London, 07 September 2006
Product name: **LYRICA**
Procedure no: **EMEA/H/C/000546/II/0007**

SCIENTIFIC DISCUSSION

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"* that received a positive opinion on 26 January 2006.

The MAH submitted on 13 January 2006 an application for Lyrica to add the indication central neuropathic pain in adults (procedure EMEA/H/C/H/C/546/II/07). The dose recommended ranges from 150 to 600 mg per day divided over two or three doses. This dose recommendation is the same as for peripheral neuropathic pain.

Neuropathic pain is defined as "Pain initiated or caused by a primary lesion or dysfunction in the nervous system". Neuropathic pains are divided into peripheral neuropathic pain due to lesion of the peripheral nervous system and central pain following lesions of the central nervous system.

In accordance to the guideline on neuropathic pain, efficacy in central neuropathic pain has to be shown separately from efficacy in peripheral neuropathic pain. For the claim "peripheral neuropathic pain", the efficacy of the tested drug should be shown in more than one clinical situation of peripheral neuropathic pain (e.g. post herpetic neuralgia, painful diabetic neuropathy). For the claim central neuropathic pain efficacy should be shown in a central pain model. The model however, should be justified. If for both peripheral and central neuropathic pain efficacy is demonstrated, the indication "general neuropathic pain" may be given.

Spinal cord injury may be considered a model for evaluating central neuropathic pain. However, the initial justification of this model by the MAH was poor and therefore subject to requests for additional information. The answers of the MAH were satisfactory. Hence the study, as performed, evaluates central neuropathic pain.

As part of this variation, the MAH has also submitted a new environmental risk assessment (ERA).

2. Non clinical aspects

The relevant pharmacological and toxicological aspects related to pregabalin development were addressed in previous assessments of the Lyrica file, indicated for epilepsy and peripheral neuropathic pain. The relevant pharmacodynamic aspects specific for the indication requested in the current variation is covered by the clinical information. No further non-clinical data is therefore required.

2.1 Pharmacology

No new non-clinical data have been submitted by the MAH; the non-clinical overview has not been updated.

In the original marketing application, the following results were reported that might be relevant to central neuropathic pain:

- Pregabalin given by intraperitoneal (i.p.) or intrathecal injection dose-dependently decreased thermal hyperalgesia induced by intrathecal injection of substance P and/or N-methyl-D-aspartate (NMDA).
- The ED50 values for i.p. and intrathecal administration of substance P were approximately 10 mg/kg and 10 µg/rat, respectively.
- Pregabalin at 30 mg/kg i.p. also prevented hyperalgesia induced by NMDA.

These results suggest pregabalin had a pharmacologic action relevant for analgesia directly on tissues of the spinal cord.

In view of existing clinical data demonstrating efficacy for central neuropathic pain, the lack of additional non-clinical is acceptable by the CHMP.

2.2 Environmental risk assessment

The Environmental Risk Assessment (ERA) provided does not suggest a risk to the environment posed by Lyrica. However, the base set requires an early life stage study in fish, which will be conducted as a follow-up measure. Once these data are available, the preliminary PEC/PNEC will be re-evaluated. Also, as a second follow-up measure, the MAH will investigate the viability of developing an analytical method with a lower LOQ, as appropriate. Pregabalin (CAS Number: 148553-50-8) has a molar mass of 159, and is water soluble at 20°C and pH 7.4 at 32 mg/L. The octanol-water partitioncoefficient logKow is -1.35 at pH 7.4 and pregabalin is hence not classified as persistent, bioaccumulative and toxic (PBT). The dissociation constants (pKa) are 4.2 for the carboxilyc acid, and 10.6 for the amine moiety of the molecule. For analytiacl verification in water a method using LC-MS-MS is available, the limit of quantification is 54 µg/L. The partition coefficient between water and sludge is determined at 13.3 L/kg (1/n 0.78); the corresponding partition coefficient between water and organic carbon is 42 L/kg. Pregabalin is not readily biodegradable and in a sludge die-away test primary degradation amounted to 18% in 21 days, whereby 1.7% mineralisation occurred. The standard acute NOEC, EC50 and LC50 for algae (P. subcapitata), daphnids (D. magna) and fish (O. mykiss) were all above water solubility (>32 mg/L). The acute EC50 of the N-acetylated pregabalin metabolite amounted to >600 mg/L. The 7-days NOEC for reproduction in daphnids (C. dubia) was below the lowest concentration tested, 0.46 mg/L. The early life stage test in fish was lacking and will be conducted as a follow-up measure. The EC50 in activated sludge is >0.1 mg/L; and the MIC in five microbial species of algae, bacteria and fungi (A. niger, T. viride, Nostoc spp. B. subtilis, C. perfringens)is 1000 mg/L.

3. - Clinical aspects

The MAH provided a GCP statement in the original variation dossier.

3.1 - Clinical pharmacology

Not applicable.

3.2 - Clinical efficacy

- Main study(ies)

One pivotal study (Study 125) was submitted: study 125 is a randomised placebo controlled trial in central neuropathic pain due to spinal cord injury. The trial lasted 12 weeks.

The design features of study 125 are summarised in the table below.

Study	Subjects	Design /Procedure	Study arms	Endpoints
Study 125 Efficacy study 2002-2004 Australia	Subjects with central neuropathic pain due to spinal cord injury	RD MC (8) DB PC PA Baseline 1 week Titration 3 weeks Fixed dose 9 weeks	Pregabalin (n= 70) Placebo (n= 67) Titration[A] Week 1 150 mg/day Week 2 300 mg/day Week 3 600 mg/day	Primary: Endpoint mean pain score "Key" secondary: - Pain sleep interference score - MOS sleep score - SF-MPQ VAS score - HADS anxiety score - PGIC score. Other secondary : - Weekly pain score - SF-MPQ -PPI Safety: AEs

[A] Titration was up to response, intolerance or maximal dose allowed i.e. 300 mg BID.
Legend: Db: Double–blind, HADS: Hospital Anxiety and Depression Scale, MOS:Medical Outcome Sleep scale, MC: Multi-centre, PA: parallel group design, PC: Placebo-controlled, PGIC: Patient's Global Impression of Change, SF-MPQ: Short-Form McGill Pain Questionnaire.

The patients included suffered from central neuropathic pain due to spinal cord injury (paraplegia/tetraplegia).
Main inclusion criteria were the presence of spinal cord injury stabilized for at least 6 months, presence of chronic neuropathic pain (i.e. the pain should be persistent for 3 months or fluctuating with remissions/relapses for at least 6 months) and a pain score > 40 mm on the SF-MPQ–VAS at baseline.

Main exclusion criteria were patients with severe pain due to other causes that cannot be distinguished from central neuropathic pain and patients who likely will be in need for treatment during the study period with drugs not permitted by the study protocol.

Concurrent co-medication needed (e.g. tricyclic antidepressants, benzodiapines) had to be kept constant during the study and should not be initiated during the study.

- Methods

The pain was assessed by means of an 11-point Likert scale ranging from 0 (= no pain) to 10 (= worst possible pain). The pain over the last 24 hours at awakening was daily scored by patient.

The primary efficacy variable was the weekly mean pain score at endpoint defined as the mean of the last seven post-randomization entries of the daily pain diary while on study drug including the day after the last day of dosing.
Efficacy analyses was based upon the intent-to-treat (ITT) population defined as all randomized patients who took at least one dose of study medication and had at least one post-randomization efficacy assessment on any efficacy scale.
The analytical method was ANCOVA controlling for study centre and adjusting for weekly mean pain score at baseline.

- Results

The main results are presented in the table below. Baseline features were homogenously distributed over the study arms except for the use of concurrent medication. However, concurrent medication was kept constant during the study and the baseline pain score between the study arms did not differ. Moreover, the effect size did not change when adjusted for the use of concurrent medication.

Main results study 125

	Placebo	**Pregabalin**	Treatment Comparisons		
			Difference	95% CI	p-value[c]
n_{ITT}	67	69			
$n_{completed}$ (% withdrawal)	37 (45%)	49 (30%)			
$n_{Wthdraw\ LOF\ /\ AE/\ /\ other}$	20 / 9 / 1	5 / 15 / 1			
Dose pathways					
150 mg/d	6.0%	7.1%			
150 -> 300 mg /d	6.0%	15.7%			
150 -> 300 -> 600 mg /d	85.1%	4.3%			
150 -> 300 -> 150 mg /d	0.0%	55.7%			
150 -> 300 -> 600 ->300 mg/d	3.0%	17.1%			
Mean daily dose fixed period	564 mg	460 mg			
Concomitant medication					
Baclofen	37.3%	54.3%			
Benzodiazepines	37.3%	40.0%			
Tricyclic anti-depressants	17.9%	34.3%			
Analgetics & antipyretics	43.3%	34.3%			
Concurrent pain medication	68.7%	75.7%			
Among which: .					
Paracetamol	32.8%	30.0%			
Paracetamol + codeine	10.4%	4.3%			
Morphine	11.9%	8.6%			
Amytriptyline	6.0%	17.0%			
Tramadol	10.4%	10.0%			
PAIN SCORE					
Mean at baseline	6.7	6.5			
Mean at endpoint	6.2	4.7			
Change [A]	**-0.43**	**-1.97**	**-1.53**	**0.92 ; 2.15**	**p< 0.001**
RESPONDERS[B]					
Improvement ≥ 30%	16.4%	42.0%	25.6%	10.9% ; 40.3%	p=0.001
Improvement ≥ 50%	7.5%	21.7%	14.3%	2.7% ; 25.9%	p=0.019
EFFECT OF SOMNOLENCE					
Patients without somnolence	61	40			
Patients with somnolence	6	29			
Mean pain score at endpoint					
Patients without somnolence	6.1	5.0	1.04	No p values, reported as significant	
Patients with somnolence	6.3	4.7	1.56	No p-values; reported not significant	
30% Responders					
Patients without somnolence	14.8%	40.0%	No p-values given; Reported as significant		
Patients with somnolence	33.3%	44.8%	No p-values reported as not significant		
50% Responders					
Patients without somnolence	8.2%	20.0%	No p-values, reported as not significant.		
Patients with somnolence at any	0.0%	24.1%			

CGI-responders[B] Very much & Much improved	6.0%	35%	30.0%	17.3% ; 42.7%	p<0.001
EFFECT of CO-MEDICATION[C] Endpoint adjusted for					
All pain medication	6.1	4.6	1.54	0.93 ; 2.15	p < 0.001
TCAs	6.1	4.6	1.51	0.88 ; 2.14	p < 0.001
Opiates	6.2	4.8	1.45	0.82 ; 2.07	p < 0.001
Anti-epileptics agents	6.5	4.9	1.55	0.93 ; 2.17	p < 0.001

ITT population, ANCOVA with study centre and baseline pain score as covariates, SE = Standard Error; CI = Confidence Interval

[A] Primary endpoint
[B]Difference in responder rated and confidence interval
[C]Ancillary analysis .

- <u>The open label extension phase of study 125 (study 202):</u>

One hundred and four patients from the controlled study (study 125) entered the open-label study (study 202). As study 202 is still on-going, interim safety data from this study is available and provided in the variation application.

3.3 - Clinical safety

Safety data incorporated the data of study 125 and the open label extension phase of study 125 (labelled as study 202). The occurrence of the adverse events (AEs) is presented in table below.

Study 202 & 125: overview of the AEs				
	Study 202	**Study 125**		
	Pregabalin	**Placebo**	**Pregabalin**	**Treatment Comparisons**
n_{safety}	104	67	70	
Median exposure days (range)	-	82 (5-98)	83 (2-103)	
Median dose mg/day (range)	-	600 (265; 600)	582 (37.5 ; 600)	
n_{safety}	104	67	70	* Rd > 5% # RR > 2 ** Rd> 10% ## RR > 4
Overall				
Any AEs	100%-	74.6%	95.7%	**
Any related AEs	-	49.3%	82.9%	**
Deaths	0.9%	0.0%	0.0	
Serious AEs	39.5%	4.5%	7.1%	
Serious AEs –treatment related	5.9%			
Severe AEs	-	11.9%	18.6%	
Discontinuation due to AEs	14.4%	13.4%	21.4%	
Among which:				
Asthenia	1.9%	0.0%	4.3%	
Oedema	1.0%	0.0%	5.7%	*
Peripheral Oedema	1.0%	3.0%	0.0%	
Somnolence	-	0.0%	5.7%	*
Hypervolemia	-	0.0%	1.4%	
Thrombocytopenia	-	0.0%	1.4%	
Euphoria	-	0.0%	1.4%	
Weight gain	1.0%	-	-	
Doses reduction/ Temporary Disc.		10.4%	30.0%	

Most common AEs > 5%					
Somnolence	26.9%	9.0%	41.4%	**	#
Dizziness	24.0%	9.0%	24.3%	**	#
Asthenia	17.3%	6.0%	15.7%	*	#
Dry mouth	14.4%	3.0%	15.7%	**	##
Constipation	18.3%	6.0%	12.9%	*	#
Oedema	9.6%	0.0%	12.9%	**	#
Amnesia		3.0%	10.0%	*	#
Headache	12.5%	19.4%	10.0%		
Peripheral edema	10.6%	6.0%	10.0%		
Amblyopia	7.7%	3.0%	8.6%	*	#
Infection	17.3%	6.0%	8.6%		
Myasthenia	7.7%	4.5%	8.6%		
Thinking abnormal	12.5%	1.5%	8.6%	*	#
Accidental injury	24.0%	9.0%	5.7%		
Diarrhea	6.7%	9.0%	5.7%		
Paresthesia	--	1.5%	5.7%		#
Urinary incontinence	--	3.0%	5.7%		
Urinary tract infection	24.0%	10.4%	5.7%		
Nausea	17.3%	--	--		
Hypertonia	12.5%	--	--		
Pain	12.5%	--	--		
Insomnia	9.6%	--	--		
Anxiety	8.7%	--	--		
Skin Ulcer	8.7%	--	--		
Abdominal pain	7.7%	--	--		
Rash	7.7%	--	--		
Chest pain	6.7%	--	--		
CPK increased	6.7%	--	--		
Neoplasm	5.8%	--	--		
Pharyngitis	5.8%	--	--		

Serious adverse events and deaths in studies 125 and 202

In study 125, 3 subjects in the placebo group and 5 subjects in the pregabalin group experienced a serious adverse event. In the pregabalin arm this concerned fecal impaction, hypervolemia-oedema-thrombocytopenia, urinary tract infection and a withdrawal syndrome. The hypervolemia-oedema-thrombocytopenia (probably due to a severe infection) and the withdrawal syndrome (increased spasticity spastic ataxia) were considered associated with medication.

In study 202 the most commonly reported serious adverse event concerned accidental injury (9 patients). In 3 subjects the fracture was in association with a fall. Serious adverse events were considered treatment-related in 6 patients (5.8%); and included constipation, delirium, hypertonia, manic depressive reaction, psychosis, stupor and urinary tract infection.

One patient in study 202 died of oesophageal cancer that was considered unrelated to treatment.

Laboratory findings

No clinical relevant changes in clinically laboratory variables were observed.

3.4 – Discussions

The efficacy of pregabalin in the treatment of central neuropathic pain has studied patients with neuropathic pain due to spinal cord injury (study 125).

Spinal cord injury might be accepted as a pain model evaluating central neuropathic pain. The injury causes disinhibition of dorsal horn neurons, thus the pain is of central origin. In addition, although as part of a retrospective review of data collected at enrollment, in about 95% of the subjects in study 125 the pain was localised at at least one dermatome below the level of the lesion. Further the pain

characteristics are congruent with what is expected for neuropathic pain. Hence it may be concluded that spinal cord injury is acceptable as a model for central neuropathic pain.

However, the CHMP is of the opinion that the justification of spinal cord injury as model for central neuropathic pain by the MAH is rather poor in the variation submission. In the dossier submitted, patients enrolled must have met IASP (International Association for the Study of Pain) criteria for central neuropathic pain and, if more than one type of pain was present, must have been able to differentiate between pain types. The patients were instructed to rate only their central neuropathic pain on a daily basis using diaries. Although central neurophatic pain is a key feature of spinal cord injury, subjects may also suffer from peripheral neurophatic pain and/or nociceptive pain due to for instance, muscle spasms. As the pain was assessed on global pain scale it remains to be settled to which degree effect size observed can be attributed to an improvement in central neuropathic pain.

The design and performance of study 125 allow a valid conclusion with respect to the efficacy in central neuropathic pain as the model is sufficiently justified. It is noted here that subjects with severe pain due to other causes that cannot be distinguished from central neuropathic pain were excluded. The criteria for this distinction however were not entirely clarified to the CHMP in the variation dossier.

The observed effect size in terms of points improvement in pain score from baseline in the study 125 is in the same order of magnitude as observed in the studies in peripheral neuropathic pain: in the peripheral neuropathy studies the difference between placebo and pregabalin 600 mg/daily was -1.47 points.
Responder rates (50% responders) were smaller in the study 125 compared to the peripheral neuropathy studies, but the difference in responder rates was the same: in the peripheral neuropathy studies the 50% responder rate was 35% for pregabalin and 18% for placebo. This was 22% and 8 % respectively in the study 125. Secondary analyses / results of secondary endpoints confirm the main effect.

Although the use of concurrent medication is unequally distributed over the study arms, this is not considered to have an impact on the evaluation of efficacy. Concurrent medication had to be stable at entry and was kept constant during the study, the difference in use of concurrent medication did not result in differences in baseline pain score. However, the frequent and relative large imbalances in co-medication over the treatment arms warrant a concern regarding the randomisation process. In addition, whether concurrent co-medication indeed remained stable should be verifiable.

Qualitatively the safety profile of pregabalin in central neuropathic pain is similar to that observed in the peripheral neuropathic pain studies. However, quantitatively the incidence of adverse events and serious adverse events is higher as compared to the studies in peripheral neuropathy. The most commonly reported adverse events in pregabalin-treated patients in central neuropathic pain were somnolence and dizziness that is consistent with the peripheral neuropathy studies. The incidence of somnolence was higher in central neuropathic pain (40%) compared to the peripheral neuropathy studies (23%). This is attributed to an underlying additive effect of the concomitant agents e.g. baclofen and benzodiazepines was given concomitantly in 50% and 40% of the patients receiving pregabalin.

As in spinal cord injury, pregabalin will often be given in combination with anti-spastic agents, the benefit/risk profile of pregabalin in central neuropathic pain due to spinal cord injury is different from that of peripheral neuropathic pain. Given the reason stated above, this safety profile can be accepted.

Based on the above discussions, the efficacy of pregabalin in a model for central neuropathic pain, i.e. spinal cord injury was demonstrated. The effect size was in the same order of magnitude as in peripheral neuropathy. The clinical relevance of the observed effect is reflected in the difference in 50% responder rates and proportion of CGI –responders. In addition, the differential drop-out forms an argument for efficacy as well as a manageable safety in favour of the product, i.e. if an effect is observed, patients continue and if safety is an issue, patients will stop.

Of note spinal cord injury is just a model for central neuropathic pain. In accordance to the guidance on neuropathic pain, if efficacy is proven in a model of central neuropathic pain this may be extrapolated to central neuropathic pain due to other causes. The difference in safety profile between peripheral and central neuropathic pain due to spinal cord injury (especially somnolence) is attributed by the CHMP to the interaction with the co-medication needed for the underlying condition rather than an intrinsic property of the product. Thus the benefit/risk can be expected to be different for central neuropathic pain due to other causes.

Considering all this, the indication *central neuropathic pain* for pregabalin is approvable. There are however concerns identified for this indication with regard to the clinical efficacy, and a warning concerning an overall increased risk of adverse events when used in subjects with spinal cord injury was considered to incorporate into the product information.

In view of the above the CHMP adopted a RSI, for which the first question is mentioned below:
Spinal cord injury as model for central neuropathic pain should be justified further.
1 - The justification presented so far was insufficient.
2 - In spinal cord injury, central and peripheral neuropathic pain often co-exist. It should be clear that the observed effect of pregabalin on the global pain scale is mainly due to an effect on central neuropathic pain and not due to an effect on peripheral pain.
3 - In spinal cord injury neuropathic pain and nociceptive pain often co-exist. It should be clear that the observed effect of pregabalin is mainly due to an effect on central neuropathic pain and not due to an effect on nociceptive pain.

To the justification of the spinal cord injury as model for central neuropathic pain, the MAH acknowledges and recognizes that the aetiologies and types of pain following spinal cord injury may be multiple. The study 125 utilised the clinical expertise of the investigators to enrolling patients with central neuropathic pain following spinal cord injury as required by the study protocol. Data on pain localization also strongly support that patients with central neuropathic pain were enrolled. The MAH concludes that the data from the study 125 clearly support a statistically significant benefit of pregabalin in the treatment of central neuropathic pain following spinal cord injury.

It is agreed by the CHMP that below level pain in spinal cord injury is centrally mediated. In complete spinal cord injuries pain sensations below the level of injury cannot be mediated by the sensory nerves. The peripheral nociceptive fibres are disconnected from dorsal horn neurons and/or spinothalamic processes results in deafferentation below the level of the lesion.

The MAH acknowledges, although implicitly, the coexistence of nociceptive, peripheral neuropathic and central neuropathic pain in spinal cord injury.

Indeed nociceptive pain can not be felt in areas where the normal sensation has disappeared. It is agreed that an effect of pregabalin on nociceptive pain above lesion level, if present, is unlikely as pregabalin has not shown efficacy in nociceptive pain. Another argument put forward by the CHMP is that the effect size of pregabalin did not change when corrected for use of concurrent medication for nociceptive pain. Of note, although the arguments above are considered sufficient, they form indirect arguments. If study 125 had included an additional NSAID (Non-steroidal anti-inflammatory drugs) arm the distinction between an effect of nociceptive and neuropathic pain could have been addressed more directly.

The differentiation between an effect on central and peripheral neuropathic pain is more difficult as pregabalin is supposed to have an effect on both.

Patients included in study 125 fulfilled the IASP (International Association for the Study of Pain) criteria of central pain although the final judgment was based on the clinical expertise of the investigator. The verification of the diagnosis showed that the vast majority of subjects had pain occurring at least one dermatomal level below the most caudal aspect of the spinal cord injury. However, the latter argument is not that strong as this was a retrospective verification of a priori sampled clinical data.

It is agreed that clinically at-level pain, more likely representing peripheral neuropathic pain, can clearly be distinguished from the regional distribution of pain required by the IASP definition of central neuropathic pain.

The CHMP considers the justification of the MAH acceptable: pain perception below the functional level of spinal cord injury cannot be mediated by the sensory nerves, thus must be of central origin.

The MAH further verified that the presence of central pain by querying the investigators to refer to source documentation collected at the time of subject enrolment after the study was completed. The CHMP is of the opinion this is an unusual practice because the ascertainment of the clinical status is critical at enrolment, not after. The CHMP requested the MAH to explain this procedure and the motives for this.

The MAH agrees that ascertainment of the clinical status and all inclusion and exclusion criteria are critical at the time of patient enrolment and this was, in fact, the procedure followed within this study. Patients with central neuropathic pain were enrolled based on the clinical expertise of the investigators and the study protocol requirements. Documentation regarding the specifics of pain localization in relationship to the injury were recorded in source documents rather than in case report forms and were, therefore, not included in the study database. The MAH agrees that this retrospective approach was not ideal; however, these data on central pain localization were collected from source documents as additional evidence to support the investigator diagnosis. These data were provided for review purposes to supplement the other data provided. The MAH confirmed that no other data were collected in this retrospective fashion.

As noted in the Common Technical Document (CTD), the response further demonstrated that the vast majority of subjects did report pain in a distribution inferior to the level of the spinal cord injury indicating the presence of central neuropathic pain.

Based on the MAH's response the CHMP is of the opinion that the purpose of this exercise is still not clear. Apparently it was felt that a verification of diagnosis was needed which implies that there were uncertainties. Though the MAH collected the information based on an opinion that the rapporteur required additional verification of the lesion level relative to the distribution of pain, the CHMP considers that the retrospective verification of the presence of central pain is of limited value as it can not be excluded that the judgment of data was coloured despite the fact that the data have been sampled prospectively.

Nevertheless these were the data provided by the MAH: pain localized to at least 1 dermatome below the level of the lesion was confirmed in the majority of the population, and imaging evidence of a lesion corresponding to the location of pain was confirmed for 75.9% of the population. Data collected with respect to patients with lesions above L2 indicate that 97.7% had central pain.
The CHMP considers that it would have been more convincing if not alone central pain was verified but also the presence of at level pain and nociceptive pain i.e. how many subjects had concomitant pain from other origin that could have polluted the pain assessments by patients. Preferably this could have been blinded e.g. the so-called source documentation could have been stripped from all information referring, hinting at the treatment received.

The CHMP considers that the issue is not fully resolved in view of the MAH's response, and therefore requested the MAH to confirm that the pain targeted concerned dominantly central neuropathic pain and to clarify if the pain evaluated was only the central neuropathic pain or if the evaluation was made on global pain.

The MAH highlighted in their response the two following key inclusion and exclusion criteria from the study:

1. Subjects were required to meet IASP criteria for central NeP.
2. Subjects with multiple types of pain, i.e., nociceptive and central neuropathic pains, could not be randomized into the study if they could not reliably differentiate between their various types of pain.

Moreover, the MAH stated that during the conduct of the study, subjects were instructed, as described in the study report, to rate their central neuropathic pain upon awakening each day.

Therefore, the MAH is confident that, based on the protocol inclusion/exclusion criteria, expertise and experience of the clinician investigators involved in the study, and screening for patients able to clearly identify and rate only their central neuropathic pain, even if multiple pain types existed, the subjects and investigators dominantly rated only their central neuropathic pain. The MAH is of the opinion that confounding of pain reporting by the presence of nociceptive pain would be minimized.

The MAH has performed several sensitivity analyses including the exclusion of patients who conservatively may have had a pre-dominance of at-lesion-level pain and of patients with complete and incomplete neurological spinal cord injury lesions. The MAH provided results of these analyses.

It is reinforced by the MAH that the subjects rated their central neuropathic pain upon awakening each day.

In view of the MAH's analyses, it is shown that the first sensitivity analysis performed revealed no large differences in effect size between the overall population and the population excluding subjects that might, only in the worst case scenario, have dominantly peripheral neuropathic pain. In the second sensitivity analysis performed, no large difference in effect size was observed between subjects with complete and incomplete spinal cord lesions. The second sensitivity analysis forms a supportive argument for an effect on central neuropathic pain. However, the inclusion and exclusion criteria form a guarantee that most patients indeed suffered dominantly from central neuropathic pain. Whether the inclusion and exclusion criteria was strictly adhered to is a matter of confidence in the trial. There are no arguments that this is not the case. Therefore the CHMP considers the MAH's response as acceptable and the issue as solved.

In view of the MAH's response to the fisrt RSI the CHMP also requested the MAH to provide data that can verify that *Pregabalin apparently has no effect on nociceptive pain (osteoarthritis and chronic low back pain).*

The MAH responded that the reports of the osteoarthritis (study 1008-031) and chronic low back pain (study 1008-104) studies were provided:

- In the osteoarthritis study only at the high dose (600 mg/day) and at only one time point (week 1) there was a significant difference in pain score between placebo and pregabalin. Ratings of sleep quality were significant different between the pregabalin 600 mg/day and placebo at each week except week 12 and also for pregabalin 300 mg/day group but only at week 1 through 5.
- In the chronic low back pain study, weekly mean pain scores showed little treatment effect. Only at week 1 was there any significant difference between either pregabalin group (300, 450, 600 mg/day) and the placebo group. Sleep interference was numerical different from placebo in favour of pregabalin that reached statistical significance for at least one dose at weeks 1, 2, 5, and 6.

The MAH stated that in both studies adverse event profile was similar to that observed in other pregabalin clinical trials in pain, with dizziness and somnolence being the most commonly reported adverse events.

No effect of pregabalin on nociceptive pain was observed in the osteoarthritis and chronic low back pain study.

The conclusion that secondary endpoints and adverse event profiles were consistent with the expected pharmacodynamic effects of pregabalin dosed within the dose range recommended for peripheral neuropathic pain look acceptable to the CHMP.

The CHMP considers, in view of the above MAH's response, that there is no argumentation that an effect on nociceptive pain confounded the effect observed on neuropathic pain in the study 125. The issue is considered as solved by the CHMP.

In view of the MAH's response to the first RSI, the CHMP requested the MAH to re-evaluate the observed effect size, in view of the imbalance effect that in study 125 the study arms were not comparable at baseline with respect to the level of anxiety as measured by the HADS-A.

To demonstrate any potential impact of the baseline HADS-A, on the pain response, an analysis of the pain response accounting for HADS-A was conducted by the MAH. Baseline HADS-A was used to divide the study population into two subgroups of roughly equal sample sizes – Low (HADS-A < 8) and High (HADS-A ≥ 8). An interaction model was run to assess the effect of the different levels of baseline HADS-A on treatment differences for pain change at endpoint.

In both groups pregabalin had greater reductions in pain than placebo. The magnitude of these differences is greater for the subjects with higher baseline HADS-A scores. However, the results are sensitive to both the small sample sizes and whether the cut-point value (HADS-A=8) is included in the low or high group. For example, if the subgroups are defined as low (HADS-A ≤ 8) and high (HADS-A > 8) – a simple shift in which subgroup gets the subjects with HADS-A scores of 8 – then for both subgroups the differences between treatments have p-values < 0.02.

The MAH stated in their response that it is notable that the imbalance baseline HADS-A scores was that the placebo patients had larger HADS-A scores than Pregabalin. Pregabalin had smaller pain response in patients with smaller HADS-A scores at baseline. Therefore, the observed treatment differences is not inflated by this imbalance.

The CHMP considers that the emphasis on p-values is inadequate as it is the impact on effect size that was subject of interest, although it point at sensitivity for the cut-off point.

The higher response in the HADS-A > 8 points probably is a chance finding given that the placebo response is reversed i.e. a large improvement for the low baseline HADS-A and lesser improvement in the higher HADS-A category.

More important what is shown is the effect size, for two levels of anxiety at baseline. Difference in effect size over the two levels of anxiety at baseline appears dramatic although the effect size is not reversed. Whether higher levels of anxiety at baseline were associated with higher baseline pain scores is not clear. The CHMP considers that the data provided make it impossible to address this.

Expected was a regression analysis with change in pain score as dependent variable and treatment, baseline painscore, baseline HADS-A score as independent variables. This way the effect size adjusted for baseline HADS-A score and baseline pain score could have been compared to the unadjusted effectsize. In addition the CHMP is of the opinion that the interaction terms should have been evaluated.

The opinion of the CHMP is that the impact of anxiety on effect size as well as the effect of the unequal distribution of anxiety level over the treatment arms were not evaluated adequately; the CHMP considers this issue as not resolved upon the MAH's response to the first RSI and therefore requested the following clarifications:

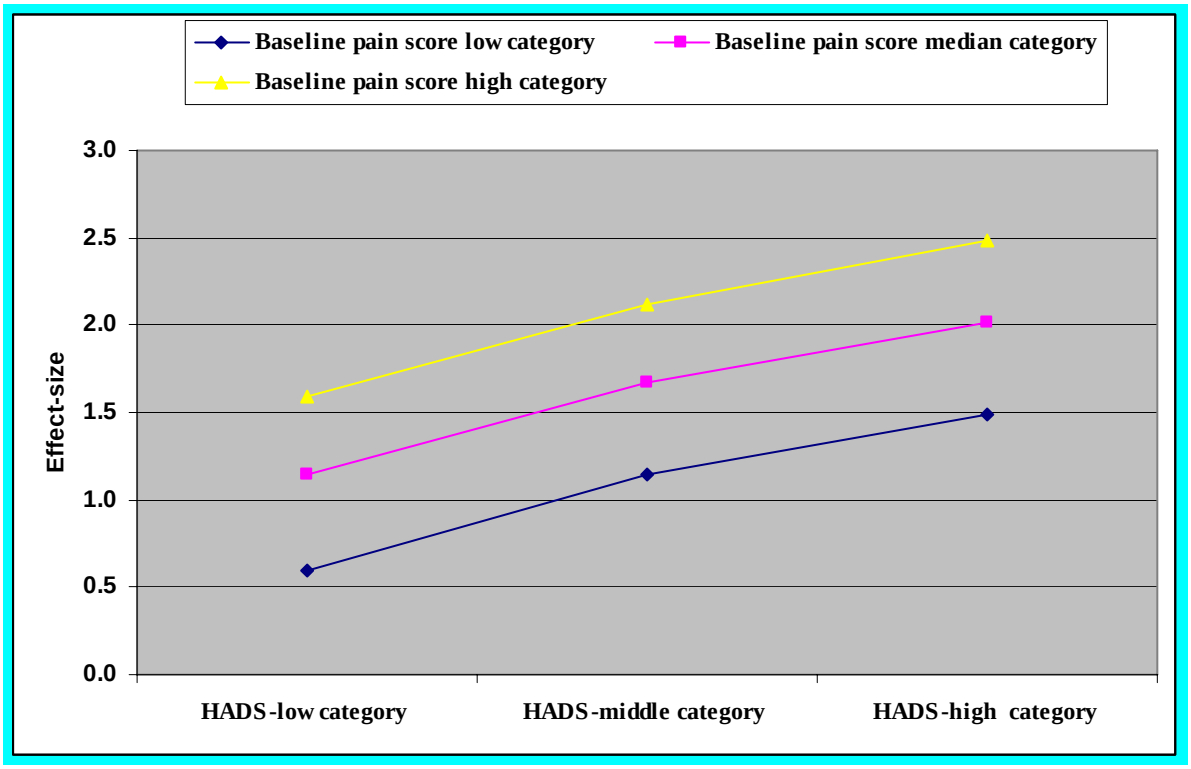
The impact of anxiety on effect size and more important, the impact of the unequal distribution of anxiety level over the treatment arms on effect size, was not evaluated adequately. This should be done as, depending on the results, this may have labelling consequences. Expected is an regression analysis with in change pain score as dependent variable and treatment, baseline pain score, baseline HADS-A score as independent variables. In addition the interaction terms should have been evaluated.

A regression analysis with change in pain score from baseline as dependent variable and treatment, centre, baseline pain, baseline HADSA as dependent variables was provided by the MAH. Baseline pain and HADS-A were treated as continuous variables.

The interaction of treatment with HADS-A and baseline pain score with treatment was significant. Therefore pregabalin and placebo were compared at various levels for both baseline pain and HADS-A.

All combinations quantitatively favoured the pregabalin treatment group and of the 9 statistical comparisons made there was a statistically significant difference between pregabalin and placebo. Therefore, while there was a baseline imbalance in HADS-A scores between treatment groups, the MAH stated that pregabalin continued to demonstrate a statistically significant treatment effect over placebo at endpoint even when making comparison at various levels of baseline HADS-A and pain scores. The MAH responded that these analyses demonstrate that the slight baseline imbalances did not bias the treatments comparisons.

The CHMP considers that the interaction of HADS-A and baseline pain score with treatment has been evaluated sufficiently. Overall there is no impact of anxiety levels on effect size. The interaction indicates that effect size increases within HADS category and within each HADS category effect size increases within each pain score category (cf. graph below).



The CHMP is in agreement that the analyses demonstrate that the slight baseline imbalances in anxiety levels did not bias the treatment comparisons. The issue is considered solved by the CHMP.

In view of the MAH's response to the first RSI, the CHMP requested the MAH to comment on the fact that the groups were not comparable at baseline regarding concomitant treatments (baclofen, tricyclic antidepressants, natural opium alkaloids) and level of anxiety. The CHMP considers that these imbalances question the appropriateness of the randomisation procedure performed.

The MAH responded that a standard randomization procedure was used as in all trials. To achieve balance in all baseline factors the randomization needs to ensure balance across several hundred different concomitant medications, medication classes, and other baseline characteristics. Hence chance imbalances will occur but the directions of the imbalances appear sufficiently random.

The question appropriately notes the imbalances seen in the study for three types of medication that may be beneficial in patients with neuropathic pain. However, these imbalances did not consistently favour the pregabalin treatment group and, in fact, a greater proportion of placebo-treated patients were taking opioids as concomitant medications.

Post hoc analyses of the subgroups taking any and those not taking any concomitant pain medications showed that the pregabalin-placebo differences on the primary endpoint (mean pain scores endpoint) were both highly significant. This was true even when those particular groups were restricted to opioids and non-opioid users and TCA and non-TCA users.

With respect to baseline level of concomitant medication the MAH provided their response in the following table.

	Placebo	**Pregabalin**
Number of subjects		
$n_{Irandomised}$	67	70
Mean baseline pain score (sd)	6.7 (1.4)	6.5 (1.4)
Concomitant medication		
Baclofen	37.3%	54.3%
Benzodiazepines	37.3%	40.0%
Tricyclic anti-depressants	17.9%	34.3%
Among with Amytriptyline	6.0%	17.0%
Analgetics & antipyretics	43.3%	34.3%

It is agreed by the CHMP that the imbalances appeared at random. Although the response is not supported by data for verification, the MAH confirmed earlier analyses of the impact of co-medication on the effect size. The CHMP is in agreement with the MAH's response; the issue is considered as solved.

Finally in view of the MAH's response to the first RSI, the CHMP requested the MAH to provide data regarding the stability of concomitant treatment during the study together with data regarding the possible rescue treatments that may have been taken by patients and to evaluate the impact of these changes in concurrent co-medication during the study on the observed effect size.

The MAH's responded that the protocol mentions the following regarding concomitant medications:
Any medication the subject takes other than the study drugs specified in the protocol, is considered concomitant medication. All concomitant medications must be recorded in the subject's medical record and on the CRFs. Concomitant treatment with analgesics, anti-inflammatories and anti-depressants is allowed with the following restrictions: Patients taking nonnarcotic analgesics (eg, acetaminophen [Paracetamol]), narcotic analgesics (eg, opioids), tricyclic antidepressants (eg, amitriptyline [Elavil]), serotonin-specific reuptake inhibitors (eg, sertraline [Zoloft]), anti-inflammatories (eg, acetylsalicyclic acid [Aspirin]), or NSAIDs, must be on a stable dose regimen (for antidepressants and narcotic analgesics: stable dose within the last 30 days prior to visit V1), and therapy may not be initiated during the study. Transcutaneous electrical nerve stimulation, and concomitant treatment with AEDs (excluding gabapentin) is also allowed at stable levels/dosages. ***If patients are on gabapentin, gabapentin must be withdrawn at least 7 days prior to visit V1.*** *Furthermore, benzodiazepines or skeletal muscle relaxants are allowed PRN to relieve spasticity (benzodiazepines must be taken at least 6 hours prior any clinic visit).*
Thus, rescue medications were neither specifically described in the protocol nor allowed.

With regard to the concomitant medication use, the MAH emphasizes that the protocol restricted or prohibited use of medications and therapies expected to affect pain response. Medications which were allowed to be taken had to be maintained at a stable dose prior to and during the study phase. With the following exceptions, subjects enrolled in the study appeared to comply with the requirements of the

protocol. The protocol violations resulting from prohibited medications are summarised in the table below:

Protocol Violation	Subject Numbers
Placebo	
Acetaminophen taken for 1 (or 2 days)	1010 (4018)
Narcotic analgesic (not specified) for approximately 1.5 months	5018
Oxycodone for 2 days	6010
Gabapentin not stopped until Visit 1	5004
Pregabalin	
Amytriptiline up to Visit 2	4004
Gabapentin >10 days after Visit 1	5001
Dextropropoxyphene plus acetaminophen PRN	1011
Narcotic analgesics (not specified)	5013

Source: 1008-000-125 study report, page 51

Given the small numbers of protocol violators (4 for pregabalin treated patients and 5 for placebo treated patients) and small number of violations due to the use of PRN medication , the MAH does not consider that there is any influence on the size of the observed treatment effect.

In view of the MAH's response the CHMP concludes that apparently compliance to the protocol was high. The use of concomitant treatments was stable. Protocol violations with respect to concurrent medication and use of rescue medication were limited. Hence a large impact on the effect size is considered unlikely. The CHMP is in agreement with the MAH's response; the issue is considered as solved.

3.5 - Pharmacovigilance

Risk Management plan

The MAH submitted an updated 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.

3.6 – Conclusion on the risk/ benefit assessment

The current procedure concerns a type II variation to add the indication of *central neuropathic pain in adults*.

Spinal cord injury may be considered a model for evaluating central neuropathic pain. The justification of spinal cord injury as model for central neuropathic pain by the MAH is accepted by the CHMP. Pain perception below the functional level of spinal cord injury cannot be mediated by the sensory nerves thus must be of central origin.

The inclusion and exclusion criterias in the study 125 were sufficient for the diagnosis of central neuropathic pain. The location of the pain differentiates between peripheral neuropathic pain (at lesion level), central neuropathic pain (below lesion level) and nociceptive pain (elsewhere). Earlier in the procedure it was discussed that verification of this diagnosis is limited as it cannot be excluded that assessment of the unblinded although prospective sampled data, is coloured by hindsight. Moreover, although the existence of pain below lesion level was verified, the (non)presence of concomitant at level pain and above level nociceptive pain was not. It appears that the latter is not possible as these data were not explicitly monitored once the in-and exclusion criteria were confirmed. The MAH has pointed out however, that all patients were required to have central pain and it is agreed with the MAH, that clinical expertise is capable of distinguishing central neuropathic pain from concomitant nociceptive and peripheral neuropathic pain in spinal cord injury, as the location is different. Additionally even in case a patient would have had both central and peripheral neuropathic pain, it was explicitly required only to score central pain and patients not able to make the distinction were excluded. The CHMP agrees that it is reasonable to assume that the effect seen is due to an effect on central neuropathic pain.

Apart from these selection criteria, pregabalin apparently has no effect on nociceptive pain as assessed in the studies in osteoarthritis and chronic low back pain. This forms an argument for an exclusive effect of pregabalin on neuropathic pain. The other way around as the efficacy of the concomitant medication for nociceptive pain is known to have a poor effect on neuropathic pain it is unlikely that the use of concurrent medication explains the observed effect size in neuropathic pain. In the study 125, concurrent medications for neuropathic pain were allowed if kept stable. However, differences in use of concurrent medication did not result in differences in neurophatic pain score at baseline. Moreover effect size did not change when adjusted for the use of concurrent medication. Further protocol violations with respect to concurrent medication and use of rescue medication were scarce. Hence pollution of the effect size due to protocol violations is considered unlikely.

The unequal distribution of anxiety level at baseline over the treatment arms did not affect effect size. Moreover, effect size adjusted for baseline HADS-A score as well as baseline pain score did not differ substantially from the effect size not adjusted for baseline anxiety levels. Hence there are no labelling consequences.

In conclusion, in view of the variation submission (EMEA/H/C/546/II/07) along with the additional data provided in the MAH's responses to the two RSI requested by the CHMP, the efficacy of pregabalin in central neuropathic pain is considered established in an appropriate model for central neuropathic pain i.e. spinal cord injury. Additionally the safety profile being qualitatively identical to

the one already approved at time of the peripheral neuropathic pain indication, the benefit/risk assessment in the treatment of central neuropathic pain indication is positive. The indication is considered approvable by the CHMP.

4. CHANGES TO THE PRODUCT INFORMATION

Changes to the Summary of Product Characteristics (SPC)

- Section 2

The CHMP is of the opinion that the excipient lactose should be listed as follows:
Each hard capsule contains 25 mg of pregabalin. Lyrica capsules also contain lactose monohydrate.
For a full list of excipients, see section 6.1.

The MAH is in agreement and amended the wording of this section accordingly. The labelling was amended accordingly.

- Section 3

The CHMP considers that the following amendment should be made (deletion crossed out):
White ~~hard capsule~~, marked "Pfizer" on the cap and "PGN 25" on the body with black ink.

The MAH is in agreement and amended the wording of this section accordingly.

- Section 4.1 "Therapeutic indication"

The MAH proposed the following text in the section 4.1 of the SPC:
*Lyrica is indicated for the treatment of peripheral **and central** neuropathic pain in adults.*

The CHMP is of the opinion that the indication is acceptable.

- Section 4.4 "Special warnings and precautions for use"
The CHMP is of the opinion that the following paragraph should be added:
…."In the treatment of central neuropathic pain due to spinal cord injury the incidence of adverse events in general, CNS adverse events and especially somnolence was increased. This may be attributed to an additive effect due to concomitant medication (e.g. anti-spastic agents) needed for this condition. This should be considered when prescribing pregabalin in this condition."

The MAH is in agreement and amended the wording of this section accordingly.

- Section 4.8

The CHMP was of the opinion that the following paragraph should be added:
…"In the treatment of central neurophatic pain due to spinal cord injury the incidence of adverse events in general, CNS adverse events and especially somnolence was increased (See 4.4).

The MAH is in agreement and amended the wording of this section accordingly.

- Section 5.1

The following text (addition underlined) was proposed by the MAH:

Clinical experience

Neuropathic pain

Efficacy has been shown in studies in diabetic neuropathy, ~~and~~ post herpetic neuralgia and spinal cord injury. Efficacy has not been studied in other models of neuropathic pain.

Pregabalin has been studied in ~~9~~10 controlled clinical studies of up to 13 weeks with twice a day dosing (BID) and up to 8 weeks with three times a day (TID) dosing. Overall, the safety and efficacy profiles for BID and TID dosing regimens were similar.

In clinical trials up to ~~13~~12 weeks for both peripheral and central neuropathic pain, a reduction in pain was seen by week 1 and was maintained throughout the treatment period.

In controlled clinical trials in peripheral neuropathic pain 35% of the pregabalin treated patients and 18% of the patients on placebo had a 50% improvement in pain score. For patients not experiencing somnolence, such an improvement was observed in 33% of patients treated with pregabalin and 18% of patients on placebo. For patients who experienced somnolence the responder rates were 48% on pregabalin and 16% on placebo.

In the controlled clinical trial in central neuropathic pain 22% of the pregabalin treated patients and 7% of the patients on placebo had a 50% improvement in pain score.

The CHMP is in agreement with the proposed wording.

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):

1. WHAT LYRICA IS AND WHAT IT IS USED FOR

The safety and effectiveness of pregabalin in patients below the age of 18 years with peripheral and central neuropathic pain, epilepsy and Generalised Anxiety Disorder has not been established.

***Peripheral and central neuropathic pain:** LYRICA is used to treat long lasting pain caused by damage to the nerves. A variety of diseases can cause peripheral neuropathic pain, such as diabetes or shingles. Pain sensations may be described as hot, burning, throbbing, shooting, stabbing, sharp, cramping, aching, tingling, numbness, pins and needles. Peripheral and central neuropathic pain may also be associated with mood changes, sleep disturbance, fatigue, and can have an impact on physical and social functioning and overall quality of life.*

2. **BEFORE YOU TAKE LYRICA**

The CHMP is of the opinion that the PL should be adapted to the updated SPC.

Take special care with LYRICA
…Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medications to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.

The MAH is in agreement and amended the wording of this section accordingly.

3. HOW TO TAKE LYRICA

The CHMP is of the opinion that the route of administration should be added, using the Ph. Eur. standard term: oral use.

…..Your doctor will determine what dose is appropriate for you.
LYRICA is for oral use only.
Peripheral and central neuropathic pain, epilepsy or Generalised Anxiety Disorder:…..

Also the CHMP is of the opinion that the following wording should be added in this section as follows:

If you stop taking LYRICA
…. After stopping long and short-term pregabalin treatment, you need to know that you may experience certain side effects. These include, trouble sleeping, headache, nausea, diarrhea, flu-like symptoms, nervousness, depression, pain, sweating, and dizziness. It is not clear at this time whether these symptoms occur more commonly or severely if you have been taking pregabalin for a longer period of time.

The MAH is in agreement and amended the wording of this section accordingly.

4. POSSIBLE SIDE EFFECTS

The PL was amended in accordance with the changes made in the section 4.8 of the SPC.

…..Certain side effects may be more common, such as sleepiness, because patients with spinal cord injury may be taking other medications to treat, for example, pain or spasticity, that have similar side effects to Pregabalin and the severity of these effects may be increased when taken together.

5. HOW TO STORE LYRICA

The CHMP is of the opinion that the order of the statements should be changed according to the QRD templates, as follows:
Keep LYRICA out of the reach and sight of children.

The MAH is in agreement and amended the wording of this section accordingly.

6. FURTHER INFORMATION

The CHMP is of the opinion that the other ingredients should be separated according to the different parts of the order of the statements, as follows:

What Lyrica contains

- *….The other ingredients are: lactose monohydrate, maize starch, talc, gelatine, titanium dioxide (E171), sodium laurilsulphate, anhydrous colloidal silica, black ink, (which contains shellac, black iron oxide (E172), propylene glycol, potassium hydroxide) and water.*
- *The 75, 100, 200, 225 and 300 mg capsules also contain red iron oxide (E172).*

The CHMP is also of the opinion that the Ph. Eur. standard term should be stated separately, as follows:

What LYRICA looks like and contents of the pack
LYRICA 25 mg capsules are ~~hard~~ white hard ~~gelatine~~ capsules, with "Pfizer" marked on the cap and "PGN 25" on the body.
The MAH is in agreement and amended the wording of this section accordingly.
In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet.

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.

3. LIST OF EXCIPIENTS
This product contains lactose monohydrate

"User Consultation" of the package leaflet (Art 59(3) and 61(1) of the amended Directive):

The MAH has provided a justification for not performing a Readability test at the time of submission of the variation dossier. The CHMP considered that the justification, which relates to the previously proposed addition of Generalised Anxiety Disorder is not applicable. Therefore, the CHMP requested the MAH to submit an updated documentation. Upon CHMP's request the MAH explained their opinion and stated that the changes due to the proposed addition of the central neuropathic pain indication are minor and do not significantly change the readability of the approved documentation. The MAH therefore proposed that the readability work carried out to date is adequate to cover the user consultation of the package leaflet.

Upon additional justification from the MAH the CHMP agrees that the proposed addition of central neuropathic pain does not significantly change the readability of the approved documentation. Therefore, the CHMP is of the opinion that additional testing is not required. The issue is considered solved by the CHMP.

CONCLUSION

On 27 July 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, 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:

Area[1]	Description	Due date[2]/Fulfilled
Non-clinical	ERA: There is insufficient evidence to replace the base set requirement of the ELS study with this general concept based on deductive science, parameterized on few empirical data on less relevant chemicals, within the current registration framework. The data requirement, as part of the base set, is maintained.	February 2007
Non-clinical	ERA: In view of the preliminary PNEC of >4.6 µg/L, the LOQ for pregabalin in water of 54 µg/L is not low enough. An analytical method for water with a LOQ at the level of 0.1 µg/L should be established.	February 2007

1. Quality, Non-clinical, clinical, pharmacovigilance

2. Due date for the FUM or for the first interim report if a precise date cannot be committed to. Please specify whether theses SOs or FUMs have been fulfilled.