

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Rufinamide: A Novel Antiepileptic Drug

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ABSTRACT

Rufinamide, a triazole derivative that is structurally distinct from currently marketed antiepileptic drugs (AEDs), is in development for the adjunctive treatment in patients with partial seizures and Lennox-Gastaut syndrome (LGS). The principal mechanism of action of rufinamide is considered to be the modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide is well absorbed after oral administration, demonstrates low protein binding, and is metabolized by enzymatic hydrolysis without involvement of cytochrome P450 enzymes, conferring a low drug interaction potential. Most common adverse effects noted are somnolence, fatigue and tremor. Rufinamide produced statistically significant seizure reduction which was maintained during long-term therapy and accompanied by good tolerability. The commonly observed adverse events were fatigue, headache and dizziness which were mild to moderate in severity. Rufinamide is generally well tolerated, and its safety profile is well-established. Rufinamide, offers a novel treatment option for patients with partial seizures and Lennox-Gastaut syndrome (LGS).

Keywords: Rufinamide; epilepsy; anti-epileptic drugs; seizures; Lennox–Gastaut syndrome; Partial seizures

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INTRODUCTION

Epilepsy is a common disorder which characterized by episodes of unprovoked excitations of neurons, termed as seizures. In developed nations, epilepsy is observed in about 1% of the population. It is largely seen in people less than 20 years of age and again in later stage of life. In adults the frequency of seizures generally lowers down. However, in old age, other diseases affecting functioning of brain combined with ageing results in increased frequency of seizures at later stages of life. [1,2]

Seizures are of many types with variability in frequency, origin like partial seizures, generalized seizures with further sub-classification, lennox-gastaut syndrome in children. Generalized seizures has origin in the cerebral hemispheres while partial seizures origin in the focal part in the brain. Lennox-Gastaut syndrome (LGS) occurs mostly in children aged 3 to 5 years. LGS which is classified under generalized epilepsy is distinguished by 3 characteristics. Firstly, one or more combination of multiple seizures types like atypical absence seizures, tonic, atonic, tonic-clonic, myoclonic, partial seizures, status epilepticus are observe. Secondly, children suffering exhibit cognitive or behavioral disorders and thirdly, the interictal electroencephalogram (EEG) consists of slow spike wave complexes. [3-5]

Epilepsy is a complex syndrome and is difficult to treat completely even with one or more combinations of anti-epileptic drugs. The commonly used anti-epileptic drugs are phenytoin, lamotrigine, oxcarbazipine, carbamazipine, phenobarbital, topiramate, valproate, levetiracetam. These anti-epileptic drugs do help to decrease the frequency of seizures, however, all patients are not completely treated and show refractory seizures. Moreover, the side-effects of these any of these anti-epileptic drugs are add to the overall burden of epilepsy. Alternatively, refractory seizures can be cured through methods like vagal nerve stimulation and surgical resection. These methods are effective in providing relief in most refractory seizures with an exception of lennox-gastaut syndrome in which they are not found to be effective.⁶ In addition to above mentioned issues in the treatment of epilepsy, the issue of drug resistance and consequent inefficacy are triggers for the development of new efficacious, well-tolerated anti-epileptic drugs. Rufinamide, a triazole derivative, developed by Novartis is one of the new anti-epileptic drugs for the treatment of various types of seizures. Its mechanism of action limits or stabilizes the neuronal sodium channel action potentials. [6, 7]

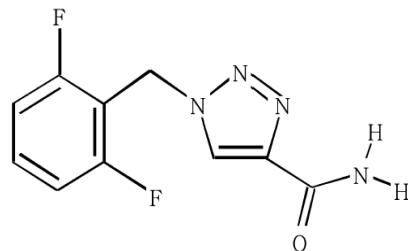
Rufinamide (CGP-33011) initially discovered by Novartis Pharmaceuticals was later developed and commercialized by Eisai Co., Japan. Rufinamide was also approved as an orphan drug for the treatment of Lennox-gastaut syndrome, comparatively, a rarer, complex form of epilepsy in United States as well as in Europe. Rufinamide, commercialized under the trade name of Invelon[®] and Xilep[®] was indicated as an add-on treatment with other anti-epileptic drugs for partial seizures with or without secondary generalization in patients >= 12 years and as an add-on treatment in Lennox-Gastaut syndrome for children >= 4 years of age. [6, 4, 9] The development history of rufinamide in clinical trials phase in as shown in the Table I:

Table I: Drug development history [8]

Feb 1996	Phase-II for Epilepsy in Japan (PO)
Apr 1996	Phase-III for Epilepsy in Switzerland (PO)
Jun 1997	Phase-II for Epilepsy in US (PO)
Apr 1999	Phase-III for Epilepsy in US (PO)
Jan 2001	Phase-II for Neuropathic pain in the US (PO)
Jun 2001	Discontinued - Phase-III for Epilepsy in Switzerland (PO)
Jun 2001	Discontinued - Phase-III for Epilepsy in the US (PO)
Jun 2001	Discontinued - Phase-II for Epilepsy in Japan (PO)
Jun 2001	Discontinued - Phase-II for Neuropathic pain in the US (PO)
Feb 2004	Rufinamide has been licensed to Eisai worldwide for the treatment of Epilepsy
Feb 2004	Phase-III for Epilepsy in Switzerland (PO)
Feb 2004	Phase-III for Epilepsy in US (PO)
Oct 2004	Rufinamide has received Orphan Drug Status for Epilepsy in Europe
May 2005	Preregistration for Epilepsy in Europe (PO)

RUFINAMIDE

Rufinamide is a chemically novel drug of a new class – triazole derivative and hence it is structurally different to present anti-epileptic drugs. Chemically, it is [1-(2,6-difluorophenyl)methyl-1*H*-1,2,3-triazole-4-carboxamide] as shown in the Figure I. [10]


FIGURE I: Chemical structure of rufinamide

MECHANISM OF ACTION

The precise mechanism of action of rufinamide is still unknown. However, rufinamide is believed to act through stabilizing excitability of neurons. It is carried out by principally prolonging the inactivated state of the voltage-gated sodium ion channels. Results from *in vitro* studies on cortical neurons from immature rats have revealed that rufinamide slows down the recovery of sodium ion channel from inactivated state after a prolonged prepulse. Thus, it reduces the abnormal firing of sodium dependent action potentials. [11,12] Moreover, clinical studies have shown it to raise the seizure threshold in general and prevent the subsequent spread of seizure. [13]

Also, radio-ligand studies on rufinamide have shown that it hardly interfere with other acetylcholine, glycine, monoamine, N-methyl-D-aspartate (NMDA), histamine, adenosine, α -amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA), γ -amino butyric acid (GABA) type of transmitter systems. Thus, the primary mechanism of rufinamide remains that of stabilization of sodium channels. [6,2,5]

PHARMACOLOGY

Preclinical pharmacological data

Rufinamide has been studied in various animal models in different type of seizures. Rufinamide when studied orally in electroshock induced tonic-clonic seizures and pentylenetetrazol induced clonic seizures showed acute anti-convulsive activity. [6] ED₅₀ was measured for both pentylenetetrazols induced and electroshock induced models and were compared to those of other anti-epileptic drugs. ED₅₀ for pentylenetetrazol induced was 45 mg/kg which was considerably lower than other drugs like phenytoin, valproate and ethosuxamide. Similarly, ED₅₀ for electroshock induced models was 23.9 mg/kg while those of others anti-epileptic drugs were >2000mg/kg, 20.1mg/kg, 9mg/kg, 664.8 mg/kg for ethosuximide, phenobarbital, phenytoin, valproate, respectively. Oral rufinamide also showed a better or at least similar effect to existing AEDs in the behavioral toxicity. [11]

Studies conducted on rufinamide intraperitoneally also showed positive results. Picrotoxin, pentylenetetrazol and bicuculline induced seizure models were used to evaluate the efficacy of rufinamide intraperitoneally. Seizures were effectively suppressed in these models also suggesting its application to a wide range of seizures. [11]

Rufinamide also showed efficacy in studies carried out on models of chronic epilepsy. For example, it was found effective in blocking seizures in rhesus monkeys with chronic aluminium induced epileptic focus. Similarly, in amygdala kindled cats it has also shown delayed firing and reduced after discharges. Moreover, the amnesia reported through electroshock induced seizure was also noted to be reduced with rufinamide. Similarly, rufinamide has shown to be have higher protective index in animal studies in comparison to other anti-epileptic drugs. [6,9]

PHARMACOKINETICS

Rufinamide is insoluble in water and has a poor solubility in stomach and intestine. Presently, rufinamide is available as a coated tablet. [1,6] Rufinamide has a comparatively slow rate of absorption. However, it is well absorbed and absorption is inversely proportional to increase in dose.⁴ Rufinamide was absorbed faster in fed state as compared to fasting state (T_{max}; 6 hours in fed and 8 hours in fast state). Similarly, area under curve i.e. AUC was also found to be higher in fed state (AUC; 81.7 vs 57.2 μ g h/ml). The increased absorption of rufinamide in fed state could be considered for administration of rufinamide with food if the high absorption level is acceptable. However, multiple dosing did not change the

pharmacokinetics of rufinamide. [4, 9, 14] Similarly, repeat dosing of rufinamide was not affected by food. Elimination half-life of rufinamide is 6-10 hours and thus steady state is achieved in 2 days. When given twice daily at 12-hourly intervals, rufinamide accumulates to the extent predicted by its terminal half-life, indicating that the pharmacokinetics of rufinamide are time-independent. Apparent volume of distribution and apparent oral clearance are dependent on the body size, specifically, the body surface area with apparent volume of distribution being proportional to the dose administered. Rufinamide has a low plasma protein binding. [9, 15] The pharmacokinetics of rufinamide are shown in Table II.

TABLE II: Pharmacokinetics of Rufinamide [11]

Bioavailability	Fed- 85%
T _{max}	4 to 6 hours
T _{1/2}	6 to 10 hours
Protein binding	26 to 34%
Volume of distribution (V _d /F)	50 to 80 L (0.8-1.2 L/kg)
Serum levels	5 to 55 mcg/mL

Rufinamide is metabolized into a non-pharmacologically active substance and has an extensive metabolism. Rufinamide is excreted through kidneys with minute quantities are observed in urine and feaces. [2] It is mainly metabolized by an enzyme caboxylesterase by hydrolysis. Rufinamide does not interfere with metabolism of drugs or other substrates metabolized by carboxylesterase. However, it does play a role in induction of CYP3A4 and increase the metabolism of those drugs which are metabolized by CYP3A4. Rufinamide has no effect on CYP1A1 and CYP1A2 as well as Cytochrome P450. [2, 9]

In pediatric patients, rufinamide shows similar pharmacokinetics to that of adults. Also, studies in geriatric patients show a similar pharmacokinetic profile to that of adults. [9] A study where rufinamide therapy was indicated as an adjunctive therapy to valproate, higher serum concentrations were noted in children as that seen in adults. [16]

In studies with special populations, it was found that pharmacokinetics were not different for rufinamide in healthy subjects and patient facing renal impairment. However, the peak concentration and AUC were relatively decreased in such patients where adjustments of dose may be necessary. No studies have yet been conducted on patients with hepatic impairment and hence it should be used cautiously in such patients. [10] A pharmacokinetic study was also carried out on comparison of two formulations; tablet and suspension. No significant difference was noted for these two different types of formulations. [2]

DRUG DRUG INTERACTIONS

Rufinamide is not extensively plasma bound. Thus, there are very less drug-drug interactions observed with rufinamide. However, epilepsy is mostly treated through multiple

anti-epileptic drugs, hence, it becoming essential to carefully select the choice of concomitant medications. [4,5] as stated above, rufinamide does not show any effect on CYP450 enzymes. It induces CYP3A4 weakly and weakly inhibits CYP2E1 [10,14] *In vitro* studies on drug interactions have shown induction of nicotinamide adenine dinucleotide phosphate cytochrome c reductase and uridine diphosphate-glucuronosyltransferase activities. [10,14]

Effects of rufinamide on other AEDs

Interactions with other anti-epileptic drugs have been notified in some studies. These studies were performed on patients already on other specified anti-epileptic drugs who were then given rufinamide or a placebo concomitantly. Pharmacokinetic analysis was performed for the range of anti-epileptic drugs like lamotrigine, phenytoin, valproate, carbamazepine, etc. Average concentration at steady state was a dependent variable. [9] Results depicted change in the clearance in drugs concomitantly administered with rufinamide. Clearance of some drugs increased e.g. Carbamazepine, lamotrigine while clearance for some other drugs decreased e.g. Phenobarbitol, phenytoin. [5,10] Decreased clearance of drugs leads to increased plasma levels of the drug. Moreover, for phenytoin it is possible that actual increased plasma levels would be greater than predicted one as it has non-linear pharmacokinetics.

Effects of other AEDs on rufinamide

Pharmacokinetic data from phase II/III trials were used to determine the effect of anti-epileptic drugs on rufinamide. Clearance of rufinamide is mildly increased by drugs like phenytoin, primidone and phenobarbitol which are CYP450 inducers [7,9] However, since rufinamide is not majorly cleared through CYP route, it is still unknown if these interactions are due to induction of CYP enzymes. Moreover, in adults the interactions of rufinamide and other anti-epileptic drugs might not be significant except in children where the decreased clearance of valproate which significantly raise the blood levels of rufinamide unlike in adults where there is not much elevation with the decreased clearance. [9,11,15] Although, increased valproate dose would lead to increased levels of rufinamide in plasma as valproate inhibits many metabolizing enzymes. [11] Other drugs have not shown any significant effect on rufinamide blood concentrations. [10]

Effects of rufinamide on other medications

Rufinamide does interact much with other anti-epileptic drugs. However, some interactions are found with other concomitant medications. For example, rufinamide might reduce the efficacy of hormonal contraceptive drugs. Rufinamide, a weak inducer of CYP3A4 might raise the clearance rate of drugs metabolized by CYP3A4 like triazolam, norethindrone, ethinyl estradiol etc. However, mild increasing of clearance of these drugs do not have clinical importance. In addition, the AUC and Cmax of trazolam were found to be reduced by concomitant use with rufinamide. [7, 10]

EFFICACY STUDIES

Most studies conducted on determining the efficacy of rufinamide are placebo-controlled studies. The patient population in these studies included those with: 1) Lennox–Gastaut syndrome, (Table-III) 2) adult partial onset seizures (for both monotherapy and adjunctive therapy), 3) pediatric partial onset seizures as adjunctive therapy, and 4) patients with refractory generalized tonic–clonic seizures. [11]

Seizures Associated with Lennox–Gastaut Syndrome

A study involving 138 patients was conducted to evaluate the efficacy of rufinamide in comparison with placebo in Lennox-Gastaut syndrome. The double-blind, parallel-group, randomized study included patients of Lennox-Gastaut syndrome aged between 4 to 30 years and having a history of minimum 90 seizures in previous month. Patients on 1-3 AEDs (except felbamate therapy) were allowed to enter the study. A 4-week baseline phase was followed by a 12-week treatment phase where patients were titrated to a maximum of 3200mg/day dose in the first 1-2 weeks. The daily increase in the dose was 45 mg/kg approximately with a twice-daily dosing schedule. (Table III)

TABLE III: Summary of Clinical Studies with Rufinamide [11]

STUDY TYPE	SEIZURE TYPE	DAILY DOSE	AGE (YEARS)	OUTCOME*
Adjunct	Lennox- Gastaut syndrome	45 mg/kg (maximum 3,200 mg) or placebo	4 to 30	↓ Drop attacks ↓Total seizures ↓ Seizure severity
Adjunct	Partial onset	200, 400, 800, 1,600 or placebo	≥15	↓ Total seizure (+)Responder rate
Adjunct	Partial onset	3,200 mg or placebo	≥16	↓ Total seizure (+)Responder rate
Monotherapy	Partial onset	3,200 mg or placebo	≥12	Fewer seizures and longer time to first, second, and third seizure for rufinamide
Adjunct [†]	Primary GTC	800 mg or placebo	≥4	No difference vs. placebo

Abbreviations: GTC, generalized tonic-clonic.

*All were significant ($p < 0.05$) except study in Reference 7

† The dose used did not provide patients with plasma rufinamide concentrations that are therapeutic for other seizure type, which could explain the lack of efficacy seen in this study.

Percent change in total seizure frequency/28 days, percent change in tonic–atonic (drop attacks) seizure frequency/28 days; and seizure severity rating from the global evaluation of the patient's condition were the primary efficacy variables. [9] Reductions in seizure frequencies were measured compared to that of baseline in rufinamide and placebo-treated patients.

Overall, rufinamide showed greater median reductions in total seizure frequency as well as drop attacks/28 days. The median reductions for total seizure frequency and drop attacks

were 32.7% and 42.5% for rufinamide respectively. Similarly, the corresponding mean reductions for placebo were 11.7% and 1.4% respectively. [9, 13]

Extension Phase

Rufinamide has also shown to be effective in long-term treatment. [11] In an open-label, extension phase of a study, patients received median dose of 1800mg/day for a median of 432 days. Responder rates and frequency of total seizures evaluated at the end of 3 years was similar to that observed at 12 weeks. Total seizure frequency was reduced by half of that at baseline in 36.9% of patients. Moreover, patients did not show any tolerance even at the end of 3 years treatment. [5, 10]

Partial Onset Seizures

Rufinamide has been evaluated as an adjunctive therapy in the treatment of partial onset seizures. In one of the studies, 313 patients with ≥ 16 years of age were included in the baseline phase. Patients with ≥ 1 seizure per 4 week in the 8 week baseline phase were eligible for the treatment phase. In the 13 week treatment phase, patients were randomised to receive either rufinamide or placebo and those in the rufinamide group were titrated upto a maximum of 3200mg/day in the initial 1-2 weeks. At the end of the 13 weeks, patients on rufinamide therapy showed a relatively greater decrease in seizure frequency. Moreover, the number of patients achieving a reduction of atleast 50% in seizure frequency compared to that at baseline were higher in rufinamide group than placebo group. Overall, rufinamide showed significantly greater efficacy in reducing the seizure frequency per 28 days in patients with partial onset seizures. [9, 11]

Another study on patients with partial onset seizures evaluated dose response to rufinamide by assessing four different doses of rufinamide i.e. 200mg, 400mg, 800mg and 1600mg each treatment compared with a placebo. Patients were first enrolled for a 12 week baseline phase and those who were eligible for the 3 month double-blind phase (≥ 9 seizures in baseline phase) were randomized to receive either of the four doses of rufinamide or a placebo. Rufinamide showed relatively greater reductions in seizure frequency with each increasing dose. Similarly, the responder rates also increased with increasing doses. Rufinamide, thus showed dose response for seizure frequency as well as responder rates. [1, 9, 11]

Efficacy of rufinamide evaluated on children revealed similar results. Patients who were treated with 1-2 concomitant AEDs in the baseline phase and had ≥ 3 seizures per month were enrolled for the following open-label phase. The open-label phase involved 1-week of titration followed by 2-weeks of treatment. The results showed that 4 out of 9 patients showed more than 50% reduction in the seizure frequency as compared to that of baseline. [1, 10]

Rufinamide was determined for its efficacy as monotherapy in comparison with placebo in a study involving patients with partial seizures. 104 patients aged ≥ 12 years with partial seizures were enrolled in the study. In the baseline phase of 2 days, patients received no other

AEDs except lorazepam in low dose. Patients who had 2-10 seizures in the baseline phase were eligible for the double-blind phase. In the double-blind phase, patients randomized to rufinamide treatment were titrated to 3200mg/day in the first 2 days and the treatment continued till patients met one of the exit criteria involving occurrence of different types of seizures or till a maximum of 10 days. Patients in the rufinamide group showed longer median time to meet the exclusion criteria compared to placebo group. Also, patients on rufinamide treatment showed comparatively longer time to first, second and third seizures and were statistically significant. [9, 11] The results of this study, thus showed efficacy of rufinamide also as a monotherapy.

Long term follow Up

An extension phase was carried out for the studies evaluating the efficacy of rufinamide in Lennox-Gastaut syndrome as well as partial seizures for determining its long-term efficacy. The extension phase of these studies were open-labelled. However, patients showed similar or greater response in the extension phase and thus were found effective in the long-term therapy also. Moreover, patients did not experience any tolerance towards rufinamide. [9, 11]

SAFETY AND TOLERABILITY

Lennox-Gastaut Syndrome shows poor prognosis. In patients with LGS, when drugs like lamotrigine, topiramate and valproate does not work, rufinamide is a considerable option. Also, it is recommended before initiation of felbamate and others anti-epileptic drugs. [3]

Studies in animals have shown that the behavioural toxicity profile of rufinamide is comparable to that of existing anti-epileptic drugs. However, clinical studies have shown adverse reactions of the central nervous system which were mild or moderately severe. Somnolence, headache, nausea, fatigue were some of the adverse reactions observed clinically. Rufinamide showed only a slightly increased adverse event profile when compared to placebo. Rufinamide showed a similar profile of adverse events in long-term studies. The commonly observed adverse events were fatigue, headache and dizziness which were mild to moderate in severity. [2, 16, 13]

No severe events like hepatic failure, pancytopenia, Stevens-Johnson syndrome, and agranulocytosis were noted with rufinamide treatment. In one the studies, cognitive disorders were assessed at 3 months after initiation of the therapy (add on therapy) and compared with that at baseline. Doses of 200, 400, 800 and 1600 mg/day were assessed in patients with age ≥ 15 years and ≤ 64 years. Cognitive tests performed for attention or psychomotor speed did not show any significant deterioration at the end of three months compared to that at baseline. Some studies showed that in comparison with rufinamide, placebo treated patients showed higher rates of cognitive disorders. This was possibly due to higher rates of somnolence in such patients. Overall, studies comparing rufinamide with baseline and that with placebo showed a good tolerability profile of rufinamide. [11, 13, 17]

Long-term use of anti-epileptic drugs is also associated with cardiac disorders like increased QT interval dispersion seen in children on antiepileptic drugs. In contrast, rufinamide have not shown any such serious effect compromising cardiac safety. [5] Studies determining QT interval with rufinamide treatment have depicted shortening of upto 20 msec. The number of patients achieving a QT shortening greater than 20 msec was highest in patients receiving 4800 mg. However, in comparison with placebo, the number of patients achieving a QT shortening of more than 20 msec was considerably higher in patients receiving doses of 3200 mg and 2400 mg. [10, 18]

Also, the degree of QT interval observed with rufinamide did not show to be potentially clinically significant. No adverse events like arrhythmias or sudden death occurred with rufinamide treatment. However, in patients with familial QT syndrome, rufinamide might increase the possibility of arrhythmias or other serious cardiac events and hence it is contraindicated in such patients. Similarly, rufinamide could also increase the possibility of arrhythmias if it is given concomitant to drugs which are known to shorten QT interval. In these patients, rufinamide should be used with caution. [10,11]

Laboratory parameters after rufinamide treatment also did not show any noteworthy values. Rufinamide which comes under category C of pregnancy categories, have shown presence in fetus in animal studies. However, only at high doses did it cause fetal toxicity. Owing to fetal toxicity results in animal, pregnancy studies have not been conducted in humans. [6,11]

However, clinical trials results are based only on a small sample of patients and it is therefore difficult to predict all toxic effects on a large population with diverse conditions.

Safety and Tolerability in Special Populations

In children, the majority side effects observed were that of status epilepticus, weight loss and somnolence. Also, status epilepticus was observed at more than double the rate of that observed in adults. Other side effects which occurred less frequently were diplopia, headache, blurred vision and nausea which was observed more in female patients. These side effects which occurred comparatively less frequently might be attributable to a low dose. In LGS patients, the rate of status epilepticus was higher compared to that of other types of epilepsy. Also, events such as rash, vomiting and somnolence were higher with rufinamide than placebo where vomiting and somnolence were also statistically significant compared to placebo. [6]

CONCLUSION

Epilepsy is such a condition where because of its complexity to treat, there are already plenty of drugs to for its treatment. However, all drugs have some side effects and some undesired profile along with its intended action and hence search for new more efficacious and safe drugs will never decrease. Rufinamide is such a drug which in comparison to presently available drugs shows efficacy for variety of seizures. It is clear from clinical studies that

rufinamide is superior to other drugs for the treatment of Lennox-gastaut syndrome. Moreover, it has also shown a safety profile comparable or better to that of other anti-epileptic drugs. Frequent side-effects of rufinamide including vomiting or somnolence can be handled by careful dose adjustments. [6] In summary, rufinamide has many advantages over current anti-epileptic drugs. Firstly, it can be used in LGS where other drugs are either ineffective or has many side-effects in children. However, drug-interactions with other AEDs should be considered when using in children in LGS. Secondly, it has a good safety profile. Cognitive and behavioural side-effects observed with other drugs are relatively seen rarer with rufinamide. Thus, elevations of dose can be done rapidly as and when desired. Another advantage is that the pharmacokinetics special populations such as renal or hepatically impaired [2,6,3]. With so many advantages over currently prescribed anti-epileptic drugs; -rufinamide is sure to find an easy acceptance in the medical community.

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