis. If an adverse event occurred with greater severity during the 2 week follow-up period, this was also termed discontinuation emergent and was counted in the DESS assessment. For the *post hoc* assessment of the full 49-study dataset, DESS were defined as any adverse event that began or increased in intensity within 10 days after the last full dose of study medication. In the healthy volunteer Study 072, withdrawal emergent signs and symptoms (WESS) were collected per protocol.
The PWC, developed specifically to measure symptoms of benzodiazepine withdrawal, rates 20 common symptoms of withdrawal and was used to determine whether patients experienced withdrawal symptoms after cessation of study medication. The symptoms measured are based on those that are potentially related to benzodiazepine withdrawal: gastrointestinal, mood, sleep, motor, somatic, perception and cognition. Patient PWC change scores were calculated by subtracting the patient's last study visit PWC score (on full dose of study medication) from the follow-up visit PWC score. A positive PWC change score was indicative of an increase in withdrawal symptoms following taper of study medication. The taper period varied across studies from 3 to 7 days, and patients receiving pregabalin 200 and 300 mg/day did not taper but stopped their study medication abruptly.

6. Discontinuation Emergent Signs and Symptoms

Overall, DESS events of insomnia, nausea, diarrhoea and headache were reported in small numbers of patients after discontinuation of short or long-term treatment with pregabalin in the GAD studies. However, in DPN Study 040, none of these events were reported in the pregabalin-treated group. These DESS are similar to the discontinuation symptoms seen with cessation of other CNS active compounds such as anti-depressants.
In a small sample of healthy volunteers exposed to pregabalin 450 to 600 mg/day for 14 weeks (Study 072), anxiety or nervousness were reported in 3 subjects following abrupt discontinuation of pregabalin, although the majority of subjects did not experience adverse events upon discontinuation of pregabalin.
The low level of DESS events and there being no evidence of patients having difficulty in discontinuing pregabalin during the protocol specified taper period of the studies leads to the conclusion that pregabalin does not appear to produce physiologic dependence beyond what might be associated with any unscheduled anxiolytic or antidepressant compound.

Physician Withdrawal Checklist.

PWC change scores of 12 to 25 have been observed with benzodiazepines and can be regarded as a potentially clinically significant indicator of a withdrawal syndrome. In the short-term adult studies of 4 to 6 weeks, PWC change scores for pregabalin-treated patients were generally small (<10 points), ranging from 1.36 to 9.41. The PWC total score was highly correlated with the HAM-A score ($p=0.0001$) prior to and after medication discontinuation in all studies, indicating that the PWC is measuring, in part, symptoms of anxiety. Clinically, a return of anxiety would be anticipated when an effective treatment is discontinued after short-term treatment of GAD. Assessment of the PWC

following long-term treatment with pregabalin allows a better comparison to withdrawal seen after long-term benzodiazepine treatment.
The effect on the PWC following long-term treatment with pregabalin was examined in Study 088, a relapse prevention study in which patients received pregabalin for up to 8 months. PWC change scores were low following discontinuation of pregabalin treatment in this study (2.05 at follow-up visit 1 and 1.87 at follow-up visit 2) and were comparable to those in the short-term studies, indicating that long-term pregabalin treatment does not result in more than mild withdrawal symptoms, just as those seen with short-term treatment. The PWC change scores of 12 to 25 seen with discontinuation of long-term benzodiazepine treatment are not seen with pregabalin.

The MAH stated that pregabalin does not appear to produce physiologic dependence beyond what might be associated with any unscheduled anxiolytic or antidepressant compound; these have been associated with generally mild discontinuation reaction syndromes. The MAH stated that this conclusion is supported by the mild effects observed in the rat dependence study, the low incidence of discontinuation-emergent adverse events and there being no evidence of patients having difficulty in discontinuing pregabalin during the protocol specified taper period of the studies.
As with all psychotropic medication, abrupt discontinuation should be avoided and this is reflected in recommended wording in the proposed SPC to guide the prescriber with an appropriate taper period following treatment.

However the CHMP did not agree with this conclusion. The studies allow a direct comparison of pregabalin with benzodiazepines (lorazepam) and venlafaxine:
- the short-term PWC results indicate that pregabalin has more or less the same properties concerning withdrawal phenomena as the benziodiazephines (lorazepam 6 mg) and venlafaxine (75 mg);
- the long-term PWC results also indicate withdrawal symptoms comparable to the short-term withdrawal symptoms.

The withdrawal phenomena observed from the PWC together with adverse events like depersonalistion, euphoria, nervousness, abnormal thinking and amnesia observed in the short-tem studies with pregabalin reflect some CNS-active properties that are also observed with benzodiazpines and other anxiolytic agents such as SSRIs and SNRIs. The MAH was requested to explain these results more extensively, including the rebound effect (see paragraph 3.3.2.d below).

7. Psychomotor effects: driving and operating machinery

Pregabalin is a CNS active drug associated most commonly with the adverse events of dizziness and somnolence. Therefore, individual patients should be advised against driving, operating machinery or undertaking potentially hazardous activities until each patient is familiar with how well they tolerate pregabalin treatment. This is reflected in the existing approved product information for neuropathic pain and epilepsy.

Three clinical pharmacology studies evaluated safety and the potential pharmacodynamic interaction between pregabalin and lorazepam, oxycodone, or ethanol, respectively, in healthy volunteers.
In addition, the cognitive and psychomotor effects of pregabalin, including the effect on driving ability and sleep, were assessed in 24 healthy subjects in Study 097.

The primary objective of this double-blind, placebo-controlled, cross-over study was to assess the effects of pregabalin (450 mg/day), relative to a standard benzodiazepine control (alprazolam, 3 mg/day), on cognitive and psychomotor function. Overall this study suggested that pregabalin is safe for use in ambulant patients performing the activities of everyday living, based on the lack of impairment on BRT (Brake Reaction Time) and lack of effect or mild impairment on other cognitive and psychomotor parameters. Although dizziness and somnolence were frequently reported adverse events, these events did not seem to impair significantly the ability to function. Overall, the combined psychomotor and cognitive function profile of pregabalin was unlike the profile exhibited by alprazolam; the psychometric profile of alprazolam was as expected for a benzodiazepine, and therefore alprazolam was an appropriate positive control.

8. Overdose

Data from the clinical pharmacology studies indicates that the 900 mg/day dose was generally well tolerated in healthy volunteers, but that it was associated with a higher incidence and duration of central nervous system adverse events. This finding limited the maximum dose explored in the Phase 2/3 programme and thus that in the proposed labelling: the maximum recommended daily dose of pregabalin is 600 mg/day.

For the purposes of this section, pregabalin overdoses were categorized in 2 ways: 1) overdoses of >600 mg that were reported in the dosing records during the Phase 2/3 trials, with a focus on those >900 mg/day, and 2) serious adverse events of overdose or suicide attempt involving pregabalin that were not recorded in the dosing records.

Based on the dosing records, 11 patients (≤0.005%) took pregabalin total daily dosages >600 mg/day during the combined controlled and uncontrolled GAD studies .These overdoses ranged from 650 to 1700 mg/day, with durations of 1 day to a maximum of 87 days. The majority of the adverse events reported during overdoses between >600 and 900 mg/day were mild in intensity, comparable to events observed with the patients' regularly scheduled doses, and without medically significant effects. Among the 2 patients who reported taking >900 mg/day (one of which was reported as a serious adverse event in the open-label extension study, Study 100), the events were mild or moderate in intensity and the patients recovered. No clinically significant abnormalities in physical examinations, vital signs, ECG, or clinical laboratory examinations were found after a review of all safety data collected from these patients.

One additional patient had serious adverse events that involved an overdose of pregabalin that was not recorded in the dosing record, with reported overdoses (by the patient or a relative) ranging from 1500 to 8000 mg. This patient also recovered.

There is no specific treatment in the event of overdose with pregabalin. Therefore, patients should be monitored and receive general supportive measures for at least 30 hours after ingestion of drug (half-life approximately 6 hours) or while symptoms and signs persist. It should also be noted that pregabalin is effectively removed from plasma by haemodialysis: over a four hour haemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%.

This is covered in the current section 4.9 of the approved SPC:

In overdoses up to 15 g, no unexpected adverse reactions were reported. Treatment of pregabalin overdose should include general supportive measures and may include haemodialysis if necessary (see section 4.2 Table 1).

3.2.d Conclusion on the original analysis and discussions:

1. Withdrawal and rebound symptoms

The adverse events in the short-term studies are the well-known pregabalin adverse events. However symptoms like depersonalisation, euphoria, nervousness, abnormal thinking and amnesia may reflect benzodiazepine-like adverse events. Based on the clinical data in the pivotal studies the MAH was requested by CHMP to discuss these effects and their relation to dependence and/or withdrawal.

The PWC short-term and long-term results indicate that pregabalin is a compound causing withdrawal symptoms after stopping. Historically data presented by the MAH are not relevant as the studies allow a direct comparison with benzodiazepines and venlafaxine. The withdrawal phenomena measured on the PWC, especially in the 600 mg dosage, seem to be comparable to benzodiazepines (lorazepam). In a single study ulitizing venlafaxine to assess assay sensitivity, the incidence of moderate to severe PWC symptoms in the pregabalin 600 mg dosage group were numerically greater than 75 mg of venlafaxine in 11 out of 20 items, while the converse was true in the remaining nine items. No statistically significant differences were noted between pregabalin and venlafaxine or placebo. A pooled analysis of all PWC data was requested by CHMP.

The MAH was requested to discuss the withdrawal symptoms thoroughly, especially in relation to the indication and duration of treatment, along with a detailed description on how this will be managed in the risk management plan.

The MAH responded that data do not support the conclusion that pregabalin has benzodiazepine-like properties and that the adverse events observed are common to other CNS-active agents. On the PWC, a scale that measures benzodiazepine-like effects, the increase in scores in short-term studies is similar for paroxetine, a non-benzodiazepine, and pregabalin (including the pregabalin 600 mg dose group), reflecting a return of anxiety.

The MAH stated that in short-term studies of 4 to 10 weeks, the PWC change scores for pregabalin-treated patients were generally small (< 5 points). These differences were much lower than the PWC change scores of 12 to 25 that are associated with discontinuation of long-term benzodiazepine treatment and are consistent with some return of anxiety.

The MAH confirmed that there was no increase in PWC change score for long-term treatment compared with short-term treatment, indicating that long-term treatment with pregabalin does not result in clinically significant medication discontinuation symptoms. Two studies evaluated the PWC in long-term treatment with pregabalin. Studies 1008-082 and 1008-088 were relapse prevention studies (450 mg/day of pregabalin per patient for up to 8 to 9 months). Least squares mean PWC change scores for pregabalin-treated patients in these studies were low and were comparable to change scores in the short-term studies (1.36 to 9.41 points). These differences were much lower than the PWC change scores of 12 to 25 that are associated with discontinuation of long-term benzodiazepine treatment and are consistent with some return of anxiety.

The MAH agreed that adverse events do occur on rapid or abrupt discontinuation. DESS were evaluated systematically and prospectively in all psychiatric studies in the Lyrica development program but were not collected in any epilepsy studies and were collected but analysed retrospectively in only one neuropathic pain study. The data from the 12 short-term double-blind controlled psychiatric studies is considered the most appropriate for inclusion in Section 4.8 of the SPC. This was reflected in the amendments made in the wording of the section 4.8 of the SPC (see section "changes to the product information"), as follows:

After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating, and dizziness. The patient should be informed about this at the start of the treatment.

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

The CHMP is in agreement with the above-proposed wording.

2. Post Hoc Analysis for Rebound Anxiety

The rebound anxiety, a feature of withdrawal syndromes, is an increase in the severity of anxiety symptoms to levels greater than pre-treatment after treatment is discontinued, but which lasts for a short duration that depends on the half-life of the drug. Rebound and relapse appear similar, but are differentiated by the severity and duration of symptoms:

- rebound anxiety occurs soon after plasma concentrations become subtherapeutic, and is associated with severe symptoms beyond baseline levels that rapidly return to termination values.
- relapse, the return of anxiety, would be expected to persist at all follow-up visits.

Short-term Study 1008-083 and long-term Study 1008- 088 were assessed post hoc for rebound anxiety, because both studies were designed with 2 follow-up visits, 1 week and 2 weeks after last full dose. Because of the short half-life of pregabalin, rebound anxiety would be observed at the first follow-up visit as elevated HAM-A score, but the HAM-A scores would return to closer to termination

values by the second follow up visit. Rebound anxiety is defined here as HAM-A score greater than or equal to the baseline value at the first follow-up visit with subsequent decrease in HAM-A score between the first and second follow-up visits.

Rebound Anxiety Analysis - Short-Term Study 1008-083: The MAH evaluated patients who completed the study and who had complete HAM-A data at baseline and at both follow-up visits; in this study patients were treated with placebo, pregabalin 300, 450, or 600 mg/day, or alprazolam 1.5 mg/day. One of 16 patients (6.3%) treated with placebo, 1 of 18 patients (5.6%) treated with pregabalin 300 mg/day, and 1 of 18 patients (5.6%) treated with pregabalin 450 mg/day had had a HAM-A total score greater than baseline at the first follow-up visit with a drop in their HAMA score between the first and second follow-up visits. However, for all 3 patients, the HAM-A total score at follow- up visit 2 did not return to termination visit values and thus is not consistent with rebound anxiety and is more consistent with a relapse of anxiety. No patient treated with pregabalin 600 mg/day had a pattern of HAM-A scores consistent with rebound anxiety; however, these patients were tapered over a longer period, so the follow-up visits may not have been timed properly to assess rebound anxiety.

Rebound Anxiety Analysis - Relapse prevention Study 1008-088: The MAH evaluated non-relapsing patients who received at least 3 months of treatment in the double-blind phase and had complete HAM-A data at open-label baseline and at both follow-up visits; patients in this study received either placebo or pregabalin 450 mg/day. A pattern of HAM-A scores consistent with rebound anxiety was not observed in any of the non-relapsers with 3 months or more of exposure to placebo or pregabalin 450 mg/day. There is no evidence for rebound anxiety in patients receiving long-term treatment.

3. Conclusion on the secondary analyses (rebound and withdrawal symptoms)

Historical data are used as an argument to demonstrate that there is a difference between pregabalin and benzodiazepines in withdrawal symptoms but the CHMP considers that that the results from the short-term studies submitted allow a direct comparison between pregablin and benzodiazepines (lorazepam) showing no difference in withdrawal symptoms between pregabalin and lorazepam 6 mg. To demonstrate that there is no difference between paroxetine and pregablin in PWC score the MAH submitted a study in social phobia that was not in the original file and which is not assessed. Moreover it should be stressed that the PWC is an instrument that measures withdrawal symptoms (new symptoms after stopping). Anxiety is only one of the 34 items on this checklist.

The CHMP considered that the argument that there was no increase in PWC change score for long-term treatment compared with short-term treatment was not relevant. The long-term placebo-controlled relapse prevention studies 1008-082 (in patients with Social Phobia) and 1008-088 (in the GAD population) showed a statistically significant difference at both follow-up visits on the PWC change (indicating more withdrawal symptoms in the patients that stopped with pregabalin). The MAH compared these long-term results to historical data arguing that the PWC scores of the patients who stopped with pregabalin were low at follow-up but a direct comparison versus benzodiazepines in study 1008-082 and 1008-088 has not been investigated.

To answer the question concerning withdrawal after long-term use versus short-term use, the CHMP requested the MAH to compare the PWC scores in the placebo-group after randomization (after the short-term open label phase) with the PWC scores of the pregabalin group (after long-term treatment). The MAH was requested to submit these data for the studies 1008-082 and 1008-088. These data, however, cannot provide information about the tapering off; they are only informative about the issue of abrupt stopping.

In its response the MAH provided a comparison of PWC scores between patients who discontinued pregabalin treatment shortly after randomization and patients who followed longer-term treatment in study 1008-088, a comparison of DESS AEs between the first 2 weeks of the double-blind phase and the end of the double-blind phase in studies 1008-82 and 1008-88 (as well as the rebound anxiety data from short-term study 1008-083 and long-term study 1008-88).

The submitted information suggests that long-treatment with pregabalin does not increase the incidence and severity of discontinuation symptoms and that there is no evidence of rebound anxiety following pregabalin treatment. However, the CHMP does not consider the information presented conclusive and the issues need to be further investigated. To address this, the MAH was requested by the CHMP to make a commitment to conduct a post-authorisation safety study to investigate withdrawal symptoms, which will include an assessment of issues such as dose, duration, and rebound anxiety. A proposal for this study will be submitted to the CHMP for discussion in the 2nd quarter of 2006, as per the Risk Management Plan submitted by the MAH.

3.2.e Spontaneous reports

The following information was available from post-marketing surveillance:

- During the period covered by PSUR 1 (07 July 2004 to 06 January 2005), 3 cases of drug withdrawal syndrome were reported.
- During the period covered by PSUR 2 (07 January 2005 to 31 July 2005), there were 11 cases reporting withdrawal symptoms. The reporter did not confirm the withdrawal symptoms upon follow-up for one of the cases. Of the remaining 10 cases, 2 were assessed as serious. In three cases one week or more was allowed for a gradual reduction in pregabalin dose prior to discontinuation. Abrupt withdrawal with no reduction was noted in four cases. An assessment regarding pregabalin withdrawal symptoms in one case was confounded by amitriptyline withdrawal on the same day. Symptoms reported more than once include the following: insomnia, diarrhoea, sweating, shivering, depression, and itching.
- A report of pregabalin withdrawal encephalopathy and splenial edema was identified through a search of the literature. This case is quite different from the possible signal currently of interest, namely withdrawal symptoms similar to those observed with benzodiazepines.

3.2.f Suicidality

Since the issue of suicidality is being discussed as a general concern the CHMP requested the company to submit the data available on this matter and incorporate amendments in the SPC if appropriate.

The MAH considers that adverse events relating to suicide attempt occur at a very low frequency with pregabalin treatment, and on the whole, are not related to pregabalin treatment, but to the patients underlying medical history and therefore no change to the SPC is warranted. The MAH takes adverse events relating to attempted suicide very seriously and will continue to actively monitor such events.

The CHMP is of the opinion that at this moment no change to the SPC is warranted, but the final discussion on this will await the analysis the MAH is doing at present, as previously requested. The MAH will continue to actively monitor such events.

4 Pharmacovigilance

Risk Management plan

The MAH submitted a risk management plan, which was revised following comments from the CHMP.

Table Summary of the risk management plan:

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Weight gain	Routine Pharmacovigilance	Warning in section 4.4 regarding weight gain in diabetics and the need to adjust hypoglycaemic medications. Weight gain in section 4.8
Peripheral oedema	Routine Pharmacovigilance	Mentioned in section 4.8
Dizziness, somnolence and the potential for accidental injury	Routine Pharmacovigilance	Warning in section 4.4 regarding dizziness and somnolence and the risk of accidental injury. Warning in 4.7 on the ability to drive and use machines Mentioned in section 4.8
Ophthalmological safety	Routine Pharmacovigilance with use of targeted questionnaire for follow up. Ophthalmological safety study	Mentioned in section 4.8
Withdrawal effects	Routine Pharmacovigilance with use of data capture aid to collect additional information from spontaneous reports. Post authorisation safety study to investigate withdrawal symptoms	Warning in section 4.2 to withdraw treatment gradually. Warning in section 4.4 regarding possible symptoms following discontinuation of treatment. Warning in section 4.8
Haemangiosarcoma	Routine Pharmacovigilance	Discussed in section 5.3

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5. CHANGES TO THE PRODUCT INFORMATION

Changes to the Summary of Product Characteristics (SPC)

- Section 4.1

The MAH proposed the following text in the section 4.1 ("*Therapeutic indication*") of the SPC is:
LYRICA is indicated for the treatment of Generalised Anxiety Disorder (GAD) in adults.

The above wording is considered acceptable by the CHMP.

- Section 4.2

In the section 4.2 ("*Posology and method of administration*") of the SPC, the MAH proposed the following wording:

Generalised Anxiety Disorder
The dose range is 150 to 600 mg per day given as two divided doses.
Pregabalin treatment can be started with a dose of 150mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300mg per day after 1 week. Following an additional week the dosage may be increased to 450mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

In view of the scientific discussions, the CHMP considered that the following underlined amendments should be made:

Generalised Anxiety Disorder
The dose range is 150 to 600 mg per day given as two or three divided doses. The need for treatment should be reassessed regularly.
Pregabalin treatment can be started with a dose of 150 mg per day. Based on individual patient response and tolerability, the dosage may be increased to 300 mg per day after 1 week. Following an additional week the dosage may be increased to 450 mg per day. The maximum dosage of 600 mg per day may be achieved after an additional week.

The CHMP is of the opinion that the above wording is acceptable.

With regards to the discontinuation of pregabalin, the CHMP considered that the text can be shortened as mentioned in the scientific discussion, however the committee was of the opinion that 'independent of the indication' should be added to avoid confusion (as this text does not only apply for the indication GAD). In addition, following QRD-review, the MAH was requested to add a cross-reference to section 4.8. The MAH agreed with the CHMP conclusion and amended the wording accordingly:

Discontinuation of pregabalin
In accordance with current clinical practice, if pregabalin has to be discontinued ~~either in neuropathic pain, epilepsy or Generalised Anxiety Disorder~~, it is recommended this should be done gradually over a minimum of 1 week independent of the indication (see section 4.8).

Concerning the paragraph "Patients with renal impairment", the formula was amended following CHMP comments that European clinical-chemical laboratories will express their results of creatinine levels in µmol/l and not in mg/dl.

Concerning the paragraph "*Use in children and adolescents"*, the CHMP was of the opinion that the definitions of age should be stated more clearly in the text, therefore the CHMP requested that the age limit of adolescents (12 – 17 years of age) be mentioned as follows:

Use in children and adolescents ~~(12 to 17 years of age)~~
Lyrica is not recommended for use in children below the age of 12 years and adolescents (12 - 17 years of age) due to insufficient data on safety and efficacy (see section 5.3).
~~The safety and effectiveness of pregabalin in paediatric patients below the age of 12 years and adolescents has not been established.~~
~~The use in children is not recommended (see section 5.3)~~

The MAH was in agreement with the change suggested by the CHMP and amended the wording accordingly.

- Section 4.4

The statement concerning lactose was moved to the end of section 4.4 as requested by the CHMP. Furthermore, the CHMP was of the opinion that the 2 following clarifications should be made into this section:

- after discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been shown. The CHMP considered that the patients populations should be informed about this at the start of the treatment and this should be reflected in the SPC.
- In addition concerning the discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin. The CHMP is of the opinion that this should be reflected accordingly.

Following discussion with the MAH, the CHMP agreed that the anxiety term could be removed based on the fact that it occurs at in incidence lower than placebo. Therefore the following wording was proposed by the CHMP (changes underlined) and then agreed by the MAH:

"*……After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain, sweating and dizziness. The patient should be informed about this at the start of the treatment.*

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. "

- Section 4.6

The following wording was suggested by the MAH:

~~*Therefore, Lyrica should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus*~~

Lyrica should not be used during pregnancy unless clearly necessary (for example if the benefit to the mother clearly outweighs the potential risk to the foetus).

The CHMP was of the opinion that the underlined section should be added and the crossed-out wording *'For example'* should be removed, leading to the following wording:

"*…..Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).*"

The MAH agreed with the comment from CHMP and amended the wording accordingly.

- Section 4.7

In view of the scientific discussion with regards to the Psychomotor effects: driving and operating machinery, the following amendment in the section 4.7 of the SPC was proposed by the MAH and adopted by the CHMP:
Lyrica may cause dizziness and somnolence and therefore may influence the ability to drive or use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medication affects their ability to perform these activities.

- Section 4.8

The CHMP was of the opinion that the order of the undesirable effects within each frequency should be modified in order to take into account the decreasing seriousness of the adverse events.

In addition, the CHMP requested that the undesirable effect *"Amnesia"* to be added as a common ADR under the Nervous system disorders. In the original application the term "amnesia" was included within "memory impairment" and the summation of the two frequencies led to "memory impairment" being described as a common adverse event. This was originally proposed by the MAH to simplify the use of the table. In the view of the CHMP request, the MAH proposed to split the two terms to comply with the request. However, to follow the frequency convention, the MAH proposed that the term *"memory impairment"* remains in "common" adverse event but *"amnesia"* (with an incidence of 0.6%) would be classed as an "uncommon" adverse event.

The proposed revised section of the table in section 4.8 for under the Nervous system disorders is shown below:

Nervous system disorders	
Very Common	*Dizziness, somnolence*
Common	*Ataxia, ~~disturbance in attention,~~ coordination abnormal, ~~memory impairment,~~ tremor, dysarthria, memory impairment, disturbance in attention, paraesthesia*
Uncommon	*Syncope, stupor, myoclonus, psychomotor hyperactivity, ~~cognitive disorder,~~ visual field defect, ageusia, dyskinesia, dizziness postural, intention tremor, nystagmus, ~~hypoaesthesia, visual field defect, nystagmus,~~ cognitive disorder, speech disorder, ~~myoclonus,~~ hyporeflexia, ~~dyskinesia,~~ hypoaesthesia, <u>amnesia,</u> ~~psychomotor hyperactivity, dizziness postural,~~ hyperaesthesia, ~~ageusia,~~ burning sensation, ~~intention tremor, stupor, syncope.~~*

In addition, the CHMP requested to change the withdrawal section beneath the adverse event table in the section 4.8 to reflect the wording adopted in the section 4.4. Furthermore, an adapted proposal for section 4.8 (as for section 4.4 mentioned above) of the SPC concerning discontinuation was also submitted by the MAH. The proposed text is as follows:

*After discontinuation of short-term and long-term treatment with pregabalin withdrawal symptoms have been observed in some patients. The following events have been mentioned: insomnia, headache, nausea, diarrhoea, flu syndrome, nervousness, depression, pain**,** sweating, and dizziness. The patient should be informed about this at the start of the treatment.*

Concerning discontinuation of long-term treatment of pregabalin there are no data of the incidence and severity of withdrawal symptoms in relation to duration of use and dosage of pregabalin.

The CHMP is in agreement with the above-proposed wording.

- Section 5.1

The following text was proposed by the MAH:

Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled studies of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study of 8 months duration.
Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1. Pregabalin has also been shown to significantly reduce scores on both the HAM-A Psychic and Somatic subscales.
In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

Based on the scientific discussion, the CHMP is of the opinion that the above wording should be amended as follows:
Generalised Anxiety Disorder
Pregabalin has been studied in 6 controlled studies of 4-6 week duration, an elderly study of 8 week duration and a long-term relapse prevention study ~~of 8 months duration~~ <u>with a double blind relapse prevention phase of 6 months duration</u>.
Relief of the symptoms of GAD as reflected by the Hamilton Anxiety Rating Scale (HAM-A) was observed by Week 1. ~~Pregabalin has also been shown to significantly reduce scores on both the HAM-A Psychic and Somatic subscales.~~
In controlled clinical trials (4-8 week duration) 52% of the pregabalin treated patients and 38% of the patients on placebo had at least a 50% improvement in HAM-A total score from baseline to endpoint.

- Other changes to the SPC

Other QRD and minor changes were introduced in some sections of the SPC, with the agreement of the CHMP.

Changes to the Package Leaflet (PL)

The PL was amended in accordance with the changes made in the SPC; any comments mentioned above for the SPC applicable for the PL were taken into account and the PL was amended accordingly. The CHMP is in agreement with the following wording in the sections of the PL mentioned below (underlined additions and deletion highlighted):

- Section 1 - ***WHAT LYRICA IS AND WHAT IT IS USED FOR***

Generalised Anxiety Disorder: *LYRICA is used to treat Generalised Anxiety Disorder (GAD). The symptoms of GAD are prolonged excessive anxiety and worry that are difficult to control. GAD can also cause restlessness or feeling keyed up or on edge, being easily fatigued, having difficulty concentrating or mind going blank, feeling irritable, having muscle tension or sleep disturbance. This is different to the stresses and strains of everyday life.*

Section 3 - ***HOW TO TAKE LYRICA***

Always take LYRICA exactly as your doctor has instructed you. You should check with your doctor or pharmacist if you are not ~~un~~sure.

Your doctor will determine what dose is appropriate for you.

Peripheral neuropathic pain, epilepsy or Generalised Anxiety Disorder: Take the number of capsules as instructed by your doctor.

If you forget to take LYRICA
It is important to take your LYRICA capsules regularly at the same time each day. If you forget to take a dose, take it as soon as you remember unless it is time for your next dose. In that case, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose~~. Do not take 2 doses at the same time to make up for the one you missed.~~

Amendments to the wording in the sections 1,2, 3, 4, 5 and 6 were suggested by the CHMP, to comply with the current version of the QRD template. The CHMP was in agreement with the related wording proposed by the MAH.

"User Consultation" of the package leaflet

According to the Articles 59(3) and 61(1) of the Directive 2001/83/EC, as amended, the CHMP requested the MAH to provide results of assessments carried out in cooperation with target patient groups on the package leaflet ('user consultation') or a justification for not performing such consultation.

The MAH provided a justification for not performing a Readability test at this time. The MAH stated that the changes to the PIL due to the proposed addition of Generalised Anxiety Disorder do not significantly change the readability. The CHMP considers this justification acceptable.

Changes to the Labelling

The labelling was changed in line with the current version of the QRD template. The MAH proposed changes, which were acceptable to the CHMP.

6 Overall conclusion and Benefit-risk assessment

Based on the review of the data on safety and efficacy, the CHMP considers that the variation application EMEA/H/C/546/II/04 for Lyrica (pregabalin), to include treatment of General Anxiety Disorder (GAD) is approvable. The safety profile of Lyrica for GAD is similar to the observed in the previously approved indications. However, the CHMP is of the opinion that withdrawal symptoms need to be monitored. The RMP includes a commitment to conduct a post-authorisation safety study to investigate withdrawal symptoms that will include an assessment of issues such as dose, duration, and rebound anxiety; a proposal for the post-authorisation study will be submitted for discussion in the 2nd quarter of 2006.

CONCLUSION

On 26 January 2006 the CHMP considered this type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet based on the observations and appropriate conclusions.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measure as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	Description	Due date[2]
Pharmacovigilance	Development activities: data associated with potential discontinuation symptoms from clinical trails will be reviewed during regularly scheduled safety review. A post-authorisation safety study to investigate withdrawal symptoms will be conducted and will include an assessment of issues such as dose, duration and rebound anxiety.	A proposal for the post-authorisation study will be submitted for discussion in the 2nd quarter of 2006.
Pharmacovigilance	The MAH will continue to monitor and assess the events by regularly scheduled safety reviews of patient data from the clinical development program and spontaneous post marketing reports (which will be prepared and submitted as appropriate). In addition, data capture aids have been developed to improve the quality of the data collected for vision related events and events associated with discontinuation symptoms.	To be included within Periodic Safety Update Reports

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.