UPSHER-SMITH RESEARCH SHOWS UNIQUE PHARMACOKINETIC PROFILE OF USL255 EXTENDED RELEASE TOPIRAMATE

Findings Presented at the 64th Annual American Academy of Neurology Meeting

Maple Grove, MN – April 26, 2012 – Upsher-Smith Laboratories, Inc. [http://www.upsher-smith.com] today announced that three posters characterizing the pharmacokinetic (PK) profile of USL255, its once-daily, extended-release (ER) topiramate formulation, were presented at the 64th Annual American Academy of Neurology (AAN) Meeting. One of the posters showed equivalent exposure between USL255 and equal doses of immediate-release (IR) topiramate at steady state, a second poster went on to confirm that switching between formulations did not affect steady-state plasma concentrations, and a third poster showed that USL255 demonstrated linear dose-proportionality. These poster presentations include data demonstrating that USL255 administered once-daily provided an improved PK profile when compared to twice-daily IR topiramate.

These data and other findings were presented on Thursday, April 26, at the 64th Annual American Academy of Neurology (AAN) Meeting in New Orleans, LA (http://www.aan.com).

“Fluctuations in plasma levels with certain anti-epileptic drugs have the potential for increased side effects at peak concentrations or break-through seizures at trough concentrations. The development of a once-daily, extended-release topiramate formulation may result in increased treatment compliance with a more consistent plasma concentration,” said Mark Halvorsen, Pharm.D., Senior Director, Clinical Development at Upsher-Smith. “We are excited to share this Phase I data with the clinicians at this year’s AAN Annual Meeting.”

Abstracts of the poster presentations can be found online at http://www.aan.com. Titles and authors are:

- “Steady-State Pharmacokinetic Profiles of Extended- and Immediate-Release Topiramate” Poster # P06.111. Authors: Tricia L. Braun, Lawrence J. Lambrecht, Wesley Mark Todd, Mark B. Halvorsen
- “Switching between Immediate- and Extended-Release Formulations Does Not Affect the Steady-State Pharmacokinetic Profile of Topiramate” Poster # P06.112. Authors: Lawrence J. Lambrecht, Tricia L. Braun, Wesley Mark Todd, Mark B. Halvorsen

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• Extended-Release Topiramate (USL255) Exhibits Linear Dose-Proportional Pharmacokinetic Characteristics" Poster # P06.128. Authors: Mark B. Halvorsen, Lawrence J. Lambrecht, Wesley Mark Todd

About The Studies

The studies, that are the subject of these posters, have been conducted by Upsher-Smith to characterize the pharmacokinetic profile of USL255. The first poster compared the steady-state PK profile of once-daily USL255 to the twice-daily IR formulation. In this Phase I, open-label, 2-way crossover study, healthy subjects were up-titrated to 200 mg of topiramate (either USL255 or twice daily IR topiramate) over 12 days and maintained on 200 mg for 14 days. On day 15, subjects were crossed over, without washout, to the other topiramate formulation through day 28. Subjects were then down-titrated off the study drug over eight days. The study results confirmed that USL255 administered once-daily provided an improved PK profile as determined by an equivalent AUC, lower Cmax, higher Cmin and a reduced fluctuation index at steady-state when compared to twice-daily IR topiramate. All treatment-emergent adverse events were mild in severity.

An additional analysis of this Phase I data, and second poster, evaluated tolerability and maintenance of steady-state plasma concentrations during a formulation switch from IR topiramate to USL255. Healthy volunteers were randomized into two groups receiving either 200 mg of USL255 once-daily or 100 mg of IR topiramate twice-daily through Period One (days 1-14). On day 15, volunteers were immediately switched to the alternate formulation for Period Two (days 15-28), without washout. Pharmacokinetic profiles were determined through blood samples taken at steady-state (days 14 and 28) and at switch (day 15). Steady-state was considered maintained if slope estimates for minimum concentrations (Cmin) were not significantly different from zero. Tolerability of USL255 and IR topiramate were evaluated through adverse events monitoring, vital sign measurements, and clinical laboratory evaluations. The results for both formulations were similar at steady-state and around the switch in formulation. Additionally, no significant differences in slope estimates were identified during conversion, suggesting that switching formulations did not affect maintenance of steady-state plasma concentrations.

The final poster assessed dose-proportionality, linearity and tolerability of USL255. In this Phase I, single-dose, open-label, 5-way crossover study, 30 healthy subjects were randomized into one of five treatment sequences with six subjects per sequence. Subjects were given each dose of USL255 (25, 50, 100, 200 and 400 mg) in varying order depending on
their assigned treatment sequence. Following each treatment, subjects entered a three week washout period with blood samples being collected throughout the first 14 days. The investigators concluded that USL255’s topiramate exposure was linear and dose-proportional from 25 mg up to 400 mg. Subsequent analyses compared dose-normalized C\text{max} values of USL255 400 mg to 200 mg, and 200 mg to 100 mg. All 90% confidence intervals were between 0.80 – 1.25 which indicates that C\text{max} changed dose-proportionally within double-dose increases between 100 mg and 400 mg. As expected, the number of subjects who experienced a treatment-emergent adverse event generally increased with ascending doses, and all were mild to moderate in severity.

USL255 is an investigational treatment being developed for the management of epilepsy in adults and is also the subject of a global Phase III clinical trial (PREVAIL). Information about the trial can be found at: http://clinicaltrials.gov/ct2/show/NCT01142193?term=upsher+smith&rank=4

**Upsher-Smith’s Expanding CNS Pipeline**

Upsher-Smith’s central nervous system (CNS) pipeline includes a number of investigational drug programs. In addition to USL255 (extended-release topiramate), USL is developing an intranasal midazolam (USL261), for the rescue treatment of seizures in patients on stable anti-epileptic drug regimens who require control of intermittent bouts of increased seizure activity, frequently referred to as seizure clusters. Another program is USL260 (tonabersat), an investigational drug and potential first-in-class neuronal gap junction modulator which is also a potential treatment for epilepsy.

**About Epilepsy**

Epilepsy is a medical condition that produces seizures affecting a variety of mental and physical functions. Almost three million people in the U.S. have some form of epilepsy with about 200,000 new cases of epilepsy diagnosed each year.¹

**About Upsher-Smith**

Upsher-Smith Laboratories, Inc. is a privately held, U.S.-based company devoted to improving health and advancing wellness since 1919. Upsher-Smith demonstrates its commitment to meeting the healthcare needs of its customers by developing, producing and marketing consumer and prescription products. In addition to its strong heritage in generics, Upsher-Smith’s branded businesses focus on women’s health, dermatology and CNS therapeutic areas. For additional information, visit http://www.upsher-smith.com.

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