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EFFICACY AND SAFETY OF CLOBAZAM THERAPY FOR SEIZURES ASSOCIATED WITH LENNOX-GASTAUT SYNDROME: RESULTS OF A PHASE III RANDOMIZED CONTROLLED TRIAL

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Background: Seizures associated with Lennox-Gastaut syndrome (LGS) are often refractory to common antiepileptic drugs, and more effective and better-tolerated treatment options are needed. In a Phase II dosage-ranging study,¹ clobazam, a 1,5-benzodiazepine, decreased the weekly frequency of drop seizures associated with LGS.

Objectives: We conducted a Phase III randomized controlled trial to demonstrate the efficacy and safety of clobazam for LGS.

Methods: In a placebo-controlled multicenter trial conducted in the United States, India, Europe, and Australia between August 2007 and December 2009, we compared 3 oral dosages of CLB with placebo as adjunctive therapy for LGS. Patients 2–60 years of age with LGS enrolled. Following a 4-week baseline phase, patients who had ≥ 2 drop seizures per week were randomized to placebo or 1 of 3 dosages of clobazam (0.25, 0.5, and 1.0 mg/kg/day), up to a maximum daily dosage of 40 mg. Treatment included a 3-week titration phase, followed by a 12-week maintenance phase. The primary endpoint was percentage decrease in mean weekly frequency of drop seizures during the maintenance vs. baseline phases for the modified intention-to-treat (mITT) population, which included all patients who had entered the maintenance phase. Safety assessments included periodic physical examinations, laboratory evaluations, and adverse event information. Statistical significance was prespecified as $p \leq 0.01$ for the primary endpoint.

Results: A total of 301 patients were screened, 238 were randomized, 217 comprised the mITT population, and 177 completed the study. At baseline, patients' mean age was 12.4 years, and 60.5% were male. Demographics and clinical characteristics were similar between groups. There was a statistically significant decrease in mean weekly frequency of drop seizures in all three groups receiving CLB vs. placebo: 68.3% for high-dosage CLB ($p < 0.0001$); 49.4% for medium-dosage CLB ($p = 0.0015$); and 41.2% for low-dosage CLB ($p = 0.0120$), vs. 12.1% for placebo. Somnolence, lethargy, drooling, upper respiratory infections, and behavioral abnormalities were the most frequent treatment-emergent adverse events reported for clobazam.

Conclusions: Clobazam 0.5 and 1.0 mg/kg/day statistically significantly decreased the weekly frequency of drop seizures associated with LGS. No new safety signals were observed vs. the Phase II study.

¹Conry JA, et al. *Epilepsia*. 2009;50:1158–66.