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Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lyrica
Pregabalin Pfizer

pregabalin

Procedure no: EMEA/H/C/000546/P46/051

Procedure no: EMEA/H/C/003880/P46/004

Note

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

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1. Introduction

On November 2015, the MAH submitted a completed paediatric study for pregabalin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study A0081231 titled "A 6-Month, Open-Label Safety Trial of Pregabalin in Adolescent Patients with Fibromyalgia" is an open-label extension study of the double-blind randomized fibromyalgia parent Study A0081180 (hereafter referred to as the "parent study").

The document provides data regarding the safety and efficacy of pregabalin in adolescent patients (12 years to 17 years old at time of enrolment in the parent study). No claims are attached to this study.

Pregabalin (LYRICA) is an α_2–δ ligand that binds with high affinity to this auxiliary subunit of voltage-gated calcium channels in central nervous system tissues. Pregabalin has been developed clinically for neuropathic pain, fibromyalgia, anxiety, and epilepsy. It is approved in the European Union (EU) for the treatment of peripheral and central neuropathic pain in adults, as adjunctive therapy in adults with partial seizures with or without secondary generalization, and for the treatment of Generalised Anxiety Disorder in adults. Pregabalin is not approved for the treatment of fibromyalgia in the EU.

In the United States (US), LYRICA is approved for fibromyalgia, neuropathic pain (associated with diabetic peripheral neuropathy, spinal cord injury, or post herpetic neuralgia), and adjunctive therapy for adult patients with partial onset seizures. LYRICA is approved for neuropathic pain and fibromyalgia in Japan.

2.2. Clinical aspects

2.2.1. Introduction

The MAH submitted a final report(s) for Study A0081231 (hereafter study 1231) titled "A 6-Month, Open-Label Safety Trial of Pregabalin in Adolescent Patients with Fibromyalgia" in which 63 subjects were enrolled which was an open-label extension study of the double-blind randomized fibromyalgia parent Study A0081180 thereafter referred to as the "parent study"). Patients were 12 to 17 years old at time of enrolment in the parent study. The last subject's last study visit (LSLV) in this trial was completed on 01 June 2015.

Pregabalin is indicated in the EU only in adults for the treatment of peripheral and central neuropathic pain, as adjunctive therapy in adults with partial seizures with or without secondary generalisation, and for Generalised Anxiety Disorder. The indication fibromyalgia has been rejected in the past because the effect was only demonstrated in the US population but not in EU studies.

2.2.2. Clinical study

Description

Study 1231 was an open-label extension study of the double-blind randomized fibromyalgia parent Study A0081180, thereafter referred to as the “parent study”. Altogether 63 subjects were enrolled. They were 12 to 17 years old at the time of enrolment in the parent study. The last subject’s last study visit (LSLV) in this trial was completed on 01 June 2015.

Methods

Objective(s)

The objective of this study was to further evaluate the safety of pregabalin in a flexible dose regimen.

Study design

After the termination visit and study drug taper in the parent study, subjects had an option of starting open-label treatment in Study 1231. The study consisted of 3 phases: dose optimization (3 weeks), flexible dose (21 weeks), and follow-up/taper (1 week).

Study population /Sample size

Eligible subjects in Study 1231 had to meet the inclusion criteria from the parent study (age 12 years to 17 years old at time of enrolment in the parent study, and the Yunus and Masi criteria for fibromyalgia), received double-blind study drug in the parent study, completed the study and wished to take open-label pregabalin.

A total of 63 subjects were screened, enrolled, and treated with pregabalin in this study. The first subject was enrolled on 01 September 2010, and the LSLV was on 01 June 2015. The 63 subjects were recruited at 19 study centers: US (14 centers; 40 subjects), India (4 centers; 20 subjects), and Czech Republic (1 center; 3 subjects). Of the 63 subjects, 33 (52.4%) subjects had previously been treated in the parent study with pregabalin, and 30 (47.6%) subjects with placebo.

Treatments

Subjects initiated pregabalin dosing at 75 mg/day and, based on tolerability and response, had their dose optimized over 3-weeks with continuation of 75 mg/day or had their dose escalated to 150, 300, or 450 mg/day. At the end of the study, subjects tapered the pregabalin dose over a 1-week period.

Outcomes/endpoints

The primary efficacy endpoint in this study was the Pain Numeric Rating Scale (pain NRS).

Statistical Methods

The efficacy analysis set included all subjects who had received at least 1 dose of study drug. There was no specific, predetermined sample size and the number of subjects enrolled was determined by the number of subjects who wanted to receive open-label pregabalin after participating in the parent study. Data for all subjects treated in the study were combined and labelled as pregabalin.

Pain NRS results were listed and summarized by treatment using descriptive statistics: n, arithmetic mean, standard deviation (SD), median, minimum, maximum and range.

No inferential or statistical testing was performed. The pain NRS is a 0 to 10 scale, with higher scores reflecting worse pain.

The baseline for pain NRS summaries was defined as the last score prior to pregabalin treatment, as follows:

- For subjects randomized to pregabalin in the parent study, the baseline was defined as the last score prior to treatment in that study (Visit 2, randomization).
- For subjects randomized to placebo in the parent study, the baseline was defined as the last score prior to treatment in Study 1231 (Visit 1).

Results

Baseline data

Baseline data are presented in table 1. The majority of subjects (53 of 63) were female. All but 2 of the female subjects (3.8%) had experienced menarche. Mean (range) age of all subjects was 14.8 (12 to 17) years. The majority of subjects were White (55.6%) or Asian (31.7%). All 63 subjects had been experiencing fibromyalgia symptoms for a mean of 2.5 years (range: 0.6 years to 11.5 years) and were diagnosed with fibromyalgia for a mean of 0.8 years (range: 0.3 years to 3.9 years) prior to study start, based on the medical history data provided at the start of the parent study. All 63 subjects met the Yunus and Masi criteria at the start of the parent study.

Table 1. Demographic Characteristics – Safety Analysis Set

Demographic Characteristics	Male (N = 10)	Female (N = 53)	Total (N = 63)
Hormonal Status - Number (%) of Female Subjects			
Premenarchal		2 (3.8)	
Menarche		51 (96.2)	
Age (years)			
Mean	14.1	15.0	14.8
SD	1.4	1.3	1.4
Range	12 to 16	12 to 17	12 to 17
Age (years) - Number (%) of Subjects			
12 years	2 (20.0)	2 (3.8)	4 (6.3)
13 years	1 (10.0)	7 (13.2)	8 (12.7)
14 years	3 (30.0)	7 (13.2)	10 (15.9)
15 years	2 (20.0)	17 (32.1)	19 (30.2)
16 years	2 (20.0)	14 (26.4)	16 (25.4)
17 years	0	6 (11.3)	6 (9.5)
Race - Number (%) of Subjects			
White	7 (70.0)	28 (52.8)	35 (55.6)
Black	0	4 (7.5)	4 (6.3)
Asian	3 (30.0)	17 (32.1)	20 (31.7)
Other	0	4 (7.5)	4 (6.3)
Weight (kg)			
Mean	60.3	61.9	61.6
SD	20.4	18.3	18.5
Range	29.8 to 105.3	31.0 to 135.5	29.8 to 135.5
Height (cm)			
Mean	165.9	161.0	161.8
SD	13.6	6.9	8.3
Range	141.0 to 184.0	147.0 to 177.0	141.0 to 184.0
Body Mass Index (kg/m^2)			
Mean	21.4	23.7	23.3
SD	4.9	6.3	6.2
Range	15.0 to 33.3	12.7 to 52.7	12.7 to 52.7

Notes: Body mass index is defined as weight/(height*.01)**2. Hormonal status was collected at screening visit of Study A0081180. All other data are from screening visit of Study 1231.
Abbreviations: CSR = clinical study report; SD = standard deviation; N = total number of subjects.
Source: Study 1231 CSR, Section 14, Table 14.1.2.1.

Efficacy results

Table 2 presents improvement in pain during the study. A mean (SD) pain score improvement from baseline of 2.1 (2.51) points was observed at Week 3, the first post-treatment assessment. Similar levels of pain improvement were maintained throughout the study. Mean (SD) pain score improvements were 1.8 (2.95) points at Week 8, and 2.1 points at Weeks 16, 24, and at last visit on study (SD: 2.60, 2.56, and 2.47, respectively). Pain score improvements were observed and maintained regardless of whether subjects had previously received pregabalin or placebo in the parent study.

Table 2. Pain Numeric Rating Scale Summary by Visit - Observed and Change from Baseline - Efficacy Analysis Set

Time Point	N	Mean	SD	Median	Range
Baseline	63	6.7	1.68	7.0	1.0 to 10.0
Visit 1	62	5.7	2.09	6.0	1.0 to 10.0
Visit 1 change from Baseline	62	-1.0	1.97	0.0	-7.0 to 3.0
Week 3	61	4.5	2.13	5.0	0.0 to 9.0
Week 3 change from Baseline	61	-2.1	2.51	-2.0	-9.0 to 3.0
Week 8	55	4.8	2.54	5.0	0.0 to 10.0
Week 8 change from Baseline	55	-1.8	2.95	-2.0	-10.0 to 5.0
Week 16	51	4.5	2.41	5.0	0.0 to 9.0
Week 16 change from Baseline	51	-2.1	2.60	-2.0	-10.0 to 4.0
Week 24/ET	55	4.6	2.47	5.0	0.0 to 9.0
Week 24/ET change from Baseline	55	-2.1	2.56	-2.0	-10.0 to 2.0
Last Visit on Study	63	4.6	2.38	5.0	0.0 to 9.0
Last Visit on Study change from Baseline	63	-2.1	2.47	-2.0	-10.0 to 2.0

Notes: Negative change indicates improvement. The pain Numeric Rating Scale (pain NRS) consists of an 11-point NRS rating from 0 (no pain) to 10 (worst possible pain). Subjects choose the number that 'best describes your pain during the past week.' For subjects randomized to pregabalin in the parent Study A0081180, the baseline is taken as the last score prior to treatment in the parent study (Visit 2, randomization). For subjects randomized to placebo in the parent study, the baseline is taken as the last score prior to treatment in Study 1231 (Visit 1, baseline). These subjects have the same baseline value as Visit 1 value. Last visit on study is a subject's last non-missing value.
Abbreviations: N = number of subjects; SD = standard deviation; NRS = Numeric Rating Scale; ET = Early Termination
Source: Study 1231 CSR, Section 14, Table 14.2.1.

Safety results

The safety analysis set consisted of all subjects who received at least 1 dose of study drug.

There were no deaths in this study.

AE: Table 3 presents Treatment-Emergent Adverse Events (TEAE) which were experienced by ≥5% of subjects. A total of 45 (71.4%) subjects experienced at least 1 TEAE; these were considered related to study drug in 29 (46.0%) subjects. The most frequently reported TEAEs were dizziness and fatigue, reported for 14 (22.2%) and 8 (12.7%) subjects, respectively.

The majority of TEAEs were mild or moderate in severity. At least 1 severe TEAE was reported for 6 (9.5%) subjects: pneumonia, migraine, appendicitis, mood swings, arthralgia, joint instability, and disturbance in attention, of which migraine, mood swings, and disturbance in attention were considered to be related to the study drug

SAE: There were 3 (4.8%) subjects who had serious adverse events (SAEs) during the study. These resulted in hospitalization due to: migraine, appendicitis, and joint instability, all of which were severe events. The SAEs of appendicitis and joint instability were not considered related to the study drug and resolved. The SAE of severe migraine was considered related to the study drug and resolved with sequelae; the sequela of the SAE was a moderate migraine not considered by the investigator to be an SAE.

There were 2 (3.2%) subjects who had TEAEs leading to discontinuation of the study drug.

Dizziness, fatigue and nausea in 1 subject were considered related to the study drug, and spinal stenosis in 1 subject was considered related to the disease process. All events leading to discontinuation resolved.

There were no AEs related to suicidal ideations or behaviour, including no suicide attempts or completed suicides. Suicidality assessments (STS, C-SSRS) did not report any suicidal behaviour. During the study, 6 (9.5%) subjects reported suicidal ideation without plan or intent on the STS questionnaire; these 6 subjects had a history of suicidal ideation on the STS at the baseline of the parent study.

Weight gain of at least 7% was reported for 18 (29.0%) subjects. There were no clinically relevant findings in physical examination, neurological examination, vital signs, laboratory test results, Tanner staging, and ECG. There were no positive pregnancy test results or pregnancies during the study.

Table 3. Treatment-Emergent Adverse Events by Preferred Term (All Causality) Experienced by ≥5% of Subjects – Safety Analysis Set

Number (%) of Subjects with Treatment-Emergent Adverse Events by Preferred Term (All Causality) Experienced by ≥5% of Subjects	Pregabalin (N = 63) n (%)
Dizziness	14 (22.2)
Fatigue	8 (12.7)
Headache	6 (9.5)
Nausea	5 (7.9)
Abdominal pain	5 (7.9)
Abdominal pain upper	5 (7.9)
Ear infection	4 (6.3)
Upper respiratory tract infection	4 (6.3)
Nasal congestion	4 (6.3)
Dysmenorrhoea	3 (5.7)

Notes: If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. For the algorithm, any missing severities have been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild. Includes data up to 999 days after last dose of study drug. Percentages of gender specific events were calculated using the corresponding gender count as denominator. Preferred terms ordered by incidence. Medical Dictionary for Regulatory Activities (MedDRA), v18.0, coding applied.
Abbreviations: MedDRA = Medical Dictionary of Regulatory Activities; N = total number of subjects; n = number of subjects within a category (expressed as a percent).
Source: Study 1231 CSR, Section 14, Table 14.3.1.2.3.

2.2.3. Discussion on clinical aspects

The adverse event (AE) profile observed in this study was consistent with the known safety profile for pregabalin as reported in the SPC.

Pregabalin is not indicated for children and adolescents and the SPC indicates that safety and efficacy of pregabalin has not been established in children and adolescents and that therefore no recommendation on a posology can be made. The SPC also indicates that pregabalin safety profile observed in two paediatric studies was similar to that observed in the adult studies.

It is considered that although some of the safety issues observed in the study, specifically mood swings and weight gain, may have different implications for children as compared to adults, since

pregabalin is not indicated for the paediatric population, the new evidence does not change the B/R balance of pregabalin. In addition, the evidence observed in this study is already reflected in the product information of pregabalin and therefore, no further actions are required in this respect.

3. CHMP overall conclusion and recommendation

The MAH has submitted a paediatric safety study for pregabalin which included 63 adolescents with fibromyalgia. The results show no new safety issue and the MAH is not requesting any changes to the product information based on this study.

Pregabalin is not indicated for children and adolescents and the SPC indicates that safety and efficacy of pregabalin has not been established in children and adolescents and that therefore no recommendation on a posology can be made. The SPC also indicates that pregabalin safety profile observed in two paediatric studies was similar to that observed in the adult studies.

It is considered that although some of the safety issues observed in the study, specifically mood swings and weight gain, may have different implications for children as compared to adults, since pregabalin is not indicated for the paediatric population, the new evidence does not change the B/R balance of pregabalin. In addition, the evidence observed in this study is already reflected in the product information of pregabalin and therefore, no further actions are required in this respect.

☒ Fulfilled:

No regulatory action required.