UPSHER-SMITH DEBUTS POSITIVE RESULTS FROM GLOBAL PHASE 3 STUDY EVALUATING USL255 (EXTENDED-RELEASE TOPIRAMATE) IN EPILEPSY PATIENTS WITH REFRACTORY PARTIAL-ONSET SEIZURES

Efficacy and Safety/Tolerability Findings Presented at 2013 American Epilepsy Society Annual Meeting

Maple Grove, MN – December 9, 2013 – Upsher-Smith Laboratories, Inc. (Upsher-Smith) today presented results from its global Phase 3 (PREVAIL) study of USL255 (extended-release topiramate), showing that the investigational drug met its primary and secondary endpoints for efficacy and demonstrated favorable safety and tolerability in epilepsy patients with refractory partial-onset seizures (POS). The data were presented for the first time at the American Epilepsy Society’s (AES) 67th Annual Meeting in Washington, DC, December 6-10, 2013.

USL255 is a once-daily, broad-spectrum antiepileptic drug specifically engineered to deliver a smooth pharmacokinetic (PK) profile. Upsher-Smith’s New Drug Application for USL255 has been accepted for review by the U.S. Food and Drug Administration (FDA).

Findings presented at the meeting showed that USL255 was associated with a significantly greater median percent reduction in weekly POS frequency compared with placebo (39.5% vs 21.6%, P<0.001) after 11 weeks of treatment. The majority of treatment-emergent adverse events (TEAEs) reported were mild to moderate in intensity and generally resolved over time. Individual neurocognitive adverse events were each observed at incidence rates of 2.4 percent or less in patients taking USL255. Although ongoing, to-date 96.8 percent of patients who completed the double-blind portion of PREVAIL elected to continue in a year-long, open-label extension study of USL255.

“Topiramate is a well-known, effective agent for the treatment of a variety of seizure disorders, but many patients experience challenging cognitive side effects while taking the immediate-release formulation of the drug,” said Steve Chung, M.D., Professor of Neurology at the Barrow Neurological Institute, Phoenix and trial investigator. “The PREVAIL trial showed that USL255, a once-daily extended-release formulation of topiramate, is efficacious across a range of seizure disorders, while maintaining a favorable adverse event profile.”
of seizure types and patient severity. This extended-release formulation appears to be a new delivery system of a very effective compound. By improving the delivery method, we hope to improve tolerability, which may lead to better seizure control in patients.”

“We are pleased with the positive results seen in this study,” said William Pullman, MB BS, BMedSc, PhD, FRACP, Chief Scientific Officer, Upsher-Smith. “Our Phase 3 trial, PREVAIL, demonstrated that USL255 was efficacious and well tolerated, particularly with respect to the low incidence of cognitive side effects. These findings support the potential use of USL255, an extended-release formulation of topiramate, as a treatment for patients with seizure disorders.”

The PREVAIL trial was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of USL255 as adjunctive therapy in patients with refractory POS. The global Phase 3 study enrolled 249 patients at 66 centers. Additional findings presented at AES include:

**Efficacy Results**

- During the three-week titration phase, USL255-treated subjects demonstrated a significantly greater median reduction from baseline in weekly POS frequency as compared with placebo-treated subjects (33.9% vs 8.6%, P<.001). This significant treatment effect was sustained during the eight-week maintenance phase (45.7% vs 22.1%, P=.001). USL255 significantly reduced POS frequency as early as week one when compared with placebo and sustained this efficacy.

- The 50 percent responder rate during the 11 weeks of treatment was also significantly greater with USL255 compared with placebo (37.9% vs 23.2%, P=.013).

- USL255 significantly reduced median weekly complex partial seizure frequency (P=.001) and was associated with a higher responder rate (P=.003). USL255 was shown to be effective in both complex partial seizures (CPS) and partial secondarily generalized seizures (PSG). USL255 was most effective in subjects taking more than two antiepileptic drugs (AEDs) and demonstrated improvement, even in the most refractory of patients (≥ 7 AEDs tried).

- Treatment with USL255 resulted in a significant improvement in time to seizure freedom (P=.004), and a significantly higher percentage of subjects achieved seizure freedom for at least 21 days prior to the last dose of study drug as compared with placebo (16.1% vs 5.6%, P=.006).
Tolerability Results

• USL255 demonstrated favorable tolerability in study subjects. The overall incidence of TEAEs was 66 percent (USL255) and 50 percent (PBO) (P=.015). Individual neurocognitive adverse events were each observed at incidence rates of 2.4 percent or less in patients taking USL255. The majority of TEAEs reported were mild to moderate in intensity and generally resolved over time. Study completion rates were 83 percent and 91 percent, respectively, with fewer than 10 percent of subjects in either group discontinuing due to adverse events.

Abstracts of the poster presentations can be found online at www.aesnet.org. To schedule an interview with an investigator, please contact Jessica Orr at jorr@klcpr.com.

About Upsher-Smith’s Phase 3 (PREVAIL) Clinical Trial

PREVAIL was conducted under a Special Protocol Assessment (SPA) agreement with the FDA. More information about the trial is available at www.clinicaltrials.gov (NCT01142193).

An open-label extension study to evaluate the safety of USL255 as adjunctive therapy in patients with refractory POS who had participated in PREVAIL is ongoing. The open-label extension study can be found by searching NCT01191086 on www.clinicaltrials.gov.

Upsher-Smith’s Epilepsy Pipeline

Upsher-Smith’s clinical development pipeline includes three investigational drugs that are being studied for the management of seizure disorders. USL255 is an investigational once-daily, extended-release topiramate for the management of epilepsy. The pipeline also includes USL261, an investigational intranasal midazolam for the rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, often called seizure clusters, which is the subject of an ongoing international Phase 3 clinical trial (ARTEMIS1) with an open-label safety extension study. In addition, USL260 (tonabersat) is in early clinical development as a potential first-in-class neuronal gap junction modulator.

About Upsher-Smith

Upsher-Smith, founded in 1919, is an independent and privately-owned specialty pharmaceutical company headquartered in Maple Grove, Minnesota that focuses on product growth and innovation for branded and generic pharmaceuticals. Upsher-Smith has a particular -more-
focus on developing therapies to assist people suffering from central nervous system diseases and also markets products relating to cardiology, dermatology, and women’s health. For more information, visit www.upsher-smith.com.

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