Safety Profile and Tolerability of Up to 1 Year of Pregabalin Treatment in 3 Open-Label Extension Studies in Patients With Fibromyalgia

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ABSTRACT

Background: Pain relief and an acceptable safety profile have been reported in randomized controlled trials (RCTs) of pregabalin in the treatment of fibromyalgia (FM) for up to 14 weeks.

Objective: To evaluate the safety profile and tolerability of pregabalin (75–300 mg BID) treatment for up to 1 year in patients with FM.

Methods: Twelve-week data were pooled from 3 open-label extension studies of pivotal RCTs. Study 1 was a 1-year extension of a 13-week RCT, and studies 2 and 3 were 12-week extensions of 14-week RCTs. The 1-year data were separately evaluated. The open-label data are summarized using descriptive statistics.

Results: Overall, 1206 patients (92.4% female) with a mean (SD) age of 48.8 (10.7) years received open-label extended pregabalin treatment. A total of 119 of 1206 patients (9.9%) permanently discontinued study participation due to treatment-emergent adverse events (all causality) at 12 weeks (pooled data) and 53 of 429 (12.4%) within 1 year. Consistent with previous RCTs, the most commonly reported treatment-emergent adverse events with open-label pregabalin treatment were dizziness, somnolence, headache, peripheral edema, and increased weight. The highest incidence rates in the pooled 12-week data were for dizziness (214 of 1206; 17.7%) and somnolence (96 of 1206; 8.0%). In ratings of severity (mild, moderate, severe), most were reported as mild to moderate. The mean (SD) change in patient-reported visual analog scale pain scores (0–100) from the open-label baseline to the end of treatment was −21 (30.5) in study 1 (1 year), −26.7 (28.8) in study 2 (12 weeks), and −20.1 (26.8) in study 3 (12 weeks).

Conclusions: The data from these extension studies suggest that the adverse event safety profile and tolerability of patients with FM treated with open-label pregabalin (75–300 mg BID) for up to 1 year were stable and were consistent with those of previous studies. ClinicalTrials.gov identifiers: NCT00151528 (A0081057 [study 1]), NCT00282997 (A0081078 [study 2]), and NCT00346034 (A0081101 [study 3]). (*Clin Ther*. 2012;34:1092–1102)

Key words: fibromyalgia, pain, pregabalin, safety profile.

INTRODUCTION

Fibromyalgia (FM) is a chronic pain disorder that is associated with other characteristic symptoms, including sleep disturbance and fatigue.[1,2] The American College of Rheumatology defines FM as chronic widespread pain lasting ≥3 months in addition to pain on palpation at 11 of 18 specified tender points.[3]

To date, the etiology of FM is not completely understood, but it seems to result from dysfunction of pain modulation in the central nervous system.[4–9] The analgesic action of pregabalin is thought to be mediated through binding to the auxiliary $\alpha 2\delta$ subunit of voltage-sensitive calcium channels. This reduces calcium

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ion influx into hyperexcited neurons and reduces the release of several neurotransmitters believed to play a role in pain processing, such as substance P and glutamate.[10]

The efficacy, safety profile, and tolerability of pregabalin treatment have been reported in 3 previously published 13- to 14-week multicenter, double-blind, randomized, placebo-controlled clinical trials of FM.[11–13] All 3 trials included 3 pregabalin arms (300, 450, and 600 mg/d). Primary efficacy end points were assessed by self-reported mean pain scores on an 11-point numerical rating scale. The first (n = 748) and second (n = 750) of these studies were conducted in the United States. Significant improvements in mean pain scores were evident in each pregabalin group versus the placebo group ($P < 0.05$).[11,12] The third study enrolled 736 patients in centers outside the United States. Significant reductions in mean pain scores were reported only with pregabalin, 450 mg/d, compared with placebo at the end of treatment ($P = 0.013$).[13] An acceptable safety and tolerability profile was reported in each of these 3 pregabalin double-blind randomized controlled trials (RCTs). Dizziness and somnolence were consistently reported as the most common treatment-emergent adverse events (TEAEs).[11–13]

Efficacy and safety profile were also reported in a 6-month withdrawal trial that initially established patients' optimal dosing of pregabalin in a 6-week open-label escalating-dose phase.[14] Patients in that trial who responded to open-label treatment (≥50% decrease in visual analog scale [VAS] pain scores and "much" or "very much" improved on the Patient Global Impression of Change scale) could then enter a 26-week double-blind phase in which they were randomized to receive either their optimal pregabalin dose (300, 450, or 600 mg/d) (n = 279) or placebo (n = 287). Efficacy was measured by the number of days taken to reach a loss of treatment response, defined as 2 consecutive VAS pain scores with <30% reduction from the open-label baseline VAS score or worsening of FM symptoms (as judged by the investigator). Kaplan-Meier estimates showed that the time taken for the first 25% of patients to reach loss of treatment response was significantly longer for patients receiving pregabalin (34 days) than for those using placebo (7 days; $P < 0.0001$). Pregabalin had an acceptable safety profile during the open-label and double-blind phases; however, more patients withdrew from the double-blind phase owing to TEAEs in the pregabalin group (16%) than in the placebo group (7%).[14]

In 2007, the US Food and Drug Administration approved pregabalin for the management of FM. Patients completing each of the three 13- to 14-week RCTs reported previously herein[11–13] were offered the opportunity to enroll in open-label extension trials. Data from these 3 extension trials are evaluated herein to assess the long-term safety profile and tolerability of pregabalin treatment for up to 1 year in patients with FM.

MATERIALS AND METHODS

Overview

Patients participating in the 13-week trial[11] were eligible for a 1-year open-label extension (study 1), and patients participating in the 14-week trials[12,13] were eligible for 12-week open-label extensions (studies 2 and 3). Studies 1 and 2 were conducted at 79 and 84 centers, respectively, in the United States. Study 3 was conducted at 51 centers in North America (Canada), Europe (Denmark, France, Germany, Italy, the Netherlands, Portugal, Sweden, Switzerland, and the United Kingdom), and Asia (India and South Korea).

The studies were performed in accordance with the Declaration of Helsinki. The institutional review board at each respective center approved the protocol. All the patients provided written informed consent once they understood the study procedures and before study procedures were initiated.

Entry Criteria

Patients were considered eligible for each open-label study if they met the inclusion criteria for the double-blind study protocol and completed the double-blind trial. The double-blind trials enrolled patients aged ≥18 years who met the 1990 American College of Rheumatology criteria for FM.[3] At screening and randomization, patients had a score of ≥40 mm on a 100-mm pain VAS and an average score of ≥4 on the daily pain diary 11-point pain rating scale (0 = no pain to 10 = worst possible pain) based on ≥4 entries in the week before randomization.

The key exclusion criteria were any active inflammatory disorders or painful conditions that might confound the assessment of FM-related pain, the presence of unstable medical disorders, creatinine clearance of ≤60 mL/min, or clinically significant psychiatric conditions, including severe depression. Patients were not