Efficacy and safety of rufinamide in pediatric epilepsy

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Abstract: Rufinamide is a novel anticonvulsant medication approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years of age and older, based upon clinical trials demonstrating clinical efficacy and tolerability. Rufinamide is especially effective for tonic–atonic seizures in Lennox–Gastaut syndrome, but is subsequently proving to be safe and effective in clinical practice for a broad patient population with refractory epilepsy. Although further research and clinical experience is needed, rufinamide holds the promise to positively impact the care of children with epilepsy. In this review, we review the use of rufinamide in pediatric epilepsy, with a focus on efficacy and safety.

Keywords: anticonvulsants, epilepsy, Lennox–Gastaut syndrome, rufinamide

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Introduction and history

Rufinamide [1-(2,6-difluoro-phenyl) methyl-1 hydro-1,2,3-triazole-4 carboxamide] is a novel anticonvulsant medication which, as a triazole derivative, is structurally unrelated to any other currently used anticonvulsant medication. In 2004, rufinamide was designated as an orphan drug for adjunctive use in the treatment of seizures associated with Lennox–Gastaut syndrome (LGS) in patients 4 years of age and older by the United States Food and Drug Administration (FDA). In 2007, rufinamide was approved for use in Europe, and this was followed by approval by the FDA in November 2008 as adjunctive treatment of seizures associated with LGS in patients 4 years of age and older. This marked the first time that a new anticonvulsant medication was available for use in the United States with an initial pediatric indication.

Proposed mechanism of action

Preclinical animal studies suggest the mechanism of action to include, at least in part, the prolongation of the recovery of sodium channels from the inactivated state, with a resultant decrease of the frequency of sustained repetitive firing in neurons [McLean *et al.* 2005]. Oral rufinamide has shown anticonvulsant activity in a broad spectrum of animal models to include pentylene-tetrazol-induced and maximal electroshock-induced seizures in mice, suggesting the possibility of broad anticonvulsant properties in humans [White *et al.* 2008].

Characteristics

Rufinamide is well absorbed (>85%) with oral administration (Table 1). Absorption may be slightly less, however, with incremental dose increases over 600 mg [Perucca *et al.* 2008], but this effect is likely not clinically significant. Peak plasma concentration occurs within 4–6 hours. Plasma protein binding is low (26–34%) and rufinamide does not affect the cytochrome P450 enzyme system [Perucca *et al.* 2008]. Metabolism is extensive (<2% is excreted unmetabolized) and occurs via hepatic hydrolysis of the carboxamide group by carboxylesterases, forming a metabolically inactive intermediate which is cleared renally. The elimination of rufinamide occurs with a plasma half-life of 6–10 hours.

Clinical efficacy

Several large, randomized, placebo-controlled trials have been published evaluating rufinamide as an adjunctive treatment in older adolescents and adults for partial-onset seizures, demonstrating significant differences in favor of rufinamide *versus* placebo in responder rates (defined as a 50%

Table 1. Rufinamide characteristics summary.

Bioavailability:
Approximately 85%, orally
Peak plasma concentration:
4–6 hours
Plasma protein binding:
26–34%
Half-life:
6–10 hours
Metabolism:
Hepatic
Extensively (<2% unmetabolized)
No involvement of cytochrome P450
No autoinduction
Excretion:
Urine

or greater reduction in seizure frequency) [Palhagen *et al*. 2001; Brodie *et al*. 2009; Elger *et al*. 2010; Biton *et al*. 2011], and with a significant linear trend of dose response [Elger *et al*. 2010]. A recent meta-analysis also supports the efficacy of rufinamide as adjunctive therapy in patients with medication-refractory epilepsy [Verrotti *et al*. 2011]. Only one randomized, placebo-controlled trial involving mostly children has been published, evaluating the use of rufinamide in the treatment of seizures associated with LGS [Glauser *et al*. 2008]. This consequential data, however, advanced the FDA approval in 2008 for the adjunctive treatment of seizures associated with LGS (in patients 4 years old and older).

Rufinamide, as such, is now clinically available to contribute to a longstanding unmet need in the treatment of pediatric epilepsy: the treatment of refractory seizures in LGS. LGS is a childhood epileptic encephalopathy, of heterogeneous etiologies, which is characterized by multiple seizure types (most commonly tonic, atypical absence, and drop attacks), electroencephalogram findings of a slow spike-and-wave pattern, and cognitive impairment [Camfield, 2011]. In addition to rufinamide, the FDA has approved felbamate, lamotrigine, topiramate, and clobazam for the treatment of LGS, although many consider valproic acid to be a first-line therapy [Montouris, 2011]. However, the multiple seizure types in LGS are often refractory to treatment, and the optimum treatment of seizures associated with LGS is awaiting further refinement and establishment [Hancock and Cross, 2009]. Some seizure types in LGS, such as atypical absence, can occur so frequently that they are near impossible to count. Thus, many studies involving rufinamide and LGS have focused on certain more easily countable seizures, such as 'drop attack' seizures, in addition to parental estimates of total seizures. The term 'tonic–atonic' seizures has been agreed upon by an international panel of child neurologists as a suitable nomenclature for 'drop attacks', due to the difficulty that caregivers can have in separating tonic and atonic seizures [Glauser *et al*. 2008]. In addition to their ability to be counted, drop attack seizures are a clinically significant outcome due to their relatively higher potential for injury [French *et al*. 2004].

Randomized, placebo-controlled trial

In 2008, Glauser and colleagues published their double-blind, randomized, placebo-controlled trial of rufinamide in patients with LGS [Glauser *et al*. 2008]. In this study, there were 74 patients randomized to adjunctive rufinamide, with an age range of 4–37 years old (median 12 years old), and 64 to placebo. The approximate target dosing was 45 mg/kg/day, achieved by 87.8% of the rufinamide-treated group, up to 3200 mg a day. After a 12-week parallel-group treatment period, the median percentage decrease in caregiver-reported total countable seizures per 28 days for those treated with rufinamide was 32.7%, compared with 11.7% with placebo ($p = 0.0015$). Responder rates for total seizures were higher in the rufinamide group (31.1%) *versus* placebo (10.9%) ($p = 0.0045$). Efficacy for tonic–atonic seizures was especially prominent, with a median percentage decrease per 28 days with rufinamide of 42.5% compared to an increase of 1.4% in the placebo group ($p < 0.0001$). Although 4.1% treated with rufinamide achieved complete cessation of tonic–atonic seizures, 3.3% in the placebo group did also ($p = 0.8414$), and no patients achieved complete seizure freedom. In regards to partial seizures, there was a median percentage decrease per 28 days with rufinamide of 71.9% compared with 11.1% in the placebo group; however, a *p*-value was not assigned, as less than 20% of the population reported partial seizures. Furthermore, based upon a seven-point Likert scale, caregivers rated a greater decrease in seizure severity with rufinamide *versus* placebo ($p = 0.0041$).

This study published by Glauser and colleagues is the only double-blind, randomized, placebo-controlled rufinamide study involving mostly

Table 2. Summary of published pediatric rufinamide studies.

Reference	Study design	Population	Countable seizure outcome	Adverse events: Total patients, most common
Glauser *et al.* [2008]	Randomized Double-blind Placebo-controlled	74 rufinamide patients Age 4–35 years LGS	≥50% decrease: 31.1% Seizure-free: none	Total 81.1% -Somnolence 24.3% -Vomiting 21.6%
Kluger *et al.* [2009]	Retrospective 12-week Observational	60 patients Age 1–50 years Mixed epilepsy types	≥50% decrease 46.7% Seizure-free 8.3%	Total 58.3% -Fatigue 18.3% -Vomiting 13.3% -Loss of appetite 10%
Coppola *et al.* [2010]	Prospective Open-label	43 patients Age 4–34 years LGS	≥50% decrease: 60.5% Seizure-free: 9.3%	Total 23.2% -Vomiting 13.5% -Irritability 6.9% -Drowsiness 2.3%
Kluger *et al.* [2010a]	Open-label extension study	124 patients Age 4–37 years LGS	≥50% decrease: 41% during last 12 months Seizure-free: none	Total 91.1% -Vomiting 30.6% -Pyrexia 25.8% -Somnolence 21%
Kluger *et al.* [2010b]	Retrospective 18-month Observational	52 patients Age 1–50 years Mixed epilepsy types	≥50% decrease 26.7% Seizure-free: 1.6%	Total 61.6% -Fatigue 18.3% -Vomiting 15% -Loss of appetite 10%
Vendrame *et al.* [2010]	Retrospective	77 patients Age 1–27 years Mixed epilepsy types	≥50% decrease: 51% Seizure-free: not reported	Total 29% -Drowsiness 13% -Rash 6%
Coppola *et al.* [2011]	Prospective Open-label	38 patients Age 4–34 years Non-LGS epileptic encephalopathies	≥50% decrease: 39.5% Seizure-free: 2.6%	Total: 28.9% -Vomiting 13.1% -Irritability 5.3% -Drowsiness 5.3%
Hausler *et al.* [2011]	Retrospective	3 patients Age 2–4 years EMA	≥50% decrease: 100% Seizure-free: 66.6%	'Transient and mild'
Joseph *et al.* [2011]	Retrospective	45 patients Age 1–20 years Mixed epilepsy types	≥50% decrease: 46% Seizure-free: none	Total: not reported -Vomiting 4.4% -Loss of appetite 4.4% -Agitation 4.4%
Mueller *et al.* [2011]	Retrospective	20 patients Age 3–23 years Dravet syndrome	≥50% decrease at 6 months: 20% ≥50% decrease at 18 months: 5%	Total 40% -Decreased appetite 15% -Fatigue 10% -Behavior change 10%
Olson *et al.* [2011]	Retrospective	38 patients 1–23 years Epileptic spasms	≥50% decrease in spasms: 53% >99% decrease: 5%	Total 37% -Decreased appetite 7.9% -Sedation 7.9%
Vendrame *et al.* [2011]	Retrospective	5 patients Age 2–3 years MMPEI	≥50% decrease: 40% Seizure-free: none	Total: 40% -Vomiting 20% -Loss of appetite 20%
Kim *et al.* [2012]	Prospective Open-label Observational	128 patients Age 1–19 years LGS	≥50% decrease: 35.9% Seizure-free:7.8%	Total 32.8% -Fatigue 11.7% -Loss of appetite 7%
Lee *et al.* [2012]	Retrospective	88 patients Age 2–43 years Mixed epilepsy types	≥50% decrease: 54,6% Seizure-free: 2.3%	Total: 31.8% - Loss of appetite 8% - Somnolence 6.8%

(Continued)

Table 2. (Continued)

Reference	Study design	Population	Countable seizure outcome	Adverse events: Total patients, most common
Moavero *et al.* [2012]	Prospective Open-label	70 patients Age 3–21 years Partial-onset seizures	≥50% decrease: 38.5% Seizure-free: 4.3%	Total 24.3% - Drowsiness 22.8% - Vomiting 10%
von Stulpnagel *et al.* [2012]	Retrospective	8 patients Age 3–20 years Doose syndrome	≥50% decrease: 75% at 6 months, 62.5% at 12 months Seizure-free: none	Total 25% -Sleepiness 12.5% -Decreased appetite 12.5%

EMA, epilepsy with myoclonic absences; LGS, Lennox–Gastaut syndrome; MMPEI, malignant migrating partial epilepsy of infancy.

children [Glauser *et al.* 2008]. Although this type of study design is considered the most scientifically rigorous, positive efficacy results are not automatically translated into effectiveness in clinical practice, due to the set patient population, titration and dosing schedules, and follow-up periods that are rigidly maintained within the boundaries of clinical trials. Thus, of complimentary importance in supporting the clinical effectiveness of rufinamide are the open-label extension study and the several observational and retrospective studies (Table 2) that have subsequently been published:

Prospective open-label studies in LGS

In the open-label extension of the original randomized controlled study, converting placebo-treated patients into a rufinamide-treated group, 124 patients, with an age range of 4–37 years old (mean 14.2 years old), were treated with adjunctive rufinamide for 10 to 1149 days (median 432 days) [Glauser *et al.* 2008; Kluger *et al.* 2010a]. During the open-label period, dosing adjustments were made at the investigator's discretion, with a median dosing of 52.9 mg/kg/day. During the last 12 months of treatment, the responder rates were 41% for total seizures and 47.9% for tonic–atonic seizures. The importance of this extension study was the demonstration of sustained efficacy over a longer time period, although still within the same limited patient population.

Two additional prospective open-label studies have also evaluated adjunctive rufinamide in LGS. In one of these studies, 43 patients with LGS, with an age range of 4–34 years old (median 15 years old) were treated with adjunctive rufinamide for 3 to 21 months (mean 12.3 months) [Coppola *et al.* 2010]. The final mean dosing was 33.5 mg/kg/day if combined with valproic acid and 54.5 mg/kg/day if not. The response rate for countable seizures was 60.5% after a mean 12-month observational period. The response rate for drop seizures was 46.5%. In another study, 128 patients with LGS, with an age range of 1–19 years old (mean 9.4 years old) were treated with adjunctive rufinamide over a 12-week maintenance treatment period [Kim *et al.* 2012]. The final mean dosing was 31.7mg/kg/day. The response rate for overall seizures was 35.9%. The response rate for drop seizures was 36.5%. These two studies confirmed the efficacy of rufinamide for seizures in LGS, but with a separate study population.

Prospective open-label studies in broader patient populations

In a prospective open-label study, 38 patients, with an age range of 4–34 years old (median 12.5 years old), with different types of childhood-onset refractory epileptic encephalopathies were treated with adjunctive rufinamide for 3–26 months (mean 11.4 months) [Coppola *et al.* 2011]. The final mean dosing was 37.9 mg/kg/day if combined with valproic acid and 36.4 mg/kg/day if not. This patient population included 22 patients with a multifocal encephalopathy with spasms/tonic seizures, eleven patients with a multifocal encephalopathy with bifrontal spike-wave discharges, four patients with Dravet syndrome, and one patient with Doose syndrome. The overall response rate for countable seizures was 39.5%.

In another prospective open-label study, 70 patients, with an age range of 3–21 years old (mean 10.7 years old), with refractory partial-onset seizures were treated with adjunctive rufinamide for and followed for 12 months [Moavero *et al.* 2012]. The final mean dosing was 42.6 mg/kg/day if combined with valproic acid and 31.8 mg/kg/day if not. At 12 months the overall seizure response rate was 38.5%. The importance of these studies was

the expansion of the identified efficacy of rufinamide into a broader pediatric patient population outside of LGS.

Retrospective studies in broader patient populations

Several retrospective studies examining the broad clinical use of rufinamide in pediatric epilepsy have also been published. In an open-label retrospective study, 60 patients, with an age range of 1–50 years old (median 11 years old), with various epilepsy syndromes, were treated with adjunctive rufinamide with results reported at 12 weeks [Kluger *et al.* 2009], and with further results for 52 out of 60 of the same patient cohort reported at 18 months [Kluger *et al.* 2010b]. The median maintenance dosing was 35.5 mg/kg/day. At 12 weeks, the overall seizure response rate for seizure reduction was 46.7%, with the highest rate in patients with LGS (54.8%), and the lowest in patients with partial epilepsy (23.5%) [Kluger *et al.* 2009]. At 18 months, the overall seizure response rate was 26.7%, with the highest subgroup still for LGS (35.5%) [Kluger *et al.* 2010b]. Although still showing long-term efficacy, there was a slight decrease in this patient cohort from 12 weeks to 18 months. It was noted by the investigators that this could be explained by the fact that the efficacy of rufinamide may be more sustained in LGS than in partial epilepsy, as patients with LGS had the highest retention rates at 18 months (51.6%), with only a 17.6% retention rate for patients with partial epilepsies.

In another retrospective study, 77 patients, with an age range of 1–27 years old (median 12 years old) with a variety of epilepsy syndromes were treated with adjunctive rufinamide, and followed for 1–10 months (median 4.4 months). The median maintenance dosing was 33.8 mg/kg/day. The overall seizure responder rate was 51%, with responder rates of 48.6% for tonic–atonic seizures, and 46.7% for partial seizures [Vendrame *et al.* 2010]. In a separate retrospective review, 45 patients, with an age range of 1–20 years old (mean 9.5 years old), with a variety of epilepsy syndromes were treated with adjunctive rufinamide for 1 to 103 weeks (mean 21 weeks) [Joseph *et al.* 2011]. The mean maintenance dosing was 30.1 mg/kg/day. The overall seizure response rate was 46%.

Our own experience has been similar. Using data collected retrospectively, 88 patients, with an age range of 2–43 years old (mean 12.1 years old), with a variety of epilepsy syndromes were treated with adjunctive rufinamide for a median duration of treatment of 9 months [Lee *et al.* 2012]. The average final dosing was 50–60 mg/kg/day. The overall seizure response rate was 54.6%.

Retrospective studies in focused patient populations

In a more focused retrospective study, Olson and colleagues examined the response to rufinamide in patients with epileptic spasms of varying etiologies [Olson *et al.* 2011]. A total of 38 patients, with an age range of 17 months to 23 years old (median 7 years old) were treated with adjunctive rufinamide for 10–408 days (median 171 days). The median maintenance dose was 39 mg/kg/day. The responder rate for epileptic spasms was 53%. Furthermore, several small (3–8 patients) focused retrospective studies have provided encouraging clinical experiences using adjunctive rufinamide for other epilepsy syndromes. This includes epilepsy with myoclonic absences [Hausler *et al.* 2011], malignant migrating partial epilepsy of infancy [Vendrame *et al.* 2011], myoclonic–astatic epilepsy (Doose syndrome) [von Stulpnagel *et al.* 2012], and a single case report with methylmalonic aciduria [von Stulpnagel *et al.* 2011].

A retrospective case series examining the use of adjunctive rufinamide for 20 patients with Dravet syndrome, however, reported low long-term efficacy, with a responder rate at 6 months of 20% and by 34 months the responder rate was 5% [Mueller *et al.* 2011]. Furthermore, seizure aggravation was reported by 30%. Patients with Dravet syndrome have also been included in other studies with heterogeneous patient populations: Kluger and colleagues reported one out of two Dravet syndrome patients responding to rufinamide [Kluger *et al.* 2009], and Coppola and colleagues reported no patient responders out of four, although one patient was reported to have a 25–49% decrease in seizures [Coppola *et al.* 2011]. However, two of the patients with Dravet syndrome in this series had resultant seizure aggravation with rufinamide treatment.

Safety and tolerability

Of equal importance to the efficacy of rufinamide, in defining its clinical effectiveness, are safety and tolerability (Table 2). In the randomized placebo-controlled trial involving mostly children [Glauser

et al. 2008], 60% of patients in the rufinamide treatment group reported adverse events, of which the most common were somnolence (24.3%), vomiting (21.6%), pyrexia (13.5%), and diarrhea (5.4%). However, the only significant differences in adverse events when comparing the rufinamide-treated to the placebo group were somnolence (24.3% with rufinamide *versus* 12.5% with placebo) and vomiting (21.6% with rufinamide *versus* 6.3% with placebo). There were no reported clinical significant changes in vital signs, physical examinations, electrocardiogram recordings, or laboratory tests.

In a pooled analysis focusing on pediatric patients (less than 16 years old) treated with rufinamide within double-blind placebo-controlled studies drawn from a rufinamide clinical studies database, 212 patients were included for analysis [Wheless *et al.* 2009]. Of those in the rufinamide treatment group, 83.5% reported adverse events, of which the most common were somnolence (17% rufinamide *versus* 8.1% placebo), vomiting (16.5% *versus* 7.1% placebo), headache (16% *versus* 8.1% placebo), and pyrexia (11.3% *versus* 10.7% placebo), with similar findings when the open-label extension patients were included. The majority of these adverse events were noted to be mild or moderate in severity. However, adverse events led to discontinuation in 7.1% in the double-blind rufinamide treated population (compared with 2% in the placebo population). Both the incidence and type of adverse events were similar across doses.

Within the pooled analysis, somnolence was the only cognitive adverse event occurring with an incidence of 10% or more [Wheless *et al.* 2009]. In a randomized, double-blinded, placebo-controlled study of patients consisting of older adolescents and adults within an age range of 15–64 years old, no serious cognitive effects were noted with 12 weeks of rufinamide treatment, measured using formal neuropsychological testing [Aldenkamp and Alpherts, 2006]. Although the applicability of this study to children cannot be assumed, it still reflects the low cognitive side-effect profile of rufinamide.

The only contraindication listed in the rufinamide packet insert is familial short QT syndrome [Eisai Inc., 2010]. QTc-interval shortening can occur with rufinamide treatment, although complications are rare [Schimpf *et al.* 2012]. When compared against a placebo-treated population, however, the percentage of electrocardiograms that evolve from normal to abnormal after rufinamide treatment is similar, with 11.3% in the rufinamide group compared with 9.6% in the placebo group [Wheless *et al.* 2009].

In addition, within the pooled analysis, there were five patients identified with possible cases of antiepileptic drug hypersensitivity syndrome [Wheless *et al.* 2009]. All cases were quickly reversible with drug discontinuation. However, more severe reactions to include Stevens–Johnson syndrome have been reported with rufinamide use [Chambel *et al.* 2012].

Drug–drug interactions

Owing to its lack of effect upon the cytochrome P450 system, rufinamide has a relatively low potential for drug–drug interactions. In regards to interactions with other anticonvulsant medications, the data available on the pharmacokinetic interactions of rufinamide are derived from a retrospective pooled analysis from previous clinical trials of adjunctive rufinamide treatment [Perucca *et al.* 2008]. Rufinamide does not modify the clearance of topiramate or valproic acid. Rufinamide may slightly increase the clearance of carbamazepine and lamotrigine, and may slightly decrease the clearance of phenobarbital and phenytoin, with all predicted changes less than 17.5% [Perucca *et al.* 2008]. Lamotrigine and topiramate do not affect the clearance of rufinamide. Valproic acid, however, may decrease the clearance of rufinamide, with the most prominent effects occurring in children. This occurrence may be due to the fact that children are on higher doses of valproic acid, rather than an age-related effect [Perucca *et al.* 2008]. In clinical practice, rufinamide dosing in children taking concomitant valproic acid may need to be decreased, on average, by approximately 50% [Perucca *et al.* 2008].

Pregnancy and teratogenicity

Rufinamide may decrease blood levels of hormonal contraceptives, but the clinical significance of this is not known [Eisai Inc., 2010]. Rufinamide is labeled as a pregnancy category C, owing to a lack of adequate well-controlled studies in women concerning pregnancy and teratogenicity.

Clinical use

The decision-making process of choosing an anticonvulsant medication such as rufinamide to treat a child with epilepsy is led by the physician but should include active participation by the family, and when appropriate, the pediatric patient. This decision should consider the summation of known efficacy data, and the described safety and tolerability profile, but within the context of each individual patient. It is known that a patient's chances of seizure freedom decrease with each subsequent failed drug trial [Brodie *et al.* 2012], and thus many patients with LGS are medication-refractory. Other nonmedication treatments for epilepsy are available and should be considered in discussion with the family and patient, to include dietary and surgical options. However, this should not preclude the consideration of further anticonvulsant medication trials, if desired by the patient or their family, as remission in medication-refractory patients is still possible after the second drug failure, although often times temporary [Berg *et al.* 2009].

Rufinamide is now one of several anticonvulsant medications (felbamate, lamotrigine, topiramate, clobazam) that have demonstrated efficacy *versus* placebo in clinical trials for the treatment of LGS [The Felbamate Study Group in Lennox Gastaut, 1993; Motte *et al.* 1997; Sachdeo *et al.* 1999; Ng *et al.* 2011]. It should be appreciated, though, that although rufinamide demonstrates efficacy *versus* placebo in clinical trials, it cannot be concluded that it is superior to other anticonvulsant medications, due to a lack of head-to-head trials.

However, the treatment goal for the child with epilepsy is not only aimed at seizure control, but is ultimately focused upon the broader schema of enhancing and maximizing quality of life for the patient and their family. This is especially pertinent in LGS due to the tendency to be refractory to medication treatment. Although rufinamide has shown clinical efficacy in the defined parameters of clinical trials, seizure-freedom rates are low. Furthermore, there is a lack of qualitative research in LGS specifically addressing the effects of anticonvulsant drugs, to include rufinamide, on the health-related quality of life on the patient and the family [Gallop *et al.* 2009]. As seizures and cognitive impairment are the two main components influencing the health-related quality of life of children with LGS [Gallop *et al.* 2010], it is a reasonable goal to strive for optimal seizure control, although not at the expense of side effects which can negatively influence quality of life.

Prescribing guidelines

The FDA indication approves the use of rufinamide to a small focused population (adjunctive use in patients 4-years-old and over with LGS), as these are the only parameters in which randomized, double-blind, placebo-controlled data exists (Table 3). However, published data, as reviewed, support the safe and efficacious use of rufinamide outside both of these parameters, although this necessitates conscientious clinical judgment for each individual patient.

In the United States, rufinamide is available in 200 mg tablets, 400 mg tablets, and as a liquid suspension of 40 mg/ml. The tablets can be taken whole, cut in half, or crushed. The plasma half-life of 6–10 hours allows for twice-daily dosing. Absorption and bioavailability appear to be hampered by the fasting states, and evidence supports increased absorption when taken with food [Perucca *et al.* 2008]. Thus, a practical recommendation is to take rufinamide twice daily with meals. An intravenous form of rufinamide is not available.

In terms of dosing, the clinical trial by Glauser and colleagues used a relatively quick titration schedule that was well tolerated, using an initial dosing of rufinamide 10 mg/kg/day in two divided doses and increasing by 10 mg/kg increments every other day to a target dosing within 7 days of 45 mg/kg/day or up to 3600 mg/day (with some flexibility to extend the titration to 14 days as clinically needed) [Glauser *et al.* 2008]. This dosing recommendation is similar to the recommended dosing on the package insert [Eisai Inc., 2010]. However, in clinical practice, a slower titration schedule tends to be utilized, and appears to be better tolerated with similar efficacy [Vendrame *et al.* 2010; Kim *et al.* 2012]. In our personal experience treating a heterogeneous population of children with rufinamide, an initial dosing of 5–10 mg/kg/day in two divided doses and increasing by 5–10 mg/kg increments every 5–7 days to a maintenance dosing of 45–50 mg/kg/day is well tolerated without compromising efficacy [Lee *et al.* 2012]. Furthermore this allows time for assessment for those patients who might respond to, and could be maintained on, low doses of rufinamide.

Routine laboratory tests, such as blood counts or liver function testing, are not required with rufinamide treatment. There is a positive correlation between steady-state plasma levels and both seizure frequency and adverse effects, suggesting the possible clinical value of measuring plasma rufinamide levels [Perucca *et al.* 2008].

Table 3. Rufinamide clinical use summary.

FDA indication:
Adjunctive treatment of seizures associated with Lennox–Gastaut syndrome in patients 4 years old and older
Clinical effectiveness:
Broad-spectrum, but especially efficacious for tonic–atonic seizures associated with Lennox–Gastaut syndrome
Contraindications:
Familial Short QT syndrome
Most common side effects*:
Fatigue
Nausea and vomiting
Decreased appetite
Availability within the United States:
200 mg tabs
400 mg tabs
40 mg/ml liquid suspension
Recommended dosing:
Package insert:
Initial: 10 mg/kg/day in two divided doses, with meals
Increase by 10 mg/kg increments every other day
Maintenance: 45 mg/kg/day up to 3600 mg/day in two divided doses, with meals
Clinical practice recommendation:
Initial: 5–10 mg/kg/day in two divided doses, with meals
Increase by 5–10 mg/kg increments every 5–7 days
Maintenance: 45–50 mg/kg/day, with meals, adjusted as tolerated

*Somnolence and vomiting were the only adverse effects more commonly reported with rufinamide treatment with a significant treatment difference *versus* placebo [Glauser *et al*. 2008].

Summary

Rufinamide is proving to be a valuable medication treatment option in pediatric epilepsy, substantiated by efficacy and safety data from both clinical trials and clinical practice. In addition to a broad spectrum of clinical efficacy, it possesses many salient features that support its effectiveness in clinical practice, which can be of essential relevance when caring for children:

- a mild side-effect profile;
- twice a day dosing;
- both tablet and liquid formulations;
- the option of a quick titration;
- a low potential for drug–drug interactions;
- routine laboratory testing is not required.

However, further research and more clinical experience are needed to further define the role of rufinamide in the treatment of pediatric epilepsy. Although current research supports short-term clinical efficacy, data on the effects on quality of life, the underlying goal in the treatment of children with epilepsy, are lacking and should be addressed in future trials. Head-to-head trials with other anticonvulsant medications have not been performed, but would help to direct best practices. Finally, long-term efficacy and possible long-term adverse effects are undefined and will require continued monitoring. For now, rufinamide is asserted as an efficacious and well-tolerated adjunctive anticonvulsant medication for the treatment of refractory pediatric epilepsy, and should be considered particularly for refractory seizures associated with LGS.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Disclaimer

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