Rufinamide: treatment of seizures associated with Lennox–Gastaut syndrome

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INTRODUCTION

In January 2009, rufinamide (RUF) was approved by the United States Food and Drug Administration. In 2005, Eisai filed a new drug submission with the United States Food and Drug Administration, seeking authorization for adjunctive therapy of seizures related with Lennox–Gastaut syndrome (LGS) in children 4 years and older and adults. RUF is a new, orally active anti-epileptic drug (AED), it is a triazole derivative that is structurally distinct from other anti-epileptic agents presently accessible. Which was granted orphan drug status in 2004 by both the Europe Union and the United States for the therapy of seizures related with LGS. While the exact mechanism of action is not identified but different in vitro studies and in investigational models, RUF has been exposed to suppress neuronal hyper excitability by prolonging the inactivation phase of voltage-gated sodium channels and also limits the recurring firing of neurons. The most common frequent adverse effects were vomiting and somnolence. Status epilepticus has been reported but were uncommon (0.9%). However, a Cochrane review has accomplished that no single AED could be considered greatly efficacious for LGS. Certainly, the efficacy of valproate as a first-line treatment, and its use in young children should be accompanied by great caution due to the risk of life-threatening hepatic toxicity. Although felbamate is approved for the treatment of LGS in the USA and some other countries (e.g., Germany), its use has been limited following reports of severe toxicity. This has led to the suggestion that, in LGS, it should be used only in patients aged over 4 years who cannot be treated adequately with other AEDs.

RUF is well-absorbed after oral administration; RUF is moderately well absorbed in the lower dose range. During frequent dosing, steady state is reached within 2 days. RUF is not comprehensively bound to plasma proteins binding and is metabolized by enzymatic hydrolysis by carboxylesterases to a pharmacologically inactive carboxylic acid derivative, lacking participation of cytochrome P450 enzymes, conferring a low drug interaction possible. In three randomized controlled trials (RCTs), RUF was effective and safe for the adjunctive treatment of

ABSTRACT

Rufinamide (RUF) is FDA-approved for adjunctive management of seizures related with Lennox–Gastaut syndrome (LGS). This new anti-epileptic drug (AED) adds to the AEDs previously used for LGS together with valproic acid, lamotrigine, felbamate, and topiramate. Its mechanism of action includes preventive the excessive firing of sodium-dependent action potentials, but RUF also exhibits a broad spectrum of action in animal models. The plasma concentration of other AEDs does not change by the RUF. Dizziness, nausea, diplopia, and ataxia vomiting and somnolence are most common adverse effects taking place with RUF. Status epilepticus has been reported, but were uncommon (0.9%). A recent randomized, double-blinded, placebo-controlled trial of RUF in patients with LGS and generalized seizures, including atypical absence and tonic-atonic seizures, showed a 32.7% median percentage decreased in total seizures and a 42.5% median percentage decreased in tonic-atonic seizures. RUF also considerably decreased seizure severity. RUF has been studied as adjunctive therapy for partial seizures in adults and adolescents. In a study of three healthy volunteers, an oral dose of 600 mg RUF recognized high absorption and monoexponential elimination with a mean half-life (t½) of 9 hrs. Excretion was mainly renal (85%) and complete (98%) within 7 days.

Keywords: Rufinamide, Lennox–Gastaut syndrome, Epilepsy, Anti-epileptic drugs
partial seizures in adults and adolescents, and the treatment of
generalized seizures coupled with LGS.1-3 Its elimination
half-life of 6-10 hrs. This is excreted in the urine. RUF pharmacokinetics is not affected by impaired renal function.
Although population pharmacokinetic modeling suggests that in the lack of interacting co-medication RUF CL/F may
be advanced in children than in adults. A study investigating the
effect of RUF on the pharmacokinetics of the CYP3A4
substrate triazolam and an oral contraceptive interaction
study showed that RUF has some enzyme-inducing potential
in man. In vitro studies, RUF showed no interactions with
benzodiazepine or gamma-amino butyric acid receptors,
5-HT1 and 5HT2 receptors, α- or β adrenoceptors, or human
recombinant metabotropic glutamate receptor subtypes 1b,
2, or 4 (mGluR1b, mGluR2, mGluR4). Conventional safety
pharmacology studies revealed no safety hazards considered
to be of relevance for clinical use.1 RUF is available as film-
coated tablets containing 200 mg and 400 mg and should be
given along with food. Children 4 years and above: initial
dose is 10 mg/kg/day in two divided doses and is increased
by 10 mg/kg/day every other day up to 45 mg/kg/day or
3200 mg/day. Adults: initial dose is 400-800 mg/day in two
divided doses and is increased by 400-800 mg every 2 days
up to 3200 mg/day.5

MECHANISM OF ACTION
Like many other seizure medications, its mechanism of
action in humans has yet to be fully elucidated; the exact
mechanism of action for RUF is unidentified. Exposure
to RUF has produced both rest and use-dependent
the drug works by lowering neuronal hyperexcitability during
persistence of the inactivation phase of voltage-gated sodium
channels. This likely limits the capacity of action potentials
to fire at a high frequency. Block of sodium currents and
channels. This likely limits the capacity of action potentials
and it reduced the recovery from inactivation. An inhibitory
effect has been observed with high doses at the mGluR5
subtype, which might contribute to seizure suppressing
activity.6 RUF also exhibits a broad-spectrum anticonvulsant
activity, suppressing maximal electroconvulsive shock-
duced seizures in both rats and mice models, and in
pentylethetrazol-test in mice.1 It does not influence the
plasma concentrations of other AEDs.6

PHARMACOKINETICS
The pharmacokinetics of RUF was comparable in children,
adolescents (18-40 years of age) and elderly (66-77 years
of age) patients.

Absorption
RUF is well-absorbed orally and reaches peak plasma
concentration in 4-6 hrs. In clinical trials, RUF was administered with food. Food increases its gastrointestinal
absorption and, therefore, it is suggested to be taken twice
day along with meals. A moderately short half-life
(6-10 hrs).5 The time to peak concentration subsequent
oral administration of RUF is 4-6 hrs under fed or fasted
circumstances with a 400 or 600 mg dose.5-6 Plasma
concentrations are dose comparative at dosages up to
1600 mg/day but decreased at higher dosages because of
decreased oral bioavailability. Absorption is similar
with administration as tablets and suspension. Absolute
oral bioavailability has not been determined but has been
predictable as at least 85% after a single 600 mg dose
under fed conditions. When administered with food, the
peak concentration was increased by 36-96% and the area
under the curve (AUC) was increased by 31-34% compared
with administration in the fasting state. With frequent
administration, steady state is reached within 2 days.4

Distribution
RUF is not comprehensively plasma protein bound
(26-35%).4,5 The amount of plasma protein binding in vitro
is low, ranging from 26.2 to 34.8% at total concentrations
of 0.25-19.6 μg/ml. The majority of the binding is to serum albumin. Thus, RUF has a low tendency for drug
interactions, depends on its low protein binding (approximately 34%) and lack of metabolism via hepatic
cytochrome P450 or reserve of the major enzyme subclasses.
The Vd/F for a subject with median body weight (67 kg)
and body surface area (BSA), calculated using the Haycock
equation was 52.7 L (0.8 L/kg) at a dose of 3200 mg/day,
and it rose to 81.6 L (1.2 L/kg) at 7200 mg/day, which is
steady with the lower bioavailability at advanced doses.3,7

Metabolism
The metabolic process has been established to be self-
governing of the hepatic cytochrome (CYP450) system.
RUF undergoes general metabolism via hydrolysis by
carboxylesterases. It is not a CYP450 substrate. The most
important metabolite, an inactive carboxylic acid derivative
(CGP 47292), accounts for 60% of the dose well again in the
urine. There are no known active metabolites.3,4,7-9

Excretion
RUF is excreted by the kidneys. The elimination half-
life is 6-10 hrs. Less than 4% of the dose is eliminated
unaffected in the urine. Clearance enhanced linearly with
BSA, whereas age, gender, and race had no result on RUF
clearance. Clearance in women is 6-14% lower than in
men, although this variation is not clinically important.5-9
Less than 7% of the dose was excreted in the urine as
slight acyl-glucuronide metabolites of CGP 47292. These
metabolites were untraceable in faces.3 The investigation
was conducted using data from five double-blind studies
involving pediatric and adult patients with poorly controlled
seizures despite previous treatment with up to three AEDs.
RUF co-administration did not influence the clearance of
topiramate or valproate, but improved the clearance
of carbamazepine and lamotrigine (LTG) and decreased clearance of phenobarbital and phenytoin (PHT).\(^7\)

**Clearance (CL/F) and half-life**

The numerical mean CL/F value was 4.8 L/hrs in 24 healthy subjects who received a single 400-mg oral dose in the fed condition. The t\(\frac{1}{2}\) was 10.3 hrs several bid 400 mg doses of the viable formulation in healthy volunteers resulted in a numerical mean CL/F of 5.1 L/hrs. In a multiple dose study of RUF (400 mg bid) in patients with epilepsy, t\(\frac{1}{2}\) was 6.9 hrs (95% confidence interval [CI] 6.3-7.6 hrs) on day 1, which was not significantly vary from the value of 7.0 hrs (95% CI 6.3-7.7 hrs) established on day. In this analysis, both BSA and body weight calculated CL/F expressed as L/hr, but BSA was a slightly superior predictor.\(^7\) RUF clearance was not changed by simultaneous LTG or topiramate, and was also unchanged by liver or kidney function. However, RUF concentrations were increased by concomitant valproate: 40% in children and 11% in adults. As a result, the RUF dosage may need correction during the addition or withdrawal of associated valproate therapy.\(^7\)

**EFFECT OF INTRINSIC FACTORS ON RUF PHARMACOKINETICS**

**Age**

The influence of old age on the pharmacokinetics of RUF was evaluated in a formal pharmacokinetic study in eight healthy young (18-40 years) and seven elderly (66-77 years) subjects after single or repeated doses. There were no differences between pharmacokinetic parameters in the two groups, and mean peak and trough plasma RUF concentrations for the two groups were nearly superimposable after 8 days of multiple oral dosing with 400 mg twice a day.

**Gender**

The effect of gender was premised in the pooled population pharmacokinetic analysis, which showed a tiny, but statistically considerable, difference involving male and female patients, with CL/F being 0.27 L/hr lesser in females, even after consideration of the lower BSA.

**Ethnic group**

No specific studies of the influence of ethnic origin on RUF pharmacokinetics have been conducted. However, this concern was evaluated in the pooled population pharmacokinetic analysis.\(^7\)

**INDICATIONS**

In 2005, Eisai filed a new drug application with the United States Food and Drug Administration, proposal approval for two epilepsy indications: (1) Add on therapy of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older, and (2) add on therapy of seizures associated with LGS in children 4 years and older and adults.\(^2,10\)

**Dosage**

RUF is offered for oral administration as film-coated tablets containing 200 mg and 400 mg and should be given along with food.

Children 4 years and above: Initial dose is 10 mg/kg/day in two divided doses and followed by increments of 10 mg/kg/day every other day up to 45 mg/kg/day or 3200 mg/day.

Adults: Initial dose is 400-800 mg/day in two divided doses and is increased by 400-800 mg every 2 days up to 3200 mg/day.\(^3\) Administration of a single 400 mg dose and multiple doses administered as 400 mg twice daily for nine doses.\(^4-9\) The dosing suggestions accepted by regulatory authorities in Europe are 200-1000 mg/day for patients without valproic acid (VPA) co-medication weighing <30 kg, 200-600 mg/day for patients co medicated with VPA weighing <30 kg, and 400-1800 mg/day, 400-2400 mg/day, and 400-3200 mg/day for patients weighing 30-50 kg, >50-70 kg, and >70 kg, respectively.\(^7\) Patients stabilized on RUF should start VPA therapy at a low dose, and titrate to a therapeutically effective dose. In a double-blind trial the RUF dose was increased as quickly as 10 mg/kg/day every two days, over a period of 7 days. The recommended titration schedule for RUF in Canada is a 5 mg/kg/day adds to every 2 weeks until satisfactory seizure control is reached.\(^8\)

**CONTRAINICATIONS**

RUF is contraindicated in patients with known short QT syndrome and should be administered with caution with other drugs that have the possible to shorten the QT interval (e.g., digoxin, statins).\(^4-8\)

**DRUG INTERACTIONS**

RUFs metabolism is dose not depended on CYP450 system, but it describes a weak inhibition of CYP2E1 and a weak induction of CYP3A4 enzymes. Due to lack of exact interaction studies, the previous mechanism cannot be recognized as the single basis for interactions with added drugs especially AEDs. A topiramate and VPA concentration does not effect by drug RUF. However, the levels of phenobarbitone (PHB) and PHT increased, and those of carbamazepine (CBZ) and LTG may be decreased by RUF. Sodium valproate increases the plasma levels of RUF while the concentrations are reduced by PHT, PHB, CBZ, primidone, and vigabatrin. RUF also decreases the plasma concentrations of triazolam, estradiol, and norethisterone. The interaction with oral contraceptives has not been well-
known, but a decrease in the level of sex steroids may result in a reduced efficacy, therefore, other non-hormonal/barrier contraceptive studies are suggested. Triazolam decrease triazolam AUC by 37% and peak concentration by 23%.5-11

ADVERSE REACTIONS

RUF has an extensive therapeutic window. Adverse reactions noticed with RUF are somnolence, nausea, vomiting, headache, pyrexia, dizziness, fatigue, tremor, and diplopia. Adverse reactions usually have been described as occurring more frequently in dosage titration, transient, and mild to moderate in severity. Adverse reactions have been noticed at frequency with dosages of 1,600 mg/day. Multiorgan hypersensitivity syndrome has shown in association with RUF therapy. One patient have to experienced rash, urticaria, facial edema, fever, elevated eosinophils, stuporous state, and severe hepatitis initiation on day 29 of RUF treatment, continuing during 30 days of continued treatment, and improved 11 days after discontinuation of RUF. Other potential cases existing with rash and one or more of the following: fever, elevated liver function tests, hematuria, and lymphadenopathy. These cases occurred within 4 weeks of starting of RUF therapy and resolved or improved on discontinuation.4-8,12 Serious adverse effects were uncommon; observed at a rate of 2.7% in the RUF therapy was associated with a lower rate of cognitive/psychiatric adverse events (such as psychomotor hyperactivity and lethargy). There was no therapeutically important change in clinical laboratory tests, physical examinations or vital signs. There were two deaths, which were not considered to be associated to RUF therapy. Thus, long-term treatment of patients with LGS does not show to be related with any increase in central nervous system adverse events.7 The incidence of ADRs has been reported to be higher in females and in adults. The risk of causing suicidal thoughts/events has been expected to be 1 in 500 people. Most of the trials incorporated in the analysis of the effect of RUF on suicidal thoughts or behavior did not extend past 24 weeks. Hence, extensive effects of this drug on suicidal behavior cannot be established at present.5

USE IN SPECIAL POPULATIONS

Pediatric or elderly

The safety and effectiveness of RUF have not been evaluated in children younger than 4 years of age, and no age-related dose changes are likely to be necessary for either pediatric or elderly populations.4-7

Pregnancy

Development toxicity, as well as decreased fetal weights, increased incidences of fetal visceral and skeletal abnormalities, and embryo-fetal death, was experiential in animal studies. RUF should be recommended during pregnancy only if the potential benefit justifies the potential risk to the fetus. RUF is in pregnancy category C.4

Lactation

Due to the possible for severe adverse reactions in infants who are breastfeeding, it is suggested that mothers stop breast-feeding or discontinued RUF.4

Renal impairment

RUF do not change in patients with severe impaired renal function compared with healthy subjects. In patients undergoing dialysis, the RUF AUC was decreased by 29% and the peak concentration was reduced by 16%. Hemodialysis began 3 hrs after a 400 mg dose (i.e., close to the Tmax). Dosage adjustments should be measured for patients undergoing dialysis. Some experimental data suggest that the renal impairment has no significant effect on RUF pharmacokinetics.3,4

Hepatic impairment

RUF pharmacokinetics has not been evaluated in patients with severe hepatic impairment, and caution is advised in those with mild to moderate hepatic impairment.

Warnings

AEDs increase the incidence of suicidal thoughts or behavior in patients taking them for any indication. Patients should be following up for the appearance or worsening of depression, suicidal thoughts or activities, or any abnormal changes in mood or behavior.4

Precautions

Patients should be careful about engaging in duties that need close attention (e.g. driving, operating machinery) until they know how they respond to this medication. Shortening of the QT interval (up to 20 msec) has been experiential in electrocardiogram studies during RUF therapy. All patients are developing a rash should be closely monitored. As with all antiepileptic agents, RUF should be withdrawn slowly to diminish the risk of precipitating seizures, seizure exacerbation, or status epilepticus. In clinical trials, RUF discontinuation was achieved by reducing the dose by approximately 25% every 2 days.4

CLINICAL TRIALS

Efficacy or safety

No dosage changes or effect on the efficacy or safety of RUF were reported in the double-blind or open-label extension phases of the pivotal trial. The single study to state a dosage
alteration with co-medication use of RUF was the Italian post-marketing study. 26 of 43 patients (60.5%) taking RUF as add-on therapy had a ≥50% seizure decline in countable seizures after a mean 12-month observational period. Complete seizure freedom was achieved in four patients (9.3%). Two patients had a 25-50% seizure reduction, while seizure incidence remained unaffected in 13 (30.2%) and improved in two patients (4.7%). Concerning the seizure type, 20 of the 26 responders (78.9%) had a ≥50% decrease in drop attacks (six patients were seizure free), and 15 of 26 responders (57.7%) had a ≥50% lessen in tonic seizures (four patients were seizure free). Tonic-clonic seizures increased by 50% or more in 5/26 responders (11.6%). Dependable data for atypical absence seizures and myoclonic seizures did not exist as these are frequently impractical to count. Among the 128 patients treated with RUF, 112 patients (87.5%) were retained after 12 weeks. The causes of early discontinuation of RUF are inadequate seizure control in 11 patients (8.6%), adverse effects in 4 patients (3.1%), and loss to follow-up of 1 patient (0.8%). The overall seizure decrease rate was 31.7%. RUF reduced the seizure occurrence by 100% (seizure freedom) in 7.8% of patients (n=10), more than 75% in 18.0% of patients (n=23), 50-75% in 10.2% of patients (n=13), and by <50% in 8.6% of patients (n=11). However, 39.1% (n=50) of patients observed no change in seizure frequency, and 16.4% (n=21) reported a more than 25% increase in seizure incidence. Patients with a ≥50% decrease in seizure frequency were defined as responders. The maximum responder rate of 39.4% (n=28) was experiential in the convulsive seizure group, after by the fall attack group (36.5%), myoclonic seizure group (33.3%), and epileptic spasm group (20%). Among ten patients who became seizure-free after RUF add-on therapy, six (60.0%) had convulsive seizures, three had drop attacks, and only one had epileptic spasms as the major seizure type. Following a 28-days baseline period, 139 qualified patients were randomized; 138 patients received either RUF (n=74) or placebo (n=64) in addition to their other AEDs. The median percentage reduction in total seizure frequency was greater in the RUF treatment group than in the placebo group (32.7% vs. 11.7%, p=0.0015). There was a difference (p=0.0001) in tonic-atomic (“drop attack”) seizure frequency with RUF (42.5% median percentage reduction) versus placebo (1.4% increase). The RUF group had a better improvement in seizure severity (p=0.0041) and a higher 50% responder rate compared with placebo for overall seizures (p=0.0045) and tonic-atomic seizures (p=0.002).

**Tolerability and safety of RUF**

These tolerability and safety data in patients with LGS are additional supported by a pooled analysis of RUF tolerability and safety in a large population of epilepsy patients, in which the data were calculated individually for patients receiving short-term or long-term treatment. The short-term safety population includes 1240 patients treated with RUF (mean age 31.7 years; mean RUF dose 1373 mg/day; mean duration of treatment 2.8 months) and 635 placebo subjects (mean age 28.6 years, mean duration of treatment 3.0 months). Somnolence was reported rather less often in this population than in the LGS study, with a frequency of 11.8% for RUF and 9.1% among placebo subjects. The rate of events in this pooled analysis indicated a pattern of premature onset and quick declaration, and a tolerability profile not significantly vary from placebo; the occurrence of the most commonly reported adverse events with RUF versus placebo were headache (22.9% vs. 18.9%), dizziness (15.5% vs. 9.4%), fatigue (13.6% vs. 9.0%), somnolence (11.8% vs. 9.1%), and nausea (11.4% vs. 7.6%). This positive tolerability and safety profile was maintained with long-term administration. RUF appears to be well tolerated in long-term use. The pooled tolerability and safety analysis involved 1978 patients examined for long-term tolerability and safety (mean age 31.3 years, mean RUF dose 1700 mg/day, maximum dose 7200 mg/day), 47% of whom were treated with RUF for at least 12 months; the most commonly reported adverse events in this population were headache (29.5%), dizziness (22.5%), and fatigue (17.7%). In other study 139 recipients who done a multicenter, double-blind, placebo-controlled, randomized study of RUF as add-on therapy for seizures associated with LGS, 124 continued into an open-label extension phase with a median treatment period of 432 days. Only 12 of these recipients finally stopped the medication due to adverse side-effects such as vomiting, pyrexia, upper respiratory tract infection, and somnolence. Two deaths occurred, which were determined to be not related to RUF treatment. In animal models, RUF decreased seizures induced by pentylenetetrazol, bicuculline, and picrotoxin, demonstrating the ability of RUF to raise the seizure threshold or defend against threshold seizures. It was also active against maximal electroshock induced seizures, a model for generalized tonic-clonic and partial seizures. It displayed an activity summary in the animal models most comparable to that of phenobarbital and sodium valproate. RUF did not affect cognitive function over a range of dosages from 200 to 1,600 mg/day administered twice daily for 12 weeks when administered as co-medication in patients with partial seizures. A recent randomized, double-blinded, placebo-controlled trial of RUF in recipients with LGS and generalized seizures, including atypical absence and tonic-atomic seizures, showed a 32.7% median percentage decrease in total seizures and a 42.5% median percentage decrease in tonic-atomic seizures. RUF also considerably reduced seizure severity. RUF has been considered as adjunctive treatment for partial seizures in adults and adolescents, though an efficacy between 11.0% and 20.4% reported in these recipients. An open-label study and in three RCT trials of a large series of children, adolescents and adults with refractory cryptogenic or symptomatic focal epilepsy as well as for the management of generalized seizures, associated with LGS treated with RUF as adjunctive drug. In addition, a recently published multicenter study from Europe using observational retrospective data, have concluded RUF to be effective in children and adults with refractory epilepsy, including LGS.
CONCLUSION

This article reviews currently available data on RUF clinical pharmacokinetics and drug interactions, as well as an introduction on correlations among plasma RUF concentrations and clinical effects. RUF adds to our current arsenal of treatment in LGS, which includes: VPA, LTG, topiramate, levetiracetam, ethosuximide, clobazam, clonazepam, zonisamide, felbamate, the ketogenic diet, vagus nerve stimulation, and corpus colostomy. RUF is effective and well-tolerated treatment for seizures associated with LGS in both RCTs and observational studies of patients with LGS. The reduction in drop attacks and tonic-clonic seizures observed with RUF is clinically relevant for patients, may lead to a better quality of life and could modify long-term outcome. Nonetheless, the number of patients treated with this medication is still limited, and a larger number of studies are required to better establish the role of RUF in the overall treatment algorithm for this syndrome.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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doi: 10.5455/2319-2003.ijbcp20141230
Cite this article as: Allu H, Muduveti PR, Vineela P, Sathish K, Saikiran KV, Siddhartha L. Rufinamide: treatment of seizures associated with Lennox–Gastaut syndrome. Int J Basic Clin Pharmacol 2014;3:937-42.