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Levetiracetam extended release for the treatment of patients with partial-onset seizures: A long-term, open-label follow-up study

Steve Chung[a,*], Hugo Ceja[b], Jacek Gawłowicz[c], Cindy McShea[d], Jimmy Schiemann[d], Sarah Lu[d,1]

[a] Banner University Medical Center, 111 E. McDowell Road, Phoenix, AZ 85006, USA
[b] Pediatric Neurology Department, Hospital Civil de Guadalajara, Coronel Calderón 777, Col. El Retiro, Guadalajara, Jalisco, Mexico
[c] Department of Neurology, Medical University of Lublin, Lublin, Poland
[d] UCB Pharma, 8010 Arco Corporate Drive, Raleigh, NC 27617, USA

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SUMMARY

This was an open-label study (N01281 [NCT00419393]) assessing the long-term safety of extended-release levetiracetam (LEV XR) in patients with partial-onset seizures (POS); the study was a follow-up to a double-blind, randomized, historical controlled, multicenter, conversion to monotherapy study (N01280 [NCT00419094]). Eligible patients initially received LEV XR 2000 mg/day; dose adjustments and the addition of other antiepileptic drugs (AEDs) were permitted. Overall, 190 patients were enrolled, 189 (99.5%) received LEV XR (safety and efficacy populations) and 166 patients (87.4%) completed the study. The study duration in completed patients was 5.5–24.6 months. Mean daily dose of LEV XR was 2131 mg/day. Treatment-emergent adverse events (TEAEs) occurred in 126 patients (66.7%); most were of mild or moderate severity. Five patients (2.6%) had a TEAE that led to treatment discontinuation. Treatment-emergent serious adverse events occurred in 22 patients (11.6%). Twenty-six patients (13.8%) experienced a psychiatric TEAE. The median 7-day normalized POS frequency was: 1.38 at N01280 study baseline; 0.50 at the first visit of N01281 (last visit of N01280); and 0.00–0.36 between all subsequent visits. Overall, 171 patients (90.5%) entered the N01281 study on LEV XR monotherapy; 65.3% (32/49) of patients remained on monotherapy for 12 months and 47.1% (8/17) for 18 months. While remaining on LEV XR monotherapy, 27/139 patients (19.4%) were seizure-free at 6 months and 8/49 (16.3%) at 12 months. In conclusion, LEV XR was well tolerated when administered as long-term monotherapy or in combination with other AEDs in patients with inadequately controlled POS.

1. Introduction

Levetiracetam (LEV) is an established second-generation antiepileptic drug (AED). An immediate-release (IR) formulation of LEV was approved in 1999 by the United States Food and Drug Administration (US FDA) as adjunctive therapy for the treatment of partial-onset seizures (POS) in adults with epilepsy. The efficacy and tolerability of LEV IR in this population was demonstrated in three multicenter, randomized, double-blind, placebo-controlled studies, involving more than 900 patients (Ben-Menachem and Falter, 2000; Cereghino et al., 2000; Shorvon et al., 2000). LEV IR is now approved for use in more than 60 countries worldwide.

In order to provide patients with the convenience of once-daily dosing, an extended-release formulation of LEV (LEV XR, Keppra XR®; UCB S.A., Brussels, Belgium) was developed. Data from clinical pharmacology studies conducted in healthy volunteers (Rouits et al., 2009) showed that, under fasting conditions, a single dose of LEV XR 1000 mg was bioequivalent to two 500 mg doses of LEV IR given 12 h apart. Data from a subsequent multicenter, randomized, double-blind, placebo-controlled study conducted in patients aged 12–70 years showed that once-daily LEV XR 1000 mg adjunctive therapy was effective and well tolerated in patients with treatment-refractory POS (Peltola et al., 2009). In 2008, the US FDA

Abbreviations: AED, antiepileptic drug; DB, double-blind; ECg, electrocardiogram; IR, immediate release; ITT, intent-to-treat; LEV, levetiracetam; OL, open-label; POS, partial-onset seizure; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; US FDA, United States Food and Drug Administration; XR, extended release.

* Corresponding author. Tel.: +1 602 406 6271; fax: +1 602 708 0852.
E-mail addresses: Steve.Chung@bannerhealth.com (S. Chung), Dr_Ceja@hotmail.com (H. Ceja), JGawlowicz@yahoo.com (J. Gawłowicz), Cindy.McShea@ucb.com (C. McShea), Jimmy.Schiemann@ucb.com (J. Schiemann), Sarah.h.Lu@gsk.com (S. Lu).
[1] GlaxoSmithKline Shanghai R&D, Building 3, 898 Halei Rd, Pudong, Shanghai 201203, China.

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approved LEV XR for use as adjunctive therapy in patients with POS, aged ≥16 years.

A pivotal multicenter, randomized, double-blind, historical controlled study (LEV XR-DB; Study N01280; NCT00419094) was conducted, in which patients with POS inadequately controlled with 1–2 AEDs were converted to LEV XR monotherapy at a once-daily dose of 1000 or 2000 mg (Chung et al., 2012). The cumulative exit rate for patients treated with LEV XR 2000 mg/day was significantly lower compared with that from a historical control population (0.375 vs 0.653); these results indicated that LEV XR 2000 mg/day was an effective withdrawal to monotherapy treatment. Patients participating in the LEX XR-DB study, who successfully completed a 2-week LEV XR up-titration phase, had the option of entering an open-label follow-up study (LEV XR-OL; Study N01281; NCT00419393) designed to assess the long-term safety of LEV XR monotherapy in patients with POS. The outcomes of the LEV XR-OL study are the focus of the current report.

2. Material and methods

2.1. Study design and treatment

The LEV XR-OL study (study N01281 [NCT00419393]) was a multicenter, open-label follow-up of LEV XR-DB (Chung et al., 2012). LEV XR-DB was a randomized, double-blind, historical controlled study conducted in patients with inadequately controlled POS. The historical control population was based on a meta-analysis of eight withdrawal to monotherapy (double-blind, randomized, parallel-group) studies (French et al., 2010). Patients were randomized to receive LEV XR 2000 or 1000 mg/day once daily (3:1 ratio) via an interactive voice response system. LEV XR 2000 mg/day once daily was the target dose for efficacy evaluation, while LEV XR 1000 mg/day once daily was included for consistency with the historical control study designs, and to maintain the study blind. The LEV XR-DB study comprised an 8-week baseline period, 2-week LEV XR up-titration period, 6-week baseline AED tapering period, 10-week monotherapy period, and entry into the LEV XR-OL study or a 1-week LEV XR down-titration period. During the first week of the 2-week up-titration period, all patients received LEV XR 1000 mg/day (2 × 500 mg tablets and 2 × matching placebo tablets once daily); during the second week, patients either continued to receive LEV XR 1000 mg/day or had their dose increased to LEV XR 2000 mg/day (4 × 500 mg tablets once daily). When patients had reached their randomized LEV XR dose, baseline AEDs were tapered and discontinued over a 6-week period according to standard medical practice. Patients who completed the study, or who met any of the protocol-defined exit criteria after the 2-week up-titration period, were eligible to enter the LEV XR-OL study. Patients had to meet at least one of the following protocol-defined criteria after the start of the baseline AED tapering period, in order to exit the study:

- a two-fold increase in POS frequency in any 4-week treatment period compared with baseline
- a two-fold increase in the highest consecutive 2-day seizure frequency that occurred during baseline
- a generalized seizure if none had occurred in the 6 months prior to randomization
- status epilepticus or a prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention

All patients transitioned into the LEV XR-OL study at a dose of LEV XR 2000 mg (4 × 500 mg tablets); LEV XR was taken once daily in the evenings. For the first 2 weeks of LEV XR-OL, the dose was to remain stable at 2000 mg/day, although, if this was poorly tolerated, a lower dose was permitted. After the first 2 weeks of treatment, dose adjustments were allowed. Where possible, patients who were on LEV XR monotherapy at the end of LEV XR-DB remained on LEV XR monotherapy, although the addition of other AEDs (excluding felbamate and herbal AEDs) was allowed.

The LEV XR-OL study comprised an entry visit (visit 1 [week 0]), a LEV XR treatment period (visits 2–8 [weeks 2, 14, 26, 38, 50, 74, and 98]), and a final/early discontinuation visit. The entry visit for LEV XR-OL was the last visit of LEV XR-DB, which occurred 2 weeks after the final dose of study drug. The final/early discontinuation visit of LEV XR-OL occurred approximately 2 weeks after the last dose of LEV XR. Early discontinuation criteria included: withdrawal of consent; adverse events, as assessed by the investigator; lack/loss of efficacy; protocol deviation; or lost to follow-up.

The study was conducted in accordance with the International Conference on Harmonisation–Good Clinical Practice, and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol (including any amendments) and informed consent (or assent, where applicable) forms were reviewed by a National, Regional, or Independent Ethics Committee/Institutional Review Board. Written informed consent was provided prior to study initiation.

2.2. Study population

Patients included in the LEV XR-OL study complied with the inclusion and exclusion criteria of the LEV XR-DB study (Chung et al., 2012). Male or female patients were aged 12–75 years and had inadequately controlled POS, defined as 2–40 seizures per 4-week period in the 8-week baseline period, despite receiving 1–2 AEDs at a stable dose for ≥4 weeks prior to screening. For patients receiving 2 AEDs, the second AED was taken at a dose lower than half of the US labelled dose. Patients could only participate in the LEV XR-OL study if they had been randomized to treatment and had completed at least the 2-week up-titration period of LEV XR-DB. Female patients of childbearing potential could participate if they used a medically accepted contraceptive method. All participants were required to provide written informed consent (or assent, where applicable) to participate in the study and had to be capable of understanding and completing diaries and adhering to the protocol. Exclusion criteria included pregnancy/lactation; status epilepticus during the previous 6 months; seizure clusters during the 8 weeks prior to screening or during baseline; pseudoseizures; use of benzodiazepines, phenobarbital, mysoline, felbamate, vagus nerve stimulation, neuroleptics, traditional herbal AEDs or ketogenic diet at the time of study entry; and any clinically significant acute or chronic illness. Concomitant treatments (other than AEDs) were allowed; CNS-active medication (other than baseline AEDs) was required to be stable for at least 4 weeks prior to visit 1 ([screening visit] of LEV XR-DB) and during the entire study period. Hormonal contraception had to have been stable for at least 3 months prior to visit 1 and during the entire study period. Additional exclusion criteria were screen failures of N01280; discontinuations prior to the end of the 2-week up-titration period of N01280; history of sensitivity to LEV; history of recurrent psychotic or major affective disorder or suicide attempts; digestive problems which could have impaired the absorption of the LEV XR formulation; history of poor compliance with visit schedule or medication intake; and any medical or surgical condition that might have interfered with the patient's participation in the study.

2.3. Study assessments

2.3.1. Safety

The primary objective was to assess the long-term safety and tolerability of LEV XR in patients with POS. Key outcomes included