Rufinamide

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Summary: Rufinamide is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs. Rufinamide was profiled for anticonvulsant activity at the National Institutes of Health and showed broad-spectrum anticonvulsant properties at nontoxic doses in animal models. 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 provides an efficacious and well-tolerated treatment option for use as adjunctive therapy in patients with partial seizures and with Lennox–Gastaut syndrome (LGS). In LGS, rufinamide is effective in controlling multiple seizure types and in reducing the severity of the seizures. The most commonly observed (≥10%) adverse experiences seen in association with rufinamide are headache, dizziness, fatigue, somnolence and nausea. Rufinamide is generally well tolerated, and its safety profile is well-established. **Key Words:** Rufinamide, epilepsy, partial seizures, Lennox–Gastaut syndrome.

INTRODUCTION

Rufinamide [1-(2,6-difluoro-phenyl)methyl-1*H*-1,2,3-triazole-4-carboxamide] is a triazole derivative structurally unrelated to currently marketed AEDs. Rufinamide was profiled for anticonvulsant activity at the U.S. National Institutes of Health (Rockville, MD) and at Novartis. Ciba-Geigy in Europe initiated the earliest clinical studies with rufinamide, under the name CGP 33101. Novartis, formed from the merger of Ciba-Geigy and Sandoz, continued the global development, using the product name RUF 331. Eisai Company, Ltd., acquired the rights to develop rufinamide for seizure disorders from Novartis in 2004.[1] Since that time, Eisai has been managing the development program.

In 2005, Eisai filed an NDA new drug application with the U.S. Food and Drug Administration, seeking approval for two epilepsy indications: 1) adjunctive treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older and 2) adjunctive treatment of seizures associated with Lennox–Gastaut syndrome (LGS) in children 4 years and older and adults.

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MECHANISM OF ACTION

The precise mechanism by which rufinamide exerts its antiepileptic effect is unknown. The antiepileptic effect of rufinamide has been assessed in several animal models of generalized and partial seizures.[2] After oral or intraperitoneal administration, rufinamide potently suppressed maximal electroshock–induced (MES-induced) tonic–clonic seizures in rodents. In a 5-day administration of rufinamide in rodents, the protection rates for single dosing were similar to those produced after 5-day dosing in the MES test. Rufinamide was also effective in antagonizing clonic seizures induced by pentylenetetrazole.

Rufinamide has been tested in animal models of partial seizures.[3] In cats, kindling development was delayed and after-discharges were suppressed. Inhibitory antiepileptic activity was also observed in kindled animals. In chronically epileptic rhesus monkeys, the frequency of seizures was reduced without any significant change in the average duration of each seizure. A reduction in electroshock-induced amnesia and an improvement in learning were observed in mice. These effects on learning and memory showed an inverted U-shaped dose–response relationship.

Based on*in vitro* studies, 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 at 1 μmol/L or higher significantly slowed sodium

channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons from immature rats. Rufinamide limited sustained repetitive firing of sodium-dependent action potentials, with an EC_{50} of 3.8 μmol/L. These effects could contribute to blocking the spread of seizure activity from an epileptogenic focus.

The interaction of rufinamide with neurotransmitter systems was also investigated. Up to 100 μmol/L of rufinamide had no effect on benzodiazepine, GABA, or adenosine uptake. In assays with stable cell lines expressing a range of human recombinant metabotropic glutamate receptors (including mGluR1, mGluR2, mGluR4, and mGluR5), rufinamide at 10 and 100 μmol/L had no significant interactions with receptors, except that for the mGluR5 receptor a 61% inhibition was observed at 100 μmol/L. The interaction of rufinamide with adrenergic receptors (α_1, α_2, and β), 5-HT_1 and 5-HT_2 receptors, histamine$_1$ receptors, and muscarinic cholinergic receptors was studied. At 10 μmol/L, the only effect noted was a weak interaction (36% inhibition) with the β-adrenergic receptor.

PHARMACOKINETICS

Rufinamide is well absorbed after oral administration; however, the rate of absorption is relatively slow and the extent of absorption is decreased as the dose is increased.[4] The pharmacokinetics do not change with multiple dosing. There is moderate intersubject variability. The extent of bioavailability of rufinamide is modestly affected by food, as shown by comparing exposure after single doses under fed and fasted conditions[5]; however, food has no effect upon repeat dosing. Rufinamide has low protein binding (approximately 34%), and its apparent volume of distribution after an oral dose is on the order of total body water (50–80 L). Because bioavailability changes with dose, the apparent volume of distribution is greater at higher doses.

Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form carboxylic acid. The metabolite has no known pharmacological activity and is excreted primarily renally. This metabolic route is not cytochrome P450 dependent, and carboxylesterase has been shown to be the enzyme responsible for hydrolysis of rufinamide. Rufinamide does not significantly inhibit metabolism of probe substrates for this carboxylesterase and thus is not expected to have drug–drug interactions through this mechanism. Rufinamide showed weak induction of CYP3A4, and no induction of CYP1A1/2 in human hepatocytes. Thus, rufinamide might induce metabolism of coadministered drugs mediated by CYP3A4.

The renal excretion of unchanged rufinamide accounts for less than 2% of the dose. Plasma half-life of rufinamide is approximately 6–10 hours. Half-life is unaffected by renal impairment and does not change notably with age. 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 (i.e., no autoinduction of metabolism).

The pharmacokinetic profile of rufinamide in the pediatric population shows no significant differences in plasma pharmacokinetic parameters as a function of age.[6] Similarly, a study evaluating pharmacokinetics of rufinamide in elderly subjects showed that there are no significant differences between younger and elderly subjects.[7]

DRUG INTERACTIONS

Effects of rufinamide on other AEDs

Populations of all subjects treated with selected AEDs concomitantly with rufinamide or placebo were investigated, with data compiled across a number of studies.[8] Population pharmacokinetic analysis of the concentrations of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate was performed, using the average concentration at steady state as the dependent variable (i.e., estimating only the apparent clearance of the AEDs and the factors affecting clearance, including the effect of rufinamide). At typical rufinamide average steady-state concentration levels (C_{avss}), the effects of rufinamide on the pharmacokinetics of other AEDs are unlikely to have clinical significance. Thus, the effects of rufinamide on predicted clearance and concentrations of these AEDs are small compared to pharmacokinetic and efficacy variability between subjects and within subjects. The decrease in clearance of phenytoin estimated at typical levels of rufinamide (C_{avss} = 15 μg/mL) is predicted to increase plasma levels of phenytoin up to 21%. Because phenytoin is known to have nonlinear pharmacokinetics (clearance becomes saturated at higher doses), then it is possible that exposure will be greater than the model prediction.

Effects of other AEDs on rufinamide

Population pharmacokinetics analysis with data pooled across phase II/III studies was used to investigate the effects of other drugs on the pharmacokinetics of rufinamide.[8] Potent cytochrome P450 enzyme inducers such as carbamazepine, phenytoin, primidone, and phenobarbital appear to slightly increase the clearance of rufinamide. However, given that most clearance of rufinamide occurs via a non-CYP-dependent route, the observed minor interactions are unlikely to be attributable to induction of CYP enzymes. Other factors explaining this interaction are not understood.

The effects of other AEDs on the pharmacokinetics of

TABLE 1. *Summary of Placebo-Controlled Studies Providing Primary Efficacy Data for Rufinamide*

Primary and supporting studies	Open-label extension studies	Indication	Population
AE/ET1	AE/ET1E	Add-on, partial seizures	Adolescents (≥15 years) and adults
021A	021AE	Add-on, partial seizures	Adolescents (≥16 years) and adults
038	038E	Monotherapy, partial seizures	Adolescents (≥12 years) and adults
022	022E	Add-on, Lennox–Gastaut syndrome	Children (≥4 years) and adults

rufinamide are unlikely to be of clinical relevance. Any effects, if they occur, are likely to be more marked in the pediatric population compared to adults. Rufinamide clearance was decreased by valproate. In children, valproate administration may lead to elevated levels of rufinamide by up to 70%. Patients stabilized on rufinamide before being prescribed valproate should begin valproate therapy at a relatively low dose and titrate to a clinically effective dose, to diminish the possibility of adverse events from higher rufinamide exposure. Valproate is known to inhibit a number of drug-metabolizing enzymes.

Effects of rufinamide on other medications

Clinical studies have shown that rufinamide can increase the clearance of some coadministered drugs. These include ethinyl estradiol, norethindrone, and triazolam, all of which are known to be metabolized to some degree by cytochrome P450 3A4. Thus, this effect is consistent with weak induction of P450 3A4 by rufinamide. Rufinamide did not affect clearance of olanzapine, and so does not appear to be an inducer of cytochrome P450 1A2.

CLINICAL STUDIES

Table 1 gives a summary of all of the placebo-controlled studies providing efficacy data for rufinamide. The clinical program included studies in adult partial seizures in both monotherapy and adjunctive therapy, in pediatric partial seizures as add-on, in patients with refractory generalized tonic–clonic seizures and in patients with LGS. Here, four major trials will be summarized.

Effectiveness in partial seizures

The effectiveness of rufinamide as adjunctive therapy in adults and adolescents was established in two multicenter, randomized, double-blind, placebo-controlled clinical studies in patients who had refractory partial-onset seizures with or without secondary generalization, and supported by a monotherapy trial also in refractory partial-onset seizures.

Study 21A (add-on). This was a double-blind, placebo-controlled, randomized, parallel-group study (n = 313).[9] Male and female adults (16 years or older) with inadequately controlled partial seizures being treated with one or two concomitant stable-dose AEDs were eligible for enrollment. The study began with an 8-week baseline phase during which each patient had at least six documented partial seizures, with at least one partial seizure occurring in each 4-week period of the baseline phase. After completing the baseline phase, patients were randomized to receive either rufinamide or placebo during the 13-week double-blind phase. The double-blind phase consisted of two periods: the titration period (1 to 2 weeks) and the maintenance period (11 weeks). During the titration period, the dose was increased from 800 to 3200 mg/day, given on a b.i.d. schedule. Final doses at titration were to remain stable during the maintenance period.

The primary efficacy variable was the percentage change in partial seizure frequency per 28 days during the double-blind phase relative to the baseline phase. Rufinamide-treated patients experienced a 20.4% median reduction in partial seizure frequency per 28 days, compared to a 1.6% median increase for placebo-treated patients (p = 0.0158).

The secondary efficacy variables were as follows:

- The total partial seizure frequency per 28 days during the double-blind phase. Analysis of these results demonstrated statistical significance in favor of rufinamide (p = 0.008).
- Response to treatment, defined as experiencing at least 50% reduction in partial seizure frequency per 28 days during the double-blind phase relative to the baseline phase: 28.2% on rufinamide vs. 18.6% on placebo (p = 0.0381).

Study AE/ET1 (add-on). This was a double-blind, placebo-controlled, randomized, parallel-group study (n = 647) (10). Male and female patients (ages 15 to 65 years) with a diagnosis of simple partial seizures, and/or complex partial seizures with or without secondarily generalized seizures, were enrolled. Patients enrolled in the study had inadequately controlled seizures despite treatment with one to three stable-dose AEDs. The study began with a 3-month prospective baseline phase. Patients with nine or more seizures during the baseline phase were eligible to continue into the double blind phase. After completing the baseline phase, patients were randomized to one of five treatment groups (Rufinamide

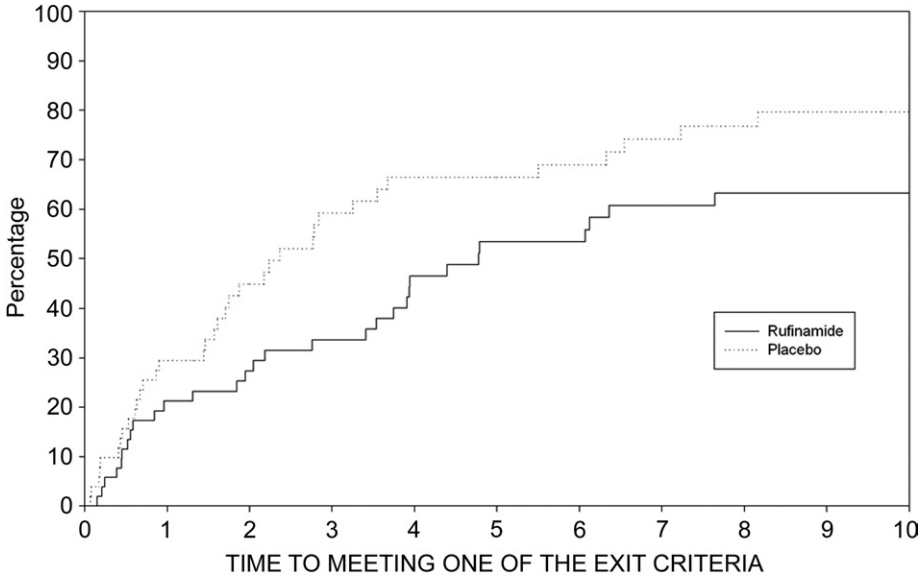

FIG. 1. Time (days) to meeting one of the four exit criteria (intent-to-treat patients in study 38).

200, 400, 800, or 1600 mg/day or placebo, given on a b.i.d. schedule) for the 3-month double-blind phase.

The primary efficacy variable was the total seizure frequency per 28 days in the double-blind treatment phase. A significant dose response ($p = 0.003$) was observed based upon a linear regression analysis, implying that an increase in dose was associated with a decrease in total seizure frequency per 28 days during the double-blind treatment phase. Pairwise comparisons between placebo and each rufinamide treatment group showed that the seizure frequency ratio was statistically significantly lower for the 400 mg/day ($p < 0.03$), 800 mg/day ($p < 0.02$), and 1600 mg/day ($p < 0.02$) groups. (The seizure frequency ratio is the total seizure frequency per 28 days in the double-blind treatment phase relative to baseline total seizure frequency per 28 days.) A significant dose response was also observed for the 50% responder rate (percentage of patients with a reduction over 50% in the number of seizures) ($p < 0.04$).

Study 38 (monotherapy). This was a double-blind, placebo-controlled, randomized, parallel-group study ($n = 104$) inpatients (≥12 years-old) with noncontrolled partial seizures that completed an inpatient evaluation for epilepsy surgery.[11] This study began with a 48-hour prospective baseline phase, during which a patient could not receive any AEDs except low-dose lorazepam. Each patient had to have experienced 2–10 partial seizures during the baseline phase after which all patients were randomized to either placebo or rufinamide. The rufinamide dose was 2400 mg/day on day 1 (titration period) and 3200 mg/day on days 2–10 (maintenance period), given on a t.i.d. schedule. Patients continued to receive double-blind treatment for 10 days or until they met one of the protocol-specified exit criteria: four partial seizures with or without partial seizures evolving to secondarily generalized seizures (exclusive of seizures occurring on day 1); or two partial seizures evolving to secondarily generalized seizures, if none were present during the one-year prior to randomization; or serial seizures requiring investigator intervention; or status epilepticus. The onset of therapeutic effect (i.e., time to first, second, third, and fourth seizures) was a secondary efficacy variable.

The primary efficacy variable was the median time to meeting one of the exit criteria: 4.8 days for the rufinamide group and 2.4 days for the placebo group ($p < 0.05$) (FIG. 1).

Statistically significant between-treatment differences were observed for the times to first, second, and third partial seizures ($p < 0.04$). The medians for the time to second and third partial seizures were over twice as large for rufinamide as for placebo. The medians to the time to second and third partial seizures were twice as large for rufinamide as for placebo. For the time to the fourth partial seizure, the comparison again favored rufinamide but failed to reach the 5% significance level ($p = 0.0509$).

Open-label extension studies in patients with partial seizures

Patients who switched from double-blind rufinamide to open-label rufinamide continued to respond to treatment with decreases in seizure frequency that were as large as, or larger than, the responses during double-blind treatment. Patients who switched from double-blind placebo to open-label rufinamide quickly responded to treatment with marked decreases in seizure frequency. As open-label treatment continued, these patients eventually attained levels of seizure reduction comparable to those in patients who had received both double-blind and open-label rufinamide. There was no

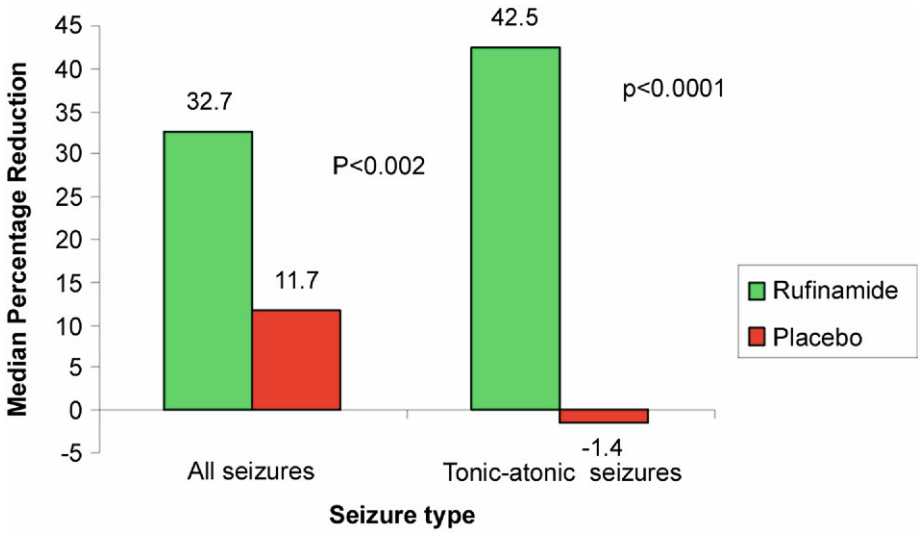

FIG. 2. Lennox–Gastaut trial (study 022): primary efficacy endpoints.

evidence of development of tolerance to the anticonvulsant effect of rufinamide.

Effectiveness in seizures associated with LGS (study 022). This was a multicenter, double-blind, placebo-controlled, randomized, parallel-group study (n = 138).[12] Male and female patients (between 4 and 30 years of age) were included if they had a diagnosis of inadequately controlled seizures associated with LGS (including both atypical absence seizures and drop attacks) and were being treated with one to three concomitant stable-dose AEDs. Each patient must have had at least 90 seizures in the month prior to study entry. After completing a 4-week baseline phase, patients were randomized to receive either rufinamide or placebo during the 12-week double-blind phase. the double-blind phase consisted of two periods: the titration period (1 to 2 weeks) and the maintenance period (10 weeks). During the titration period, the dose was increased to approximately 45 (mg/kg)/day, given on a b.i.d. schedule. Final doses at titration were to remain stable during the maintenance period.

The primary efficacy variables were as follows.

- The percent change in total seizure frequency per 28 days;
- The percent change in tonic–atonic (drop attacks) seizure frequency per 28 days; and
- The seizure severity rating from the global evaluation of the patient's condition.

Results of the primary efficacy variable analyses were as follows.

- **Variable 1.** Rufinamide-treated patients had a 32.7% median reduction and placebo-treated patients had an 11.7% median reduction in total seizure frequency per 28 days in the double-blind phase relative to the baseline phase ($p < 0.002$) (FIG. 2).
- **Variable 2.** Rufinamide-treated patients had a 42.5% median reduction and placebo-treated patients had a 1.4% median increase in tonic–atonic seizure frequency per 28 days in the double-blind phase relative to the baseline phase ($p < 0.0001$) (FIG. 2).
- **Variable 3.** An improvement in seizure severity was observed in 53.4% of the rufinamide-treated patients compared to 30.6% of the placebo-treated patients in the seizure severity rating from the global evaluation of the patient's condition. There was a significant difference between the two treatment groups in favor of rufinamide ($p < 0.005$).

The secondary efficacy variables were as follows.

- **Variable 4.** The percentage of patients who experienced at least a 50% reduction in tonic–atonic seizure frequency per 28 days, relative to baseline, was significantly higher in the rufinamide group (42.5%) than in the placebo group (16.7%) (p = 0.0020) (Fig. 3). The observed odds ratio of 3.81 indicates that patients who received rufinamide were approximately four times more likely to experience at least a 50% reduction in tonic–atonic seizure frequency, compared with those receiving placebo.
- **Variable 5.** The reductions with rufinamide were considerably larger than those with placebo and were similar in magnitude to the changes seen for total seizure frequency. The difference between the groups favoring rufinamide was statistically significant for atonic seizures ($p < 0.02$) and for com-

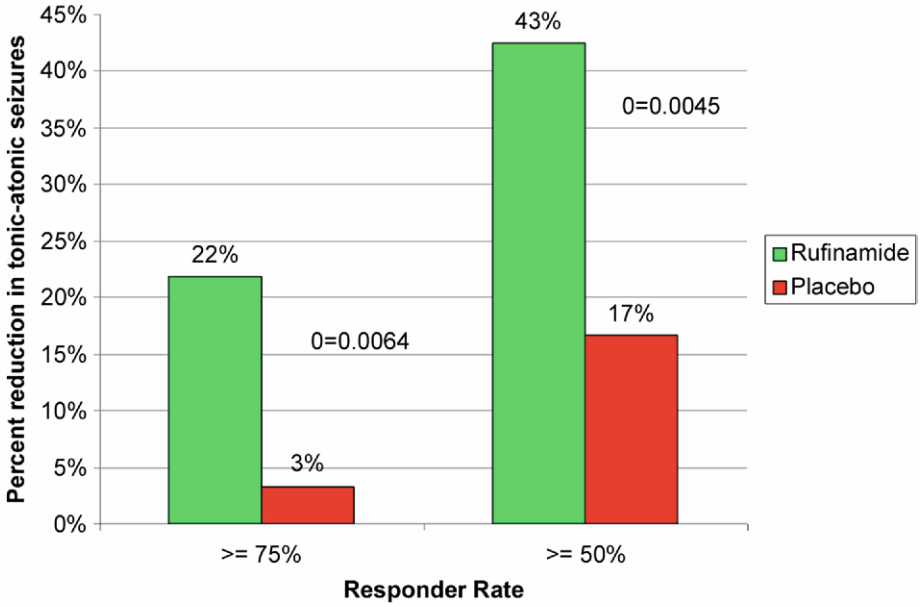

FIG. 3. Lennox–Gastaut trial (study 022): Cumulative proportion of patients showing percent reduction in tonic–atonic seizure frequency per 28 days relative to baseline (intent-to-treat patients).

bined absence and atypical absence seizures ($p < 0.03$).

LGS study: Open-label extension. The group of LGS patients who switched from double-blind rufinamide to open-label rufinamide continued to respond to treatment, with decreases in seizure frequency that were as large as, or larger, than the responses during double-blind treatment.[13] The group of patients who switched from double-blind placebo to open-label rufinamide quickly responded to treatment, with marked decreases in seizure frequency. As open-label treatment continued, these patients eventually attained levels of seizure reduction comparable to those of patients who had received both double-blind and open-label rufinamide. There was no evidence of development of tolerance to the anticonvulsant effect of rufinamide.

SAFETY

In the population of all rufinamide-treated patients with epilepsy, 1978 patients received rufinamide during the double-blind phase, the extension phase, or both.[14] The total exposure to rufinamide in this population was 2552.96 patient-years. The mean daily dose was 1700 mg/day. The duration of exposure ranged from less than 1 month to 4 years or more. More than half of the 939 patients with median doses of less than 1600 mg/day were treated for at least 6 months. More than half of the 1039 patients with median doses of 1600 mg/day or more were treated for at least 12 months. Three main safety populations were analyzed in double-blind studies: all treated patients with epilepsy, adult treated patients with partial seizures, and all patients with LGS.

All treated patients with epilepsy, double-blind studies

A first population included all patients with epilepsy during the double-blind period. The most commonly observed (≥10%) adverse experiences seen in association with rufinamide and at a higher frequency than in placebo-treated patients were headache, dizziness, fatigue, somnolence and nausea.

Approximately 8% of 1240 rufinamide-treated patients and 4% of 635 placebo-treated patients discontinued due to adverse events. The adverse experiences most commonly associated with discontinuation of rufinamide (>1%) were dizziness (1.8%), fatigue (1.6%), and headache (1.1%).

Adjunctive therapy in adult treated patients with partial seizures, double-blind studies

A second population included all adult patients with partial seizures receiving adjunctive therapy with rufinamide during the double-blind period (TABLE 2). The most commonly observed (≥10%) adverse experiences seen in association with rufinamide and at a higher frequency than in placebo-treated patients were headache (27.6%), dizziness (19.4%), fatigue (17.6 %), nausea (11.7%) and somnolence (10.4%).

Approximately 10% of 720 rufinamide-treated patients and 6% of 290 placebo-treated patients discontinued due to adverse events. The adverse experiences most commonly associated with discontinuation of rufinamide

TABLE 2. *Adverse Events Occurring in Rufinamide-Treated Patients in Adults With Partial Seizures*

Adverse events	Patients with adverse events, no. (%)	
	Rufinamide ($N = 720$)	Placebo ($N = 290$)
Any adverse event	580 (80.6)	236 (81.4)
Headache	199 (27.6)	76 (26.2)
Dizziness	140 (19.4)	33 (11.4)
Fatigue	127 (17.6)	34 (11.7)
Nausea	84 (11.7)	29 (10)
Somnolence	75 (10.4)	21 (7.2)
Diplopia	71 (9.9)	9 (3.1)
Tremor	44 (6.1)	13 (4.5)
Vision blurred	43 (6)	9 (3.1)
Nystagmus	38 (5.3)	13 (4.5)
Vomiting	35 (4.9)	13 (4.5)
Abdominal pain upper	26 (3.6)	7 (2.4)
Anxiety	26 (3.6)	5 (1.7)
Ataxia	26 (3.6)	1 (0.3)
Constipation	23 (3.2)	8 (2.8)
Back pain	23 (3.2)	4 (1.4)
Vertigo	22 (3.1)	2 (0.7)
Dyspepsia	21 (2.9)	8 (2.8)
Convulsion	20 (2.8)	7 (2.4)
Abdominal pain	19 (2.6)	6 (2.1)
Nervousness	16 (2.2)	4 (1.4)
Anorexia	15 (2.1)	2 (0.7)

Adverse events occurring in more than 2.0% of rufinamide-treated patients at higher incidences with rufinamide than placebo in double-blind, adjunctive therapy studies in adults with partial seizures.

(>1%) were dizziness (2.6%), fatigue (2.4%), headache (1.8%) diplopia (1.5%), nausea (1.4%), and ataxia (1.1%).

Adjunctive therapy in all patients with LGS, double-blind studies

In the third population, patients with LGS, the most commonly observed (≥10%) adverse experiences seen in association with rufinamide and at a higher frequency than in placebo-treated patients were somnolence (24.3%) and vomiting (21.6%) (TABLE 3).

Approximately 8% of 74 rufinamide-treated patients and 0% of 64 placebo-treated patients discontinued due to adverse events. The adverse experiences most commonly associated with discontinuation of rufinamide (>2%) were vomiting (4.1%), somnolence (2.7%), and rash (2.7%).

Other adverse events of interest

The tolerability of rufinamide is generally good. During clinical development there were no cases of Stevens–Johnson syndrome, hepatic failure, agranulocytosis, or pancytopenia. The incidence of cognitive disorders in the rufinamide-treated patients was slightly higher than that in the placebo-treated patients, mostly due to the occurrence of somnolence. The incidence of psychiatric disorders was similar with rufinamide and with placebo, and these disorders rarely led to discontinuation. Serious adverse events causally related to rufinamide were infrequent.

Serious antiepileptic drug hypersensitivity syndrome occurred in association with rufinamide therapy. Signs and symptoms of this disorder were diverse; typically, however, although not exclusively, patients presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, liver function abnormalities, and hematuria. In clinical trials, this syndrome occurred in close temporal association to the initiation of rufinamide therapy and in the pediatric population. If this reaction is suspected, rufinamide should be discontinued and alternative treatment started. Thus, all patients who develop a rash while taking rufinamide must be closely supervised.

Estimates of the incidence of treatment-emergent status epilepticus among patients treated with rufinamide are difficult, because standard definitions were not used.

TABLE 3. *Adverse Events Occurring in Rufinamide-Treated Patients With Lennox–Gastaut Syndrome*

Adverse events	Patients with adverse events, no. (%)	
	Rufinamide ($N = 74$)	Placebo ($N = 64$)
Any adverse event	60 (81.1)	52 (81.3)
Somnolence	18 (24.3)	8 (12.5)
Vomiting	16 (21.6)	4 (6.3)
Fatigue	7 (9.5)	5 (7.8)
Decreased appetite	7 (9.5)	3 (4.7)
Nasopharyngitis	7 (9.5)	2 (3.1)
Headache	5 (6.8)	3 (4.7)
Rash	5 (6.8)	1 (1.6)
Rhinitis	4 (5.4)	3 (4.7)
Ataxia	4 (5.4)	0 (0)
Psychomotor hyperactivity	3 (4.1)	2 (3.1)
Convulsion	3 (4.1)	1 (1.6)
Ear infection	3 (4.1)	1 (1.6)
Epistaxis	3 (4.1)	0 (0)
Nystagmus	3 (4.1)	0 (0)
Status epilepticus	3 (4.1)	0 (0)
Contusion	2 (2.7)	1 (1.6)
Head injury	2 (2.7)	1 (1.6)
Loose stools	2 (2.7)	1 (1.6)
Sinusitis	2 (2.7)	1 (1.6)
Acne	2 (2.7)	0 (0)
Dizziness	2 (2.7)	0 (0)
Eating disorder	2 (2.7)	0 (0)
Exanthema	2 (2.7)	0 (0)
Influenza	2 (2.7)	0 (0)
Oligomenorrhea	2 (2.7)	0 (0)
Pneumonia	2 (2.7)	0 (0)

Adverse events occurring in more than 2.0% of rufinamide-treated patients at higher incidences with rufinamide than placebo in a double-blind, adjunctive therapy study in Lennox–Gastaut syndrome.

In controlled trials, 11 of 1240 (0.9%) patients had episodes that could be described as status epilepticus in the rufinamide-treated patients, compared with none in the placebo-treated patients.[10]

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