



## One More Weapon in the Fight Against Drop Seizures in Lennox-Gastaut Syndrome

### Randomized, Phase III Study Results of Clobazam in Lennox-Gastaut Syndrome.

Ng YT, Conry JA, Drummond R, Stolle J, Weinberg MA, on behalf of the OV-1012 Study Investigators. *Neurology* 2011;77:1473–1481.

**OBJECTIVE:** To evaluate efficacy and safety of clobazam, a 1,5-benzodiazepine, as adjunctive therapy for Lennox-Gastaut syndrome (LGS). **METHODS:** Patients aged 2-60 years were randomized to placebo or clobazam 0.25, 0.5, or 1.0 mg/kg/day. Study consisted of 4-week baseline, 3-week titration, and 12-week maintenance phases, followed by a 2- or 3-week taper or continuation in an open-label extension. Primary endpoint was percentage decrease in mean weekly drop seizure rates during maintenance vs baseline phases for modified intention-to-treat (mITT) population. Secondary outcomes included other seizure types, responder rates, and physicians' and caregivers' global assessments. **RESULTS:** A total of 305 patients were screened, 238 were randomized, and 217 composed the mITT population. Of patients enrolled after a protocol amendment, 125/157 (79.6%) completed. Average weekly drop seizure rates decreased 12.1% for placebo vs 41.2% ( $p = 0.0120$ ), 49.4% ( $p = 0.0015$ ), and 68.3% ( $p < 0.0001$ ) for the clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups. Responder rates ( $\geq 50\%$ ) were 31.6% (placebo) vs 43.4% ( $p = 0.3383$ ), 58.6% ( $p = 0.0159$ ), and 77.6% ( $p < 0.0001$ ) for clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups. Physicians' and caregivers' assessments indicated clobazam significantly improved symptoms. Somnolence, pyrexia, upper respiratory infections, and lethargy were the most frequent adverse events reported for clobazam. **CONCLUSIONS:** Clobazam significantly decreased weekly drop seizure rates in LGS. No new safety signals were identified. Classification of evidence: This study provides Class II evidence that clobazam as adjunctive therapy is efficacious, in a dosage-dependent manner, in reducing mean weekly drop seizure rates of patients with LGS over 12 weeks.

### Commentary

On October 21, 2011, the U.S. FDA announced the approval of clobazam, a 1,5-benzodiazepine, now marketed as Onfi, for the treatment of children ages 2 years and older with Lennox-Gastaut syndrome (LGS). The timing couldn't have been better, with the annual meeting of the Child Neurology Society in Savannah, Georgia, the following week. Although clobazam is widely available and utilized worldwide outside the United States (1), this announcement was greeted with approval by many child neurologists in attendance. The study by Ng et al., which directly led to this FDA decision, was discussed in detail in a platform presentation at this conference as well as by one of the coauthors, Dr. Joan Conry from Children's National Medical Center in Washington, DC.

Drs. Ng and Conry, along with dozens of other co-investigators, embarked on this large clinical trial, one of the largest to date for Lennox-Gastaut syndrome. Previous positive results had been demonstrated in a smaller phase-II study published in *Epilepsia* in 2009 (2), justifying this phase-III, double-blind,

placebo-controlled, industry-sponsored trial entitled "CONTAIN." The stated hypotheses were to evaluate how effective clobazam was against the drop (and total) seizures in LGS and to assess its safety in a larger trial. Although the inclusion criteria allowed ages 2 to 60 years, the vast majority were children, with more than half under age 11 years. These patients had daily drop seizures (mean approximately 100 per week) that were defined as potentially even causing injury: a population most child neurologists unfortunately have to treat with some regularity. The study group certainly chose a particularly problematic seizure type to tackle.

Once enrolled, these patients were randomized to one of four groups: placebo; or clobazam 0.25 mg/kg/d, 0.5 mg/kg/d, or 1.0 mg/kg/d. In the previous phase-II study, 1.0 mg/kg/d clobazam had been identified as the most potentially efficacious (2). Despite 238 patients being initially randomized, there was a large early discontinuation rate, which the authors attribute to an easy route for participants to discontinue a possible placebo arm and join the open-label extension phase. Halfway through the study, this study attribute was stopped in the protocol and discontinuations decreased significantly.

Results were impressive for the stated objective of decreasing drop seizures, with a 41.2% decrease at low-dose (0.25 mg/kg/d), 49.4% (0.5 mg/kg/d), and 68.3% (1.0 mg/



kg/d) compared with only 12.1% for placebo. It is quite clear throughout the results section that the high dose of clobazam was optimal, and even though there was no significant difference in the reduction in “non-drop” seizures overall, high-dose clobazam did show statistical significance for these seizures as well. Approximately three out of four patients in the high-dose group had >50% reduction in drop seizures; but most strikingly, one of four were seizure-free during the maintenance period. As highlighted by Dr. Conry during her presentation at the Child Neurology Society, this was quite rewarding for parents of children with extremely devastating injury-provoking seizures. Side effects were minimal and primarily somnolence and drooling, more so at the higher doses.

An important but unanswered question of this study is the long-term benefit of clobazam, and if the seizure freedom achieved by some patients will persist beyond the several months period of this study. In their discussion, the authors mention that a long-term, open-label extension study is underway. Similarly remarkable, and perhaps an early answer to this question, 206 (87%) of 238 chose to continue clobazam in the open-label extension study, and at the time of publication 89% had taken clobazam for >1 year. Certainly this would suggest a perceived benefit occurred for these study patients. Further information about whether age or concurrent anticonvulsants influenced efficacy would also be useful. In addition, it would be important to know if chronic use of clobazam may lead to later difficulty using rescue benzodiazepines such as diazepam or lorazepam.

This study, along with recent FDA approvals of vigabatrin for infantile spasms and rufinamide for Lennox-Gastaut

syndrome seem to indicate a trend in both industry and regulatory agencies to make important therapies available to children who need them (3, 4). Whereas, in the past, anti-convulsants would be approved solely for partial epilepsy in adults, now there appears to be a subtle shift towards more targeted and novel indications in children. For U.S.-based parent and patient-run support groups, such as the Lennox Gastaut Syndrome Foundation and Dravet.org, trying to make treatments available internationally and in clinical trials with potential pediatric uses (e.g., stiripentol, ganaxolone, ezogabine) more widely accessible in the U.S., it is an excellent trend to witness (5).

by Eric Kossoff, MD

#### References

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