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Committee for Medicinal Products for Human Use (CHMP)

Lyrica

(pregabalin)

Procedure No. EMEA/H/C/000546/P45 024

CHMP assessment report for paediatric use studies submitted according to Article 45 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

Disclaimer: The assessment report was drafted before the launch of the European Medicines Agency's new corporate identity in December 2009. This report therefore has a different appearance to documents currently produced by the Agency.

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I. RECOMMENDATION

Based on the 2 clinical studies on Lyrica (pregabalin) submitted in accordance with Article 45 of Regulation (EC) No1901/2006, as amended, the Rapporteur deems that **no further regulatory action** is required.

II. INTRODUCTION

The MAH, Pfizer, submitted on December 12, 2008 one set of completed studies conducted in patients with *partial seizures with or without secondary generalisation* (controlled plus open label extension; Study1008-034 and Study 1008-035, respectively) containing some paediatric data (12 to 17 years old), in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use. In addition and in response to EMEA's letter dated March 2, 2009, a short critical expert overview (2 pages) was provided on April 2, 2009 to supplement the Article 45 submission.

These studies will be discussed in detail under section II.3 Clinical aspects.

The complete data analysis of Study 1008-034 and an interim analysis of Study 1008-035 were previously included and assessed as part of the initial marketing authorisation application which included the indication adjunctive therapy with partial seizures with or without secondary generalisation as well as peripheral neuropathic pain. An EU approval was granted in July 2004 and the MAH agreed to undertake a pediatric clinical development plan as part of their post marketing commitment (follow-up measure).

Pfizer stated that the submitted paediatric study does not influence the benefit risk for Lyrica and that there is no a consequential regulatory action.

In addition, Pfizer conveyed that the follow-up measure to conduct a paediatric development plan in epilepsy is currently on-going and consists of the following studies:

- Study A0081074: Pregabalin BID pharmacokinetics and tolerability study; randomized, double-blind, placebo-controlled with dose escalation in one month to 16 years old children. (on-going)
- Study A0081075: Open-Label extension to Study A0081074. (on-going)
- Study A0081041: double-blind, placebo-controlled, efficacy and safety in pediatric patients of 5-16 years old. (planned)
- Study A0081042: double-blind, placebo-controlled, efficacy and safety in paediatric patients 1 month to 4 years old. (planned)

III. SCIENTIFIC DISCUSSION

III.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Not applicable

III.2 Non-clinical aspects

Not applicable

III.3 Clinical aspects

1. Introduction

Pregabalin is the active substance of Lyrica. Pregabalin is indicated in the EU for the *treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalisation and for the treatment in adults of generalized anxiety disorder*. The recommended dose range is 150 to 600 mg per day given in either two (BID) or three doses (TID).

Pfizer submitted the following clinical studies for assessment in accordance with the Paediatric Work Sharing Procedure Article 45:

- Study 1008-034: Pregabalin BID add-on trial: a randomized, double-blind, placebo-controlled, parallel group, multicenter study in patients with partial seizures (12 to 17 years old, 25 out of 455 patients).
- Study 1008-035: Pregabalin BID open-label add-on trial: an open-label, multi-center follow-on study to determine long-term safety and efficacy in patients with partial seizures (12 to 17 years old, 21out of 623 patients).

As previously mentioned, the complete data analysis of Study 1008-034 and interim analysis of Study 1008-035 were part of the clinical development program assessed in granting the initial marketing authorisation in the EU in 2004. For study 1008-034 it was concluded that the data had no significant relevance for the paediatric population due to the limited number of paediatric studies. Since no additional data was submitted, this conclusion is maintained.

Hence in this application, only Study 1008-035 contains new data to be assessed.

However, for a complete overview on paediatric data also the data for study 1008-034 is discussed.

2. Clinical study(ies)

According to the Critical Expert Overview, 36 pediatric patients were included in the 2 submitted studies. The breakdown of the number of pediatric patients by age and gender in the two studies is as follows:
- 12 years: 3 (1F/2M)
- 13 years: 6 (3F/3M)
- 14 years: 2 (0F/2M)
- 15 years: 6 (2F/4M)
- 16 years: 8 (3F/5M)
- 17 years: 11 (4F/7M).

Study 1008-034: **Synopsis**

Title: Pregabalin BID Add-On Trial: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-center Study in Patients With Partial Seizures

Study dates: November 11 – September 17, 1999

Study objectives:
To evaluate the efficacy and safety of dosages of pregabalin administered BID as add-on treatment in patients with partial seizures.

Study participants
Patients (≥ 12 years of age) with partial seizures (simple partial, complex partial, and/or secondarily generalized tonic clonic), no adequate seizure control on standard (anti-epileptic

drugs) AEDs and and were receiving 1 to 3 standard AEDs at doses within an acceptable therapeutic range were recruited.

Methodology:
After an 8-week baseline period, 455 patients entered a 12-week, randomized, double-blind, parallel-group, placebo-controlled and multi-center study. Randomization was to either placebo, or to 1 of 4 pregabalin dose groups: 50, 150, 300, or 600 mg/day administered BID. No active comparator was used.

Outcomes and end-points
Responder rate (the percent of patients who had at least a 50% reduction in 28-day seizure frequency compared to baseline seizure frequency), response ratio, number and percent of patients seizure-free, among others, were measured.

Safety was evaluated using frequency and intensity of adverse events; physical, opthalmological and neurological examinations; 12- lead electrocardiogram (ECG) with a 2-minute cardiac rhythm strip; and laboratory tests including hematology, blood chemistry, and urinalysis during the trial period. Standard plasma/serum AED concentration and plasma pregabalin concentrations were assessed.

Results and discussion
Participants' flow

Treatment	Withdrawal for adverse event N (%)	Withdrawal for lack of efficacy N (%)	Completed Study N (%)
Placebo	5 (5.0)	5 (5.0)	87 (87)
50 mg/day PGB/BID	6 (6.8)	1 (1.1)	78 (88.6)
150 mg/day PGB/BID	1 (1.1)	1 (1.1)	81 (94)
300 mg/day PGB/BID	13 (14.4)	2 (2.2)	71 (78.9)
600 mg/day PGB/BID	21 (23.6)	4 (4.5)	61 (68.5)

Efficacy
Summary of the responder's analysis (%)

Treatment	Responder Rate n/N (%)	Treatment differences		p-value
		Percent (SE)	95% CI	
Placebo	14/100 (14)			
50 mg/day PGB/BID	13/88 (15)	0.8 (5.1)	[-9.3, 10.8]	0.840
150 mg/day PGB/BID	27/86 (31)	17.4 (6.1)	[5.5, 29.3]]	0.006
300 mg/day PGB/BID	36/90 (40)	26.0 (6.2)	[13.8, 38.2]	< 0.001
600 mg/day PGB/BID	45/89 (51)	36.6 (6.3)	[24.1, 49.0]	< 0.001

Patients in the 150, 300 and 600 mg/day pregabalin groups had significantly greater responder rates compared to placebo. Pregabalin showed a significant linear response (increase in responder rate) with increasing dose. Consistent results were observed in the response ratio. As to the number and percent of patients seizure-free, trends were seen favoring the 300 and 600 mg/day doses of pregabalin compared to placebo at the 28- and 42-day seizure-free periods.

Safety

The majority of adverse events in the placebo and in all pregabalin groups were mild or moderate in intensity. The incidence of overall adverse events, and of withdrawals due to adverse events, showed a dose-related increase at the 300 and 600 mg/day doses relative to the control group. There was a dose-related increase in the incidence of CNS adverse events and weight gain at the 150, 300 and 600 mg/day doses. The incidence of serious adverse events was relatively low (ranging from 2% to 4% per group) and comparable in the placebo and pregabalin groups. There were no deaths. In the 600 mg/day pregabalin group, a greater percentage of patients had moderate or severe adverse events compared to the patients in the placebo group.

There were no meaningful treatment-related differences in clinical laboratory values, vital signs, electrocardiograms (ECGs), or the results of neurological, physical, or opthalmological examinations.

MAH Conclusions
Pregabalin administered BID at doses of 150, 300 and 600 mg/day is highly effective as add-on therapy when compared to placebo, exhibiting a clear dose response in the primary and secondary efficacy parameters.

Pregabalin 50 mg/day is not an effective dose while 150 mg/day is the minimum effective dose.

Pregabalin, with no initial titration, is well-tolerated at doses of 50, 150 and 300 mg/day and less but still tolerated by most at 600mg/day.

RAPPORTEUR'S COMMENTS

The different pediatric age groups were not represented. Only adolescents (12 - 17 years old) were included in the study and their number is very limited (25 out of 455 patients). No separate analysis for this age group was submitted. On the other hand, whatever efficacy and safety outcomes generated would have virtually no significant relevance for the whole pediatric target population due to the limited number of paediatric subjects.

Study 1008-035: **Synopsis**
Title: Pregabalin BID Open-Label Add-On Trial: An Open-Label, Multicenter Follow-On Study to Determine Long-Term Safety and Efficacy in Patients With Partial Seizures

Study dates: January 27, 1999 – November 7, 2005

Study objectives
To obtain information on open-label long-term safety and tolerance of pregabalin administered as adjunctive therapy at doses from 100 to 600 mg/day administered BID in patients with partial seizures and to evaluate the long-term efficacy of pregabalin as adjunctive treatment with AEDs in patients with partial seizures.

PATIENT POPULATION
Patients included were those who completed or exited early the preceding double-blind study (Protocol 1008-034) as well as new patients (due to an amendment) ≥ 4 partial seizures in the 2 months prior to screening.

STUDY DESIGN

An open-label, uncontrolled, multi-center trial consisting of 2 study phases, 7 days at 400 mg/day BID, followed by an extended open-label treatment phase during which the pregabalin dose may be adjusted for efficacy and tolerability according to clinical signs and symptoms from 100 to 600 mg/day BID.

TREATMENT
All patients were introduced directly to a common dose of 400 mg/day BID of pregabalin open-label treatment for 1 week. Following this transition phase, patients either continued 400 mg/day or had the dose adjusted between 100 and 600 mg/day. Open-label treatment continued for up to 338 weeks provided that therapeutic response and tolerability were maintained.

EFFICACY PARAMETERS
Responder rate (proportion of patients with a 50% or greater reduction in seizure frequency during open-label treatment compared to baseline), response ratio and percent change in 28-day seizure rate from baseline to open-label treatment, among others, were measured.

SAFETY PARAMETERS
Frequency and intensity of adverse events; physical, opthalmological, and neurological examinations; 12-lead electrocardiogram (ECG) with a 2-minute cardiac rhythm strip; and laboratory tests including hematology, blood chemistry and urinalysis during the trial period.

Results
Participants' flow

Disposition	Any Dose Pregabalin N = 623	
Entered Study	623	(100.0%)
Withdrawals	526	(84.4%)
Status epilepticus	0	(0.0%)
Lack of efficacy	199	(31.9%)
Adverse event	75	(12.0%)
Lack of compliance	27	(4.3%)
Other/administrative	116	(18.6%)
Patient did not meet requalification criteria	109	(17.5%)
Completed	97	(15.6%)

Patients' exposure to pregabalin
Four hundred ninety four (79%) of the patients received at least 24 weeks of pregabalin exposure, 381 (61%) received at least 52 weeks (1 year) of pregabalin exposure, 193 (31%) received at least 104 weeks (2 years) of pregabalin exposure and 132 (21%) received at least 156 weeks (3 years) of pregabalin exposure.

Efficacy
A responder rate of 37% and a median percent reduction from baseline in seizure frequency of 38% were seen for the ITT population during the initial 84-day (12-week) period of open-label. For the cohort of patients followed for 2 years, the responder rate and median percent change at subsequent intervals were maintained over time. Consistent results were observed in the response ratio. A total of 8% of the ITT patients were seizure - free for the 6 months since the last observation.

Safety

Adverse event category	**Any dose pregabalin**
	N = 623

Number (%) of Patients with AEs	
All AEs	593 (95.2)
Associated AEs	504 (80.9)
Number (%) of Patients with AEs by Maximum Intensity	
All AEs	
Mild	123 (19.7)
Moderate	323 (51.8)
Severe	147 (23.6)
Associated AEs	
Mild	192 (30.8)
Moderate	263 (42.2)
Severe	49 (7.9)
Number (%) of Patients Withdrawn due to AEs	
All AEs	70 (11.2)
Associated AEs	61 (9.8)
Number (%) of Patients with non-fatal Serious AEs	
All AEs	99 (15.9)
Associated AEs	9 (1.4)
Number (%) of Patients Withdrawn due to Serious AEs	
All AEs	10 (1.6)
Associated AEs	7 (1.1)
Number (%) of Patients Who Died	
All deaths	7 (1.1)
All deaths due to associated AEs	0 (0.0)

Most frequently occurring events by decreasing frequency

Adverse event Preferred Term	Number (%) of Patients		Adverse event Preferred Term	Number (%) of Patients
Dizziness	231 (37.1)		Depression	53 (8.5)
Accidental injury	192 (30.8)		Peripheral edema	51 (8.2)
Somnolence	188 (30.2)		Back pain	51 (8.2)
Infection	160 (25.7)		Dyspepsia	49 (7.9)
Weight gain	129 (20.7)		Nervousness	47 (7.5)
Headache	125 (20.1)		Sinusitis	45 (7.2)
Pain	118 (18.9)		Anxiety	43 (6.9)
Asthenia	101 (16.2)		Diarrhea	42 (6.7)
Amblyopia	88 (14.1)		Constipation	42 (6.7)
Ataxia	80 (12.8)		Confusion	42 (6.7)
Nausea	80 (12.8)		Vomiting	40 (6.4)
Diplopia	67 (10.8)		Urinary tract infection	39 (6.3)
Rash	65 (10.4)		Pharyngitis	37 (5.9)
Thinking abnormal	62 (10.0)		Hypesthesia	37 (5.9)
Flu syndrome	62 (10.0)		Ecchymosis	36 (5.8)
Tremor	60 (9.6)		Abdominal pain	32 (5.1)
Amnesia	55 (8.8)		Arthralgia	28 (4.5)
Insomnia	55 (8.8)			

Of the 623 patients who received pregabalin, 593 (95%) experienced at least 1 adverse event and from whom 504 (81%) were considered related to treatment. Most adverse events were mild or moderate in intensity. Severe adverse events occurred for 147 patients (24%) and from whom 49 patients (7.9%) were considered treatment-related. A total of 75 (13%) withdrew due to adverse events and from whom 61 patients (10%) were considered related to treatment. Seven patients died and none of the deaths was considered associated with pregabalin treatment. The adverse event profile for the uncontrolled studies was similar to that seen in the controlled studies, with central nervous system adverse events, accidental injury, peripheral edema and weight gain being the most frequent.

MAH Conclusions
Pregabalin shows efficacy similar to that seen in the double-blind studies in terms of responder rate (37% of patients) and median percent reduction from baseline (38%) in the ITT patient population during the initial 84-day (12 week) period of open-label.

Pregabalin appears to have a sustained anti-convulsant effect with long term use. For the cohort of patients followed for 2 years, the responder rate and median percent change were maintained over time.

During the open-label studies, 8% of pregabalin patients in the ITT population were seizure-free for 6 months at the last observation.

The adverse event profile for the uncontrolled studies is similar to that seen in the controlled studies, with central nervous system adverse events, accidental injury, peripheral edema and weight gain being the most frequent.

Overall, the results of this study indicate that pregabalin is effective and generally well-tolerated in this patient population during long-term exposure.

RAPPORTEUR'S COMMENTS

This is an open-label designed study and as such, is of limited value for efficacy assessment.

A very high percentage of the patients (31.9%) dropped-out mainly due to lack of efficacy in comparison with12% who withdrew due to adverse events. Based solely on this, no conclusion can be drawn on efficacy.

The paediatric sample size is very small. No children were included and only 21 adolescents (12 -17 years old) out of 623 patients were recruited in the study. A separate analysie of the data from the last mentioned pediatric age group was not presented. However, even if these would have been provided, the clinical relevance in the whole pediatric target population is questionable as the number is too small for an estimate of efficacy and safety.

The reported common adverse events are what to be expected from the mode of action of pregabalin. CNS adverse events like dizziness, somnolence and headache as well as accidental injury, infection and weight gain are the most common ones.

The frequencies of the most common adverse events are considerably higher in the long term safety study as compared to the short term efficacy study. This might be due to the fact that the incidences accumulative.

	short-term (N=1480)	long-term (N=5232)
a. dizziness	29%	34%
b. accidental injury	4%	29%
c. somnolence	23%	27%
d. infection	8%	22%
e. weight gain	6%	24%
f. headache	12%	20%

More important these are dominantly data for adults, only 21out of 623 patients were between 12 to 17 years and no children are included. Hence in general, the MAH's overall conclusion is accepted.

IV. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

- **Overall conclusion**

Based on the 2 studies submitted, the overall conclusions of the MAH are endorsed. Nothing new could be said about Study 1008-034 as this was assessed previously. The open-label extension Study 1008-035 contains some data not previously assessed but efficacy assessment is limited due to its open-label and uncontrolled design. Moreover and most important, the number of children and adolescent patients included in the studies is very limited and hence the concrete clinical relevance of the results to the paediatric population still remains to be confirmed.

The overall safety profile of pregabalin in studies 1008 035/036 is what can be expected from the mode of action of the compound. However, the population is dominamt an adult population. Whether the efficacy and safety is the same for children and adolescents remains to be substantiated.

In conclusion, the additional data submitted do not allow a benefit/risk assessment of Lyrica used in children and adolescents. The following wording in section 4.2 of the current SPC is still valid:

"Use in children and adolescents
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."

Therefore, no changes in the SPC are required.

- **Recommendation**

No further regulatory action is required. The studies in children agreed with the MAH at the time of registration need to be awaited.

V. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable