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PROPRIETARY DRUG NAME/GENERIC DRUG NAME: Lyrica® / Pregabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NCT NO.: 00150449

PROTOCOL NO.: Protocol 1008-100

PROTOCOL TITLE: A 1-Year Open-Label Safety Extension Study of Pregabalin (CI-1008) in Patients With Anxiety Disorders

Study Center(s): One-hundred-and-thirteen (113); 100 in Europe (UK [39], Germany [10], Netherlands [9], Spain [9], France [8], Poland [8], Belgium [7], Ukraine [4], Austria [2], Estonia [2], Italy [1], Latvia [1]) and 13 in South Africa.

Study Initiation and Completion Dates: 10 January 2001 to 10 March 2006

Phase of Development: Phase 3

Study Objective(s):

- To enable subjects who have participated in pregabalin efficacy studies in anxiety disorders to continue receiving pregabalin treatment
- To evaluate under open-label conditions the long-term safety and tolerability of pregabalin in doses ranging from 150 to 600 mg/day
- To evaluate under open-label conditions the effect of pregabalin on the severity of illness, following either continuation of pregabalin treatment or after switching from an active comparator or placebo in the previous efficacy study

METHODS

Study Design: This was a nonrandomized, multicenter, open-label, safety extension study of pregabalin in subjects with anxiety disorders (generalized anxiety disorder [GAD], social anxiety disorder [SAD], and panic disorder [PD]). Subjects were treated with pregabalin for a maximum duration of 12 months. The intent was for subjects to enter this study immediately after completing participation in the preceding efficacy study including any protocol specified follow-up period and visits. The study consisted of 3 phases: a titration phase, a flexible dosing phase, and a taper/follow-up phase.

Number of Subjects (Planned and Analyzed):
Planned: The number of subjects enrolled in this long-term extension study depended on the number of subjects who received study medication in Studies 1008-081, -087, -091, and -152 and who elected to continue with open-label treatment.

Analyzed: 528 subjects

Diagnosis and Main Criteria for Inclusion: Subjects from short-term efficacy studies of pregabalin in GAD (1008-087 and -152), SAD (1008-081) and PD (1008-091) were eligible for this study. Women of childbearing potential had to have had a negative serum pregnancy test at termination of the preceding double-blind study.

Study Treatment: Treatment was with pregabalin 100 mg capsules administered at a dose of between 200 and 600 mg/day in divided doses. Treatment was administered twice daily (BID).

Efficacy Evaluations: Severity of symptoms was measured on a 7-point clinician rated scale ranging from 1 (not at all ill) to 7 (among the most extremely ill) using the Clinical Global Impression of Severity (CGIS).

Safety Evaluations: Adverse event (AE) data (occurrence, intensity, and relationship to study drug), clinical laboratory tests (hematology, clinical chemistry), concurrent medications, physical examination, and 12-lead electrocardiograms (ECGs)

Statistical Methods: Safety and efficacy data were summarized for the intent-to-treat (ITT) population, defined as all subjects who received at least 1 dose of study medication in this open-label study. Results of all efficacy and safety evaluations were summarized using descriptive statistics. No inferential analysis was planned.

RESULTS

Subject Disposition and Demography: A summary of subject disposition is presented in Table S1, below.

Table S1 Summary of Subject Disposition

	Disposition, N (%)[a]	
Subjects Entered in Open-Label Study[b]	528	
Completed Treatment Phase		299 (56.6)
Withdrawn During Treatment Phase:	229	(43.4)
Adverse Event[c]	51	(9.7)
Lack of Compliance	19	(3.6)
Lack of Efficacy	40	(7.6)
Lost to Follow-up	20	(3.8)
Other/Administrative Reasons[d]	52	(9.8)
Withdrew Consent	47	(8.9)
Entered Taper/Follow-Up Phase[e]	421	(79.7)
Completed Taper/Follow-Up Phase	384	(91.2)
Withdrawn During Taper/Follow-Up Phase:	37	(8.8)
Adverse Event	6	(1.4)
Lack of Compliance	4	(1.0)
Lost to Follow-Up	12	(2.9)
Other/Administrative Reasons	11	(2.6)
Withdrew Consent	4	(1.0)

[a]Denominator for the percentage calculations is the number of subjects who entered the open-label study; during the taper phase, the denominator is the number who entered the taper phase.
[b]Subjects took at least 1 dose of pregabalin.
[c]The number for discontinuations due to AEs was based on data from the case report form disposition pages. The number obtained from analysis of the AE reports is greater by 2 (see Table S5). The 2 systems were not reconciled before the database was closed.
[d]Includes those discontinued following the Ministry of Health or EC decision.
[e]All subjects with a follow-up status.

Of the 528 subjects enrolled, 202 (38.3%) were men and 326 (61.7%) were women. The majority of subjects were white (96.4%). Subjects ranged in age from 18 to 89 years with a mean (median) age of 48.6 years (45.5 years). One hundred forty-two subjects (26.9%) were ≥65 years of age. The mean (median) weight was 73.5 kg (72 kg), ranging from 40 to 137 kg. Subject characteristics were recorded at the baseline visit of the preceding double-blind study.

Efficacy Results: A summary of efficacy results is presented in Table S2, below.

Table S2 Summary of Clinical Global Impression of Severity (CGIS)

Pregabalin	Week 0	Week 27	Week 51/ Termination	Endpoint
N = 528	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Number Assessed	528	360	491	495
Not at All Ill	25 (4.7)	56 (15.6)	95 (19.3)	97 (19.6)
Borderline Ill	77 (14.6)	137 (38.1)	156 (31.8)	157 (31.7)
Mildly Ill	168 (31.8)	125 (34.7)	148 (30.1)	149 (30.1)
Moderately Ill	180 (34.1)	37 (10.3)	64 (13.0)	64 (12.9)
Markedly Ill	63 (11.9)	4 (1.1)	22 (4.5)	22 (4.4)
Severely Ill	15 (2.8)	1 (0.3)	6 (1.2)	6 (1.2)
Among the Most Extremely Ill Subjects	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Number Assessed for Endpoint is the number of subjects with a CGIS Form at 1 or more visit post Week 0.

Safety Results: The majority of subjects (404 of 528, 76.5%) experienced at least 1 AE during the study. Almost half (246 of 528, 46.6%) of the subjects experienced an AE that was associated with pregabalin treatment. Differences in incidence of AEs by gender or age were small. Data were sparse for comparisons by race. Most AEs were mild or moderate in intensity.

A summary of all AEs that were reported in ≥10 subjects, along with the number of these AEs that were considered to be related to pregabalin, is presented in Table S3, below.

Table S3 Summary of All and Associated TESS Adverse Events by Decreasing Frequency in ≥10 Subjects, (N = 528)

Adverse Event Preferred Term	All Adverse Events		Associated Adverse Events	
	n	Percent	N	Percent
Dizziness	82	15.5	66	12.5
Infection	56	10.6	0	0
Insomnia	49	9.3	25	4.7
Headache	46	8.7	28	5.3
Somnolence	45	8.5	40	7.6
Accidental Injury	37	7.0	3	0.6
Pharyngitis	35	6.6	0	0
Weight Gain	33	6.3	29	5.5
Diarrhea	30	5.7	10	1.9
Nausea	29	5.5	18	3.4
Asthenia	27	5.1	21	4.0
Back Pain	25	4.7	1	0.2
Depression	25	4.7	5	0.9
Nervousness	23	4.4	12	2.3
Pain	22	4.2	4	0.8
Dyspepsia	20	3.8	7	1.3
Chest Pain	19	3.6	4	0.8
Bronchitis	18	3.4	1	0.2
Abdominal Pain	17	3.2	5	0.9
Anxiety	17	3.2	10	1.9
Constipation	17	3.2	11	2.1
Dry Mouth	15	2.8	11	2.1
Hypertension	14	2.7	5	0.9
Amnesia	13	2.5	11	2.1
Rash	13	2.5	5	0.9
Thinking Abnormal	13	2.5	12	2.3
Arthralgia	12	2.3	2	0.4
Flu Syndrome	12	2.3	1	0.2
Peripheral Edema	12	2.3	2	0.4
Urinary Tract Infection	12	2.3	1	0.2
Amblyopia	11	2.1	10	1.9
Cough Increased	11	2.1	1	0.2
Rhinitis	11	2.1	3	0.6
Otitis Media	10	1.9	0	0
Sleep Disorder	10	1.9	7	1.3

TESS= Treatment-emergent symptoms scale

One subject died during the study. In the opinion of the investigator and study sponsor, the subject's worsening ischemic heart disease leading to death was due to coronary artery atherosclerosis and was not related to pregabalin.

Thirty-seven subjects experienced a total of 47 SAEs, 3 of which were possibly (1 event of anxiety and 1 of rectal disorder) or probably (somnolence) associated with treatment. The relationship of 1 SAE of neoplasm to treatment was unknown. A summary of SAEs reported during the study is presented in Table S4, below.

Table S4 Summary of All Serious Adverse Events (N=528)

Preferred Term	Number (%) of Subjects[a]
Overdose	4 (0.8)
Chest pain	3 (0.6)
Neoplasm	3 (0.6)
Angina pectoris	2 (0.4)
Anxiety	2 (0.4)
Dizziness	2 (0.4)
Infection	2 (0.4)
Myocardial infarct	2 (0.4)
Syncope	2 (0.4)
Abdominal pain	1 (0.2)
Adenoma	1 (0.2)
Angioedema	1 (0.2)
Atrial fibrillation	1 (0.2)
Bone pain	1 (0.2)
Breast carcinoma	1 (0.2)
Bronchiectasis	1 (0.2)
Carcinoma	1 (0.2)
Cerebral ischemia	1 (0.2)
Cyst	1 (0.2)
Depression	1 (0.2)
Diarrhea	1 (0.2)
Gastrointestinal hemorrhage	1 (0.2)
Hyperglycemia	1 (0.2)
Hypoxia	1 (0.2)
Migraine	1 (0.2)
Myocardial ischemia	1 (0.2)
Peripheral vascular disorder	1 (0.2)
Pneumonia	1 (0.2)
Prostatic carcinoma	1 (0.2)
Rectal disorder	1 (0.2)
Somnolence	1 (0.2)
Urinary tract disorder	1 (0.2)
Vestibular disorder	1 (0.2)

[a]Some subjects were withdrawn because of more than 1AE.

The SAEs of overdose of study drug in 4 subjects were all considered by the investigators to be definitely not related to pregabalin. All 4 subjects recovered by 1 day after the overdoses. Three were withdrawn from the study and 1 was permitted to continue after a temporary discontinuation of study drug.

Fifty-three subjects (10.0%) withdrew from the study due to AEs. A summary of all AEs leading to withdrawal is presented in Table S5, below.

Table S5 Summary of Withdrawals Due to TESS Adverse Events

	Pregabalin (N = 528)	
Preferred Term	**n**	**Percent**
Dizziness	15	2.8
Somnolence	6	1.1
Weight Gain	6	1.1
Nausea	4	0.8
Headache	3	0.6
Overdose	3	0.6
Abdominal Pain	2	0.4
Asthenia	2	0.4
Chest Pain	2	0.4
Depersonalization	2	0.4
Myocardial Infarct	2	0.4
Thinking Abnormal	2	0.4
Abnormal Dreams	1	0.2
Amnesia	1	0.2
Anxiety	1	0.2
Atrial Fibrillation	1	0.2
Carcinoma	1	0.2
Confusion	1	0.2
Constipation	1	0.2
Depression	1	0.2
Diarrhea	1	0.2
Dyspepsia	1	0.2
Ear Disorder	1	0.2
Gastrointestinal Hemorrhage	1	0.2
Healing Abnormal	1	0.2
Hyperuricemia	1	0.2
Hypesthesia	1	0.2
Impotence	1	0.2
Incoordination	1	0.2
Increased Appetite	1	0.2
Infection	1	0.2
Insomnia	1	0.2
Lab Test Abnormal	1	0.2
Myocardial Ischemia	1	0.2
Nausea and Vomiting	1	0.2
Neoplasm	1	0.2
Nervousness	1	0.2
Neurosis	1	0.2
Peripheral Edema	1	0.2
Rash	1	0.2
SGPT Increased	1	0.2
Urinary Tract Disorder	1	0.2
Urticaria	1	0.2
Vertigo	1	0.2

TESS= Treatment-emergent symptoms scale

One additional subject was not included in the listing of AEs that led to withdrawal although did have "discontinued" for an action for the AE dizziness. This subject did not have "adverse event" listed as the reason for withdrawal in the subject status/listing of termination.

There were no clinically meaningful changes in clinical laboratory values and few potentially clinically important changes in vital signs. Seventeen of the 461 subjects assessed (3.7%) had new clinically significant abnormal ECG finding recorded during the study. Significant weight gain (≥ 7% increase from baseline) occurred for 116 of 476 subjects (24.4%) for whom data were available. Weight gain was reported as an AE for 33 subjects (6.3%). Six subjects withdrew due to weight gain. Except for an increase in weight, there were no clinically important changes in the results of physical examinations.

CONCLUSION(S):

- Pregabalin, in doses ranging from 150 to 600 mg/day under open-label conditions for the durations observed in this interim report, was well-tolerated in subjects with anxiety disorders.
- Most AEs were mild or moderate in intensity.
- The AE profile in this long-term open-label study is primarily what is expected of a CNS-active agent and is similar to that seen in double-blind studies.
- Three SAEs (rectal disorder, somnolence, and severe anxiety) were considered possibly or probably associated with treatment.
- Approximately 10% of subjects withdrew due to AEs.
- No clinically meaningful trends in clinical laboratory values were observed.
- Significant weight gain (≥ 7% increase from baseline) occurred for 116 of 476 subjects (24.4%) for whom data were available during their pregabalin treatment.
- At the termination visit, 81% of the subjects were considered mildly ill, borderline ill, or not at all ill, as compared with 46% at the first visit.