A review of the efficacy and safety of extended-release topiramate in the adjunctive treatment for refractory partial-onset seizures

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Abstract: Topiramate has been widely utilized worldwide as an effective medication against partial- and generalized-onset seizures. Extended-release topiramate was developed to provide patients with the convenience of once-daily dosing and potentially improved tolerability by reducing serum concentration fluctuation. USL255 is a once-daily, extended-release formulation of topiramate, which was recently approved in the USA. Compared with immediate-release topiramate taken twice daily, once-daily USL255 provides equivalent topiramate exposure with a 26% reduction in plasma fluctuations. A multinational, phase III, randomized, double-blind, placebo-controlled clinical trial in patients with refractory partial-onset seizures demonstrated that USL255 (200 mg/day) significantly improved seizure control and was well tolerated with low overall neuropsychiatric and neurocognitive adverse events.

Keywords: epilepsy, extended release, partial seizures, topiramate, qudexy XR, trokendi XR

Introduction

Epilepsy is a common and chronic neurological disorder that affects about 50 million people worldwide [WHO, 2012]. Since the treatment of epilepsy often requires prolonged treatment with antiepileptic medications (AEDs), treatment adherence is a key factor in achieving better seizure control. However, nonadherence is quite common among epilepsy patients, which may result in increasing seizure frequency and poor tolerability, and ultimately adversely affecting quality of life and increasing epilepsy-related healthcare costs. Various factors may contribute to nonadherence including side effects, frequent daily dosing, lack of efficacy, social pressure, and cost [Davis, 2008]. Even though clinicians may not alter many of these factors, dosing frequency can be modified by utilizing extended-release (XR) formulations, as an inverse relationship between the number of daily doses and compliance has been reported [Cramer *et al.* 1995, 2002]. In addition, immediate-release (IR) AEDs can be limited by peak toxicity such as dizziness, blurred vision, somnolence, gastrointestinal symptoms, and unsteadiness. On the other hand, low trough levels may be associated with

breakthrough seizures theoretically. For these reasons, several AEDs are now available in XR formulation with a notion that XR AEDs can improve adherence, minimize peak concentration-related adverse events, and possibly provide better seizure control [Sommerville, 2006]. Currently, XR formulations are available for carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, valproate, and topiramate [Leppik and Hovinga, 2013; Medical Letter on Drugs and Therapeutics, 2013].

XR topiramate (TPM-XR) was developed to provide patients with the convenience of once-daily dosing, potentially improving compliance as well as the efficacy–tolerability ratio. USL255 (Qudexy XR™) was developed by Upsher-Smith Laboratories (Maple Grove, MN, USA) and received US Food and Drug Administration (FDA) approval in March 2014. Even though the clinical study of USL255 was limited to partial-onset seizure (POS) patients as an adjunctive therapy, a much broader indication was granted by FDA based on pharmacokinetic equivalence to TPM-IR without actual clinical trials: initial monotherapy in patients aged 10 years or older with POS or primary generalized

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Table 1. Pharmacokinetic parameters of USL255 200 mg once daily *versus* immediate-release topiramate 100 mg twice daily at steady state.

	USL255	Immediate-release topiramate
Area under curve (mg h/L)	158 [32]	153 [33]
Peak plasma concentration (mg/L)	7.9 (1.5)	8.4 (1.7)
Trough plasma concentration (mg/L)	5.3 (1.2)	5.0 (1.2)

tonic-clonic seizures (PGTC), and as adjunctive therapy in patients 2 years of age or older with POS, PGTC, or seizures associated with Lennox–Gastaut syndrome (LGS) [Topiramate Extended-release Prescribing Information, 2014]. This article discusses the efficacy and tolerability of USL255 in patients with partial epilepsy.

Properties of topiramate

Topiramate is known as a broad-spectrum AED that works against both POS and generalized-onset seizures. It has been available in the USA since 1996. Its mechanisms of actions include blocking voltage-dependent sodium channels, inhibition of carbonic anhydrase, anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor antagonist, and enhancement of gamma-aminobutyrate acid [Lyseng-Williamson *et al.* 2008]. Topiramate is 15–41% bound to plasma proteins [Topamax®, 2014]. It is primarily eliminated unchanged in urine (70–80%) when administered alone or without hepatic enzyme-inducing medications [Garnett, 2000]. The remaining 20–30% undergoes hepatic metabolism *via* glucuronidation, hydroxylation, and hydrolysis [Topiramate Prescribing Information, 2014]. *In vitro*, topiramate is a mild inhibitor of cytochrome P450 2C19 (CYP2C19) and a mild inducer of cytochrome P450 3A4 (CYP3A4) [Topiramate Prescribing Information, 2014]. In general, topiramate does not affect the pharmacokinetics of concomitant AEDs, but the pharmacokinetics of topiramate are affected by CYP-enzyme-inducing AEDs [Lyseng-Williamson *et al.* 2008]. Strong CYP-enzyme-inducing AEDs, such as carbamazepine or phenytoin, increase the clearance and reduce plasma concentrations of topiramate [Bialer *et al.* 2004; Britzi *et al.* 2005; Mimrod *et al.* 2005].

Pharmacokinetics of USL255

USL255, once-daily TPM-XR, was formulated using a proprietary coated-bead technology to deliver a consistent release of topiramate over a 24-h

dosing interval with low drug plasma fluctuations [Chung *et al.* 2014]. Pharmacokinetic studies showed that USL255 has a linear dose–concentration curve of oral dosage of 50–1400 mg/day with low interpersonal variability [Clark *et al.* 2014]. Once-daily oral USL255 provided the equivalent plasma exposure (area under curve [AUC]) when compared with twice-daily oral TPM-IR. In addition, USL255 provided a lower maximum plasma concentration ($C_{\max}$) and a higher minimum plasma concentration ($C_{\min}$), which resulted in a significantly decreased fluctuation index of 38% compared with 53% in TPM-IR [Lambrecht *et al.* 2011; Bialer *et al.* 2013]. Table 1 shows the difference in $C_{\max}$ and $C_{\min}$ differences between USL255 and TPM-IR. After a single 200 mg oral dose of USL255, $C_{\max}$ and $C_{\min}$ peak plasma concentrations ($T_{\max}$) are reached in about 20 h, which is much slower than TPM-IR (about 1 h) [Lambrecht *et al.* 2011]. Steady state is reached approximately 5 days following daily dosing of USL255, and $T_{\max}$ at steady state is reached in 6 h [Bialer *et al.* 2013]. Consumption of food did not affect $C_{\max}$ or AUC [Lambrecht *et al.* 2011]. USL255 is packaged as time-release beads in capsules and can be sprinkled on food without affecting its XR properties [Clark *et al.* 2014]. The mean effective half-life of USL255 is 55.7 h under fasted conditions and 72.5 h with food [Lambrecht *et al.* 2011].

Clinical studies of USL255

The efficacy, safety, and tolerability of USL255 has been recently evaluated in a multinational, randomized, placebo-controlled, phase III study in adults (18–75 years) with POS [Chung *et al.* 2014]. A total of 249 adult epilepsy patients were randomized 1:1 to adjunctive treatment with once-daily USL255 (200 mg/day) or placebo (USL255, $n = 124$; placebo, $n = 125$). Patients received stable doses of 1–3 AEDs, and had eight or more POS with or without secondary generalization and 21 or fewer consecutive seizure-free days during the 8-week baseline phase. The most common concomitant AEDs were carbamazepine, valproic acid

Figure 1. Median percentage reduction from baseline in weekly seizure frequency during the titration and maintenance phase: USL255 *versus* placebo ($p < .001$).

and its derivatives, lamotrigine, and levetiracetam during the study. After the 8-week of baseline phase, USL255 was titrated over 3 weeks with a starting dose of 50 mg/day, and followed by the 11 weeks of maintenance phase. Titration occurred in 50 mg/week increments to the maintenance dosage of 200 mg/day [Chung *et al.* 2014].

Efficacy

The primary efficacy endpoint was median percentage reduction from baseline in weekly seizure frequency during the titration plus maintenance phase, and the secondary endpoint was 50% responder rate (proportion of subjects with 50% or greater reduction) [Chung *et al.* 2014]. Efficacy measures included clinician-reported global impression of change (CGI-C), and the patient-reported quality of life in epilepsy questionnaire (QOLIE-31-P). The median percentage seizure reduction was significantly greater with USL255 than placebo (39.5% *versus* 21.6%, $p < .001$) (Figure 1), as well as the 50% or greater responder rate in weekly seizure frequency patients (37.9% *versus* 23.2%, $p = .013$). Efficacy of USL255 was observed early in treatment as the significant median seizure frequency reduction was seen as early as week 1 with USL255 (50 mg/day) compared with placebo (28.6% *versus* 9.2%, $p = .02$). Subgroup analysis also revealed a significant seizure reduction was seen both in patients who were taking three or more concomitant AEDs and two or fewer concomitant AEDs [Chung *et al.* 2014].

Improved CGI-C score was also reported in USL255 compared with placebo ($p = .002$), suggesting an improved clinical status of patients. In

addition, QOLIE-31-P also showed significant improvement with USL255 *versus* placebo on the seizure worry subscale ($p < .001$) without significant worsening on other subscales [Chung *et al.* 2014]. These results indicate that USL255 reduced the impact of seizure worry without causing significant unwanted physical or mental medication side effects.

Safety and tolerability

Overall, reported treatment-emergent adverse events (TEAEs) were low during the study (less than 15%), and the most common TEAEs associated with USL255 were somnolence 12.1% (2.4% in placebo), dizziness 7.3% (5.6% in placebo), paresthesia 6.5% (2.4% in placebo), weight decrease 6.5% (0% in placebo), fatigue 5.6% (4.8% in placebo), and headaches 4% (5.6% in placebo) (Figure 2). TEAEs related to neurocognitive and neuropsychiatric symptoms were reported in less than 2.5% of patients in USL255-treated patients [Chung *et al.* 2014]. Table 2 compares individual neurocognitive TEAEs in USL255 *versus* placebo-treated patient groups. It was noted that the disturbance in attention was reported higher in placebo than in USL255 (3.2% placebo *versus* 2.4% USL255). One patient in both the USL255- and placebo-treated groups reported an incidence of rash.

Most TEAEs were mild or moderate in intensity, less than 10% of patients in each treatment group discontinued the study due to TEAEs. Other known safety concerns associated with TPM-IR, such as metabolic acidosis, kidney stones, and glaucoma were not reported associated with USL255 during the study [Chung *et al.* 2014].

Figure 2. Reported treatment-emergent adverse events (%): USL255 *versus* placebo.

Table 2. Individual neurocognitive treatment-emergent adverse events in USL255 and placebo-treated patients.

	USL255 <i>n</i> = 124 (%)	Placebo <i>n</i> = 125 (%)
Aphasia	3 (2.4)	0
Disturbance in attention	3 (2.4)	4 (3.2)
Dysarthria	3 (2.4)	1 (0.8)
Memory impairment	3 (2.4)	1 (0.8)
Amnesia	1 (0.8)	0
Cognitive disorder	1 (0.8)	0
Encephalopathy	1 (0.8)	0
Mental impairment	1 (0.8)	0
Speech disorder	1 (0.8)	0

Discussion

Compared with an IR formulation, an ideal XR formulation would have a lower C_{max} , which may improve peak dose tolerability, and a higher C_{min} , which may improve seizure control. Therefore, it is not surprising that many AEDs are now available in XR formulation. TPM-IR has been widely used since 1996, and now XR formulations of topiramate are also available. USL255 is a newly approved XR formulation of topiramate made available as a capsule that can be swallowed intact or opened and sprinkled on to a small amount of soft food for children and elderly patients with swallowing difficulties. Like TPM-IR indications, TPM-XR was approved by the FDA as an initial monotherapy in patients 10 years of age or older with POS or PGTC, and as an adjunctive therapy in patients aged 2 years or older with POS, PGTC, or seizure

types associated with LGS [Topiramate Extended-release Prescribing Information, 2014]. This allows clinicians the flexibility to use TPM-XR as either a first-line or add-on treatment for seizures in a broad patient population. The sprinkle formulation of USL255 is quite a useful option for younger patients with epilepsy as well as older patients with dysphagia. For the adjunctive treatment of POS, the USL255 clinical study demonstrated efficacy in patients with refractory epilepsy, with favorable tolerability. In addition to once-daily dosing of TPM-XR, the clinical study suggested that the USL255 might cause less cognitive side effects than TPM-IR. A meta-analysis by the Cochrane Collaboration of nine trials of adjunctive TPM-IR (200–1000 mg/day) for epilepsy found higher incidences of dizziness, fatigue, nausea, somnolence, and abnormal thinking were significantly

associated with TPM-IR [Jette *et al.* 2008]. In addition, individual neurocognitive and neuropsychiatric TEAEs have been reported in TPM-IR clinical trials in up to 20% of patients with 200 mg TPM-IR [Faught *et al.* 1996]. It is noteworthy that the clinical study with USL255 in similar patient populations reported much lower incidences of individual neurocognitive or neuropsychiatric TEAEs (less than 2.5%). This improvement in overall tolerability may be due to the reduced plasma topiramate fluctuations and lower steady-state C_{max} provided by USL255. However, the comparison of TEAEs between TPM-IR and USL255 should be made with caution since study design, subject characteristics, and duration of study may be different. For example, the difference in reported neurocognitive TEAEs between TPM-IR and USL255 may be due to lower target dosage and slow titration of USL255 compared with the previous studies of TPM-IR. In addition, weight decrease was reported only in 6.5% during the USL255 study, which may be due to the short duration of the study.

Conclusion

Clinical study demonstrated that once-daily XR formulation of topiramate (USL255) is a well-tolerated and efficacious adjunctive treatment for refractory POS, that can provide benefit for both pediatric and adult patients with a variety of epilepsy types.

Conflict of interest statement

SC is a consultant for Acorda Therapeutics, Eisai, Lundbeck, SK Life Science, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, UCB, and Upsher-Smith Laboratories, is on the speaker's bureau of Cyberonics, Eisai, GlaxoSmithKline, Lundbeck, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, and UCB SA, and receives grant and research support from Acorda Therapeutics, Eisai, GlaxoSmithKline, Medtronic, Lundbeck, SK Life Science, UCB, and Upsher-Smith Laboratories.

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