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Results of Long-Term, Open-Label Extension Study Evaluating ONFI® (clobazam) CIV Presented at American Epilepsy Society Annual Meeting

Longest and largest study of an AED in LGS assessed safety and efficacy through six years

Late-breaker presentation at AES focuses on data in patients who received ONFI for three years

San Diego, Calif., Dec. 3, 2012 – Data from a long-term, open-label extension study (OLE) evaluating ONFI (clobazam) Tablets CIV for the adjunctive treatment of drop seizures associated with Lennox-Gastaut syndrome (LGS) were presented as a late-breaking poster at the annual meeting of the American Epilepsy Society (AES).[1] A 1,5-benzodiazepine, ONFI was approved by the U.S. Food and Drug Administration (FDA) in 2011 for the adjunctive treatment of seizures associated with LGS in adults and children as young as two.[2]

This study enrolled patients with a current or previous diagnosis of LGS aged 2 to 60 years old. Patients had previously completed one of two double-blind clinical trials evaluating ONFI as adjunctive therapy for drop seizures associated with LGS, and qualifying patients were given the option of tapering off ONFI or continuing in the OLE. Of 306 patients previously enrolled in these two earlier studies, 267 entered the OLE during the enrollment period of Dec. 28, 2005 through Dec. 15, 2009. Approximately 70 percent (188 of 267) of these patients remained in the study until its conclusion on March 23, 2012.[1]

The primary efficacy endpoint of the study was median percentage decrease in average weekly rate of drop seizures measured at eight separate time points from month 3 through three years, compared with last assessment before first dose of ONFI. Results from this endpoint include 113 patients who received ONFI for three years.[1] Further results for those patients who received ONFI for greater than three years are expected to be published during 2013.

“While LGS represents a small percentage of patients an epilepsy specialist typically treats, the diagnosis often requires a significant amount of time, resources and attention because of the frequency and severity of seizures,” said Yu-tze Ng, director of epilepsy at the University of Oklahoma College of Medicine and lead investigator of the study. “It’s important to collect long-term data because these challenging seizures associated with LGS typically continue throughout the patient’s life.”

LGS is a rare and severe form of epilepsy that is typically diagnosed in childhood and often persists into adulthood.[4,5,6] LGS is associated with multiple types of seizures with periods of frequent seizures, and daily seizures are common.[7] Some of these seizures, including atonic, tonic and myoclonic seizures, may cause falls and are called “drop seizures” (also referred to as “drop attacks”), which may result in injury.[8]

“There is no quick fix for LGS. The diagnosis takes patients, their families and health care teams on a long-term journey from childhood diagnosis into the adult years, from one seizure type to the next, while multiple AEDs are used to manage the condition,” said Juliann Paolicchi, MD, director of the pediatric comprehensive epilepsy program at Weill Cornell Medical College in New York, as well as co-investigator of the study. “We are pleased that Lundbeck was able to partner with a group of clinical researchers to investigate the use of ONFI for this difficult to treat disorder.”

The most common adverse events experienced in this OLE (≥15%) included upper respiratory infection, pyrexia, somnolence, pneumonia, fall and otitis media. A total of 79 (29.6%) patients discontinued the study for the following reasons: patient/parent/caregiver request (33 patients), lack of efficacy (15), adverse events (10), death (9) and “other reasons” (12).[1]

About the Presentation
This study was presented at AES on Saturday, Dec. 1, 11:45 a.m. – 1:45 p.m., during Poster Session 1 at the San Diego Convention Center in Hall B, Ground Level.

About the Study
This multicenter, open-label extension study of ONFI (clobazam) was designed to assess the long-term safety and efficacy of open-label ONFI as adjunctive therapy for patients with seizures associated with LGS. The study included 267 qualifying patients who had completed one of two randomized controlled trials – a Phase II dose-ranging study (N=68) or a pivotal Phase III study (N=238; CONTAIN Trial).[1]

Patients were eligible to continue on to the open-label study if no more than 14 days elapsed since their last dose in the dose-ranging study (Phase II) or the CONTAIN Trial.[1] For patients from the CONTAIN Trial, ONFI was started at a target dosage of 0.5 mg/kg/day (maximum 40 mg/day). This dosage was maintained for 48 hours, and thereafter adjusted per clinical need. For patients from the dose-ranging study who chose to continue in the open-label study, the unblinded physician adjusted or maintained the dosage the patient was previously receiving.[1]

About ONFI® (clobazam) Tablets CIV
ONFI is an oral antiepileptic drug developed in the United States by Lundbeck, and is available in 5-mg, 10-mg, and 20-mg tablets. ONFI is a 1,5-benzodiazepine.[2] The exact mechanism of action for ONFI is not fully understood, but is thought to involve potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the $GABA_A$ receptor.[9]

Indication
ONFI is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.

Important Safety Information
- ONFI causes somnolence and sedation. In clinical trials, somnolence or sedation were reported at all effective doses and were dose-related. In general, somnolence and sedation begin within the first month of treatment and may diminish with continued treatment. Prescribers should monitor patients for somnolence and sedation, particularly with concomitant use of other central nervous system (CNS) depressants. Prescribers should caution patients against engaging in hazardous activities requiring mental alertness, such as operating dangerous machinery or motor vehicles, until the effect of ONFI is known.
- ONFI has a CNS depressant effect. Patients should be cautioned against the simultaneous use with other CNS depressant drugs or alcohol, and cautioned that the effects of other CNS depressant drugs or alcohol may be potentiated.
- As with all Antiepileptic drugs (AEDs), ONFI should be gradually withdrawn to minimize the risk of precipitating seizures, seizure exacerbation or status epilepticus. Withdrawal symptoms have been reported following abrupt discontinuation of ONFI; the risk of withdrawal symptoms is greater with higher doses.
- Patients with a history of substance abuse should be under careful surveillance when receiving ONFI or other psychotropic agents because of the predisposition of such patients to habituation and dependence. In clinical trials, cases of dependency were reported following abrupt discontinuation of ONFI. The risk of dependence increases with increasing dose and duration of treatment.
- AEDs including ONFI increase the risk of suicidal thoughts or behavior in patients. Patients, their caregivers, and families should be informed of the risk and advised to monitor and report any emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior, or thoughts of self-harm. If these symptoms occur, consider if it may be related to the AED or illness because epilepsy itself can increase these risks.
- The most commonly observed adverse reactions reported in an LGS randomized, double-blind placebo-controlled, parallel group clinical trial who received clobazam as adjunctive therapy (≥10% in any treatment group; low, medium or high dose and at least 5% greater than placebo respectively) were somnolence or sedation (32% vs. 15%), somnolence (25% vs. 12%), pyrexia (17% vs. 3%), lethargy (15% vs. 5%), drooling (14% vs. 3%), aggression (14% vs. 5%), irritability (11% vs. 5%), ataxia (10% vs. 3%) and constipation (10% vs. 0%).

For more information, please see the ONFI **full Prescribing Information** and **Medication Guide**.

About Lundbeck in the U.S.
A wholly-owned subsidiary of H. Lundbeck A/S, Lundbeck in the U.S. is headquartered in Deerfield, Illinois, and is committed to accelerating our work in central nervous system (CNS) disorders, including challenging seizure disorders. Additionally, Lundbeck employees actively support and participate in hundreds of epilepsy awareness events each year as part of their ongoing commitment to make a difference for those impacted by epilepsy. For more information, please visit lundbeckus.com.

About Lundbeck
H. Lundbeck A/S (LUN.CO, LUN DC, HLUYY) is an international pharmaceutical company highly committed to improving the quality of life for people suffering from psychiatric and neurological disorders. For this purpose, Lundbeck is engaged in the research, development, production, marketing and sale of pharmaceuticals across the world. The company's products are targeted at disorders such as depression and anxiety, psychotic disorders, epilepsy and Huntington's, Alzheimer's and Parkinson's diseases.

Lundbeck was founded in 1915 by Hans Lundbeck in Copenhagen, Denmark. Today Lundbeck employs approximately 6,000 people worldwide. Lundbeck is one of the world's leading pharmaceutical companies working with psychiatric and neurological disorders. In 2011, the company's revenue was DKK 16.0 billion (approximately EUR 2.2 billion or USD 3.0 billion). For more information, please visit www.lundbeck.com.

ONFI is a registered trademark of Lundbeck.

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Sources

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