DATA PUBLISHED IN EPILEPSIA SHOWS USL261 (INTRANASAL MIDAZOLAM) DEMONSTRATED A PROMISING PHARMACOKINETIC PROFILE, INCLUDING INCREASED RELATIVE BIOAVAILABILITY, WHEN COMPARED WITH INJECTABLE MIDAZOLAM ADMINISTERED INTRANASALLY

Investigational USL261 Shows Promise as a Potential Alternative Therapy for Patients with Epilepsy Who Experience Seizure Clusters

Maple Grove, MN - November 9, 2015 – Upsher-Smith Laboratories, Inc.’s, (Upsher-Smith) USL261 (intranasal midazolam), a novel, investigational midazolam formulation optimized for intranasal delivery, demonstrated increased relative bioavailability with similar pharmacodynamic effects in healthy volunteers when compared with injectable midazolam administered intranasally (MDZ-inj IN). The Phase I study was published in the November issue of Epilepsia, a leading, authoritative source for current research results on all aspects of epilepsy.

USL261 is being developed for rescue treatment of seizures in patients who require control of intermittent bouts of increased seizure activity, also known as seizure clusters or acute repetitive seizures. It is intended to be delivered intranasally, without active inhalation by the patient. USL261 has been granted orphan drug designation for this use by the Food and Drug Administration (FDA).

“The goal of rescue therapy for seizure clusters is to quickly administer an effective treatment that will rapidly cease the seizure cluster so that it doesn’t progress to status epilepticus,” said Barry Gidal, PharmD, RPH, Professor of Pharmacy and Neurology, University of Wisconsin School of Pharmacy. “The results of this study demonstrate that USL261 has increased relative bioavailability with similar pharmacodynamic effects when compared with injectable midazolam administered intranasally.”

About the Study

The Phase I study examined the pharmacokinetics, pharmacodynamics, and safety/tolerability of USL261 in healthy volunteers. The randomized, single-center, in-patient, open-label, five-way crossover study consisted of five dosing periods separated by a washout period of at least three days. For each study period, all participants were confined to the clinic the evening prior to dosing through approximately 12 hours post-dosing. Twenty-five healthy adult subjects between the ages of 18 and 42 years were
randomized to one of five different treatment sequences in which they received in random order: USL261 (2.5, 5.0, 7.5 mg), injectable midazolam administered intravenously (MDZ-inj IV) (2.5 mg) and MDZ-inj IN (5.0 mg).

In this study, increasing USL261 doses corresponded with increases in midazolam exposure (area under the concentration time curve [AUC] and maximum observed plasma concentration [C_{max}]), with all doses demonstrating rapid median time to peak plasma concentration (T_{max}; 10 – 12 min).

**USL261, MDZ-inj IV and MDZ-inj IN**

**Mean Plasma Concentration of Midazolam**

Source: *Epilepsia* © ILAE. November 2015 print issue.

Mean midazolam plasma concentrations for all formulations and delivery routes. Inset is a detail of the first 60 minutes post-dose.

Further, when compared with an equivalent dose of MDZ-inj IN (5.0 mg), USL261 demonstrated improved relative midazolam bioavailability (by more than 30 percent) with similar pharmacodynamic effects and safety/tolerability profiles. USL261 dosed up to 7.5 mg was generally well tolerated in this study. The most common drug-related treatment-emergent adverse events were nasal discomfort, throat irritation, increased lacrimation, and dysgeusia (i.e. complaints about the taste).

**About Epilepsy**

Epilepsy is a medical condition that is characterized by recurrent seizures. More than two million people in the U.S. are estimated to be affected by epilepsy, with about 150,000 new cases of epilepsy diagnosed each year. Epilepsy can be associated with profound physical, psychological and social consequences that negatively impact people’s lives.
About Seizure Clusters

Seizure clusters, also referred to as acute repetitive seizures, seizure flurries, crescendo seizures, cluster seizures, or bouts of increased seizure activity, consist of multiple seizures which occur over a relatively brief period of time with a pattern distinguishable from the patient’s usual seizure pattern.²

Reports of seizure cluster prevalence vary depending on the population evaluated. Seizure clusters have been associated with worse seizure control.³ In a study conducted in a tertiary epilepsy center in patients with a broad range of seizure control, the prevalence of seizure clusters was close to 30%.³ The number of patients with epilepsy in the United States who experience seizure clusters has been estimated to be 152,000.⁴,⁵,⁶,⁷

About Upsher-Smith

Upsher-Smith Laboratories, Inc., founded in 1919, is a growing, fully integrated pharmaceutical company dedicated to its mission of delivering high-value, high-quality therapies and solutions which measurably improve individuals’ lives. As a family-owned pharmaceutical company, we are able to adapt and thrive in a dynamic healthcare environment. Our world is constantly evolving, and we are continually adapting to the ever-changing needs of patients, physicians, pharmacists, and healthcare organizations. Where there is a need, we will work to deliver solutions that simplify access to treatment, deliver better health outcomes, and enhance life. Upsher-Smith has a particular focus on developing therapies for people living with central nervous system (CNS) conditions, such as seizure disorders. For more information, visit www.upsher-smith.com.

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References