Introduction

Despite the importance of medication adherence for successful management of seizure disorders, nonadherence continues to be a significant problem in patients with epilepsy. Nonadherence to treatment, including delayed or missed antiepileptic drug (AED) dosing, can lead to increased seizure occurrence, reduced quality of life, frequent hospitalization and emergency room visits, and higher rates of morbidity/mortality. As use of extended-release (XR) AEDs has been shown to improve drug adherence, Upsher-Smith Laboratories, Inc. developed USL255, Qudexy™ XR (topiramate) extended-release capsules, as a once-daily (QD) treatment for epilepsy. USL255 was approved by the FDA (11 March 2014) as initial monotherapy for partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures (patients aged ≥2 years) and adjunctive therapy for POS, PGTC, or seizures associated with Lennox-Gastaut syndrome (patients aged ≥2 years). The efficacy and safety of USL255 as adjunctive treatment for POS was recently evaluated in a multinational phase 3 study (PREVAIL, NCT01421139). Delayed administration of XR AEDs, taken less frequently than immediate-release dosing, may lead to a decrease in plasma concentrations from steady-state values to below minimum therapeutic concentrations.

The objective of these analyses was to predict the impact of delayed-dose administration of USL255 QD (taken 6, 12, 18, or 24 hours later than scheduled) in a simulated steady-state pharmacokinetic (PK) profile.

Methods

Data for these post hoc analyses were obtained from a phase 1, open-label, single-dose study evaluating the PK profile of USL255 200 mg administered in the fasted state to 36 healthy adults (age 18–65 years). Blood samples were drawn within 1 hour prior to dose (0 h), every 2 hours up to 32 hours post-dose, and at 46, 48, 72, 96, 120, 168, 216, 264, and 336 hours post-dose. Using the single-dose data, nonparametric superpositioning was used to predict steady-state PK profiles of USL255 200 mg/day. Compliance dosing of USL255 QD administration for 14 days was utilized to achieve simulated steady-state conditions. After 14 days of simulated compliant dosing, a 6-, 12-, and 24-hour delay in USL255 administration was simulated, with QD dosing resuming after the late dose. For the 24-hour delay, two doses were assumed to be taken together (ie, double dose).

Results

Simulation of Mean-Predicted Steady-State Plasma Concentrations

Steady-state conditions were reached within 14 days of simulated dosing of USL255 200 mg/day. The mean steady-state profile obtained from superpositioning single-dose data was visually similar to the mean steady-state profile obtained from a separate study evaluating USL255 200 mg administered QD for 14 days (Figure 1), thus supporting the appropriateness of simulation methodology to predict steady-state topiramate levels.

Simulation of a Delayed USL255 Dose

Following administration of USL255 6, 12, 18, or 24 hours later than scheduled, mean-predicted topiramate plasma concentrations incrementally decreased prior to the next scheduled dose compared with plasma concentrations resulting from compliant dosing of USL255 200 mg/day (Figure 2).

Conclusions

Simulated delayed administration of a single USL255 dose 6, 12, 18, or 24 hours later than scheduled led to incremental decreases in topiramate plasma concentrations prior to the next scheduled dose. Within 1 day after delayed-dose administration, Cmin values were at or above the steady-state Cmin levels with compliant dosing. Since Cmax is commonly associated with efficacy, quickly achieving concentrations above Cmin is clinically important. For the 6, 12, and 18 hours delayed-dose scenarios, Cmax values did not increase >30% above compliant dosing. As tolerability may be related to Cmax, minimizing increases in Cmax may alleviate unwanted adverse events.

These data demonstrate a fast return to steady-state topiramate plasma concentrations after delayed administration of USL255. Once-daily USL255, Qudexy™ XR (topiramate) extended-release capsules, has favorable pharmacokinetic properties that may reduce the impact of a delayed dose.

References