

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-911**

**OTHER REVIEW(S)**

**MEMORANDUM**  
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**  
**CONTROLLED SUBSTANCE STAFF**

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**Date:** August 31, 2006

**To:** Russell Katz, M.D., Director  
Division of Neurology Products (HFD-120)  
Office of Drug Evaluation I

**Through:** Deborah Leiderman, M.D., Director  
Michael Klein, Ph.D., Team Leader  
Controlled Substances Staff (HFD-009)

**From:** Patricia Beaston, M.D., Ph.D., Medical Officer  
Controlled Substances Staff (HFD-009)

**Subject:** Rufinamide (NDA 21-911, submitted November 17, 2005)  
Indication: Adjunctive therapy for seizure.  
Proposed Dose: 400 mg to 3200 mg daily.  
PDUFA Due Date: September 17, 2006

Consultation requested for assessment of abuse liability.  
Consult date: November 30, 2005.

**Company:** Eisai Medical Research

This memorandum describes the CSS appraisal of the abuse liability of rufinamide and proposes language for the label.

Materials reviewed: The submission and its amendments in the EDR; the Pharmacology/Toxicology reviews (submitted to IND 33,534); and the Filing Communication (January 24, 2006).

For the reader's convenience the consult is structured as follows: in the summary the question/issue raised by the consulting Division is stated; the drug, its mechanism of action (if known), and proposed indications are listed; pertinent findings related to the question/issue are summarized; and recommendations including comments to the company are provided. The remainder of the document provides more detailed data and discussions to support the recommendations.

## **I. SUMMARY**

The Division of Neurology Products consulted the Controlled Substance Staff (CSS) on the abuse potential of rufinamide (NDA 21-911).

**Drug:** Rufinamide, a new chemical entity, is a triazole derivative under development as adjunctive therapy for 1) treatment of partial-onset seizures with and without secondary generalization in adults and adolescents 12 years of age and older; and 2) treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults. (Orphan Drug designation granted October 8, 2004.)

**Mechanism of Action:** The mechanism of action of rufinamide is unknown. The primary *in vitro* pharmacodynamic data indicate that rufinamide interacts with the inactivated state of the sodium channel and slows conversion to the active state thereby reducing the frequency of action potentials.

**Proposed Dose:** The proposed dose range of rufinamide is 400 to 3200 mg/day (orally with \_\_\_\_\_), given as divided doses twice daily. The dose is titrated with a recommended starting dose of 400-800 mg/day with increments of 400-800 mg every 2 days. b(4)

**Significant Findings from Related Compounds:** Three anticonvulsants have been found to act by a similar mechanism as rufinamide. Phenytoin, carbamazepine, and lamotrigine all act at the sodium channel to decrease excitability. In addition, lamotrigine is structurally similar to rufinamide<sup>1</sup>. None of these anticonvulsants were shown to have an abuse liability and a review of literature and the AERS and DAWN data did not demonstrate patterns of abuse.

**Regulatory Background:** NDA 21-911 for rufinamide was submitted November 17, 2005. A letter outlining deficiencies, including those from CSS, was sent to Eisai on January 24, 2006. Eisai responded to these deficiencies on May 23, 2006.

**Comments and Recommendations:** Rufinamide is a new chemical entity under development as add on therapy for the treatment of seizures. *In vitro* assays do not demonstrate significant binding of rufinamide for receptors associated with drugs of abuse. Preclinical studies using monkeys did not demonstrate either withdrawal or self administration associated with rufinamide.

Formal testing for abuse potential in human subjects was not performed. However, neither the Phase 1 and Phase 2 studies enrolling healthy volunteers nor the Phase 3 studies enrolling patients with epilepsy revealed a pattern or incidence of adverse events suggestive of abuse liability of rufinamide.

The available preclinical and clinical data do not suggest an abuse liability for rufinamide.

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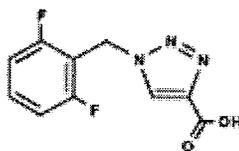
<sup>1</sup> Rogawski, M.A. (2006) Diverse mechanisms of antiepileptic drugs in the development pipeline. *Epilepsy Res.* 69:273-294.

Proposed language for the label:

**DRUG ABUSE AND DEPENDENCE:** The available clinical data in healthy subjects and in patients with epilepsy do not demonstrate a pattern of drug liking, euphoria, or other symptoms that would suggest a liability for abuse.

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CGP 47292

**COMMENT:** Although Eisai states that CGP 47292 is an inactive metabolite, little data could be found to support this statement. The Toxicology section states that no studies were performed assessing metabolites. The Pharmacokinetics/Pharmacology section did not contain binding studies for any metabolites. This section did provide a brief synopsis of Study 59/88 (July 1989) which reports that neither CGP 47292 nor CGP 47291 (another metabolite) suppressed electroshock-induced seizures in mice or rats.

### 3. Animal Studies

a. Behavioral Studies: The effects of rufinamide (30, 100 and 300 mg/kg) on the central nervous system (CNS) were evaluated in mice by assessing the Modified Irwin Screen Test, locomotor activity, motor coordination (rotorod), body temperature, and sleeping time induced by hexobarbitone. No effects on the CNS were seen following a single administration of rufinamide at 30 mg/kg. At doses of 100 mg/kg and 300 mg/kg, rufinamide appeared to induce a mild, transient, CNS depressant effect which was seen as a reduction in spontaneous locomotor activity at 4 hours after dosing. In addition to this, at 300 mg/kg rufinamide, a slight increase in exploratory activity was recorded at 2 and 6 hours after dosing in the Irwin screen.

b. Animal Abuse- and Dependence-Related Assessment. Two studies were performed:

1) Study CBG 792/962323 to assess 'physical dependence'. Cynomolgus monkeys were given CGP 33-101 (rufinamide) or diazepam (an active comparator) by oral gavage twice daily for 2 28-day periods.

Dosing Schedule for study CBG 792/962323					
Drug Dose BID	Days 1-28	Days 29-35	Days 36-49	Days 50-63	Days 64-70
CGP 33 101	200 mg/kg	No drug	200 mg/kg	400 mg/kg	No drug
Diazepam*	5 mg/kg	No drug	10 mg/kg	15 mg/kg	No drug

\*Diazepam was increased during the study to 'maintain the presence of a behavioral depressant effect'.

On study days 24 and 59, each animal received 5 mg/kg Ro 15-1788 (flumazanil), a benzodiazepine antagonist, and monitored for signs of withdrawal.

No overt signs of withdrawal were reported in the animals receiving CGP 33 101 during the two abstinence periods or in response to Ro 15-1788.

2) Study CBG 791/962163 to assess 'psychological dependence'. Cynomolgus monkeys were studied for self administration of CGP 33 101 by gastric intragastric cannula.

“Drug seeking” was assessed by lever presses by the animal to obtain the study drug. This study did not use an active comparator. Instead, ‘historical data’ consisting of data obtained from similar studies performed at the same study center using drugs known to be associated with abuse was used for comparison.

After an initial acclimation period (minimum 14 days), the CGP 33 101 replaced the vehicle. After 6 weeks (3 2-week periods of 5 mg/kg, 10 mg/kg, 20 mg/kg, respectively) no increases in lever presses were observed. A 2 to 3 week period of involuntary injections of 20 mg/kg every 3 hours was attempted and did not result in any increase in lever pressing. The interpretation of these results was that ‘drug seeking’ behavior was not demonstrated with CGP 33 101.

### **C. Clinical Studies**

The clinical studies included PK and QT studies in healthy subjects (male or female); PK and efficacy studies in patients using 1 to 3 ‘fixed dose’ antiepileptic drugs (AEDs); and one study in patients with diabetic neuropathy. A formal abuse study was not performed.

#### **Studies enrolling subjects without epilepsy:**

More than 600 ‘healthy subjects’ and the 123 patients with diabetic neuropathy were enrolled in Phase 1 or Phase 2 and Phase 3 studies, respectively. All studies were reviewed for summary tables, case report forms and AE data files. To examine AEs associated with rufinamide use, specific attention was given to study E2080-A001-002 (QT study) because it enrolled the greatest number of healthy subjects in an individual study (115), was over a period of 20 days duration, and had exposures up to 7200 mg for 3 days. To examine for potential withdrawal phenomena, special attention was given to studies E2080-A001-002 (QT study) and E2080-A001-001 (MTD study) because in addition to intra-study safety monitoring, patients were contacted by phone 4 and 5 days after the end of the study and queried about adverse events. Study CRUF331 0201, for diabetic neuropathy, was also examined in detail because it was 4-weeks in duration.

In study E2080-A001-002 (QT study) 670 TEAEs were reported in the 117 subjects dosed – 384 in the rufinamide group (88% of the 58 subjects) and 286 in the placebo group (83% of the 59 subjects). The majority of AEs were classified under the system organ class (SOC) of nervous system and included balance disorder, burning sensation, attention disturbance, dizziness, dysgeusia, head discomfort, headache, hyperreflexia, hypoaesthesia, memory impairment, paraesthesia, sensory disturbance, somnolence, speech disorder, and tremors. Headache, nausea, and dizziness were the most common AEs reported in the post-treatment period and were few in number, reported in greater number in the placebo group, and did not suggest symptoms of withdrawal.

In study E2080-A001-001 (MTD study), 44 TEAEs were reported in the 20 subjects dosed – 37 in the rufinamide group (67 % of the 15 subjects) and 3 in the placebo group (60% of the 5 subjects). Headache was the most commonly reported AE (53% rufinamide, 40% placebo). Other AEs reported included dizziness (2 rufinamide), visual disturbance (1 rufinamide, 1 placebo). No post-treatment AEs were reported.

Study CRUF331 0201 enrolled 123 diabetic patients and examined the use of rufinamide 1200 mg BID for 4 weeks for the treatment of diabetic neuropathy. In this study, nausea was the most commonly reported AE (23.0% of 61 rufinamide treated patients; 12.5% of placebo treated patients), followed by headache (16.4% and 10.9%) and dizziness (11.5% and 3.1%). Other AEs were infrequently reported.

Summary: The most commonly reported AEs in the studies enrolling subjects without epilepsy were headache, nausea and dizziness. In addition to the nervous system AEs (as outlined for study E2080-A001-002 above), there were rare AEs reporting difficulty concentrating, euphoria, feeling drunk, nervousness, and anxiety. The AEs reported in these studies did not suggest 'likeability' or abuse liability associated with rufinamide.

#### **Studies enrolling patients with epilepsy:**

In all, 1875 patients with epilepsy were enrolled in double-blind studies with randomization of 1240 patients to rufinamide and 635 patients to placebo. Patients had a variety of seizure disorders which included the seizure subtypes of simple, complex, and partial seizures evolving to secondarily generalized seizures, primary generalized seizures, and seizures associated with LGS.

Most of the studies enrolled patients who were taking 1 to 3 ACDs including but not limited to carbamazepine, valproate, phenytoin, clonazepam, lamotrigine, vigabatrin, diazepam, phenobarbital, primidone, oxazolam, topiramate, and gabapentin. There were 2 monotherapy studies (enrolling a total of 275 patients) in which patients were limited to concomitant treatment of low-dose lorazepam.

Patients were exposed to up to 7200 mg rufinamide daily (median daily dose 1600 mg). The majority of patients (93%) were exposed to rufinamide for > 1 month with 47% completing 12-24 months, and 22% completing 24-36 months. Patients discontinued from treatment had the dose of rufinamide tapered over several days to decrease the risk of seizure.

The most commonly reported treatment emergent adverse events (defined as > 10% of patients) were headache, dizziness, fatigue, nausea, somnolence, vomiting, nasopharyngitis, and upper respiratory infection. The most commonly reported adverse events (defined as > 1% of patients) during the tapering period (882 rufinamide-treated patients) were headache, vomiting, somnolence, insomnia, and upper respiratory infection. Less commonly reported neurological and psychiatric adverse events both during the treatment and tapering periods were diverse and were similar between rufinamide and placebo treatment groups.

Summary: The psychiatric and neurological AEs in the studies enrolling subjects with epilepsy were consistent with those described for other ACDs with similar mechanisms of actions. Although interpretation of adverse events in patients receiving multiple centrally acting drugs is limited, the addition of rufinamide to the treatment regimen in these patients did not produce a pattern of adverse events that would suggest 'likeability' or abuse liability.

**Appendix: Summary of binding studies.**

Study (Year)	Ligand	Receptor	Concentration $\mu\text{M}$	% Inhibition
NO1-NS-4-2361 (1987)	$^3\text{H}$ -Flunitrazepam	Benzodiazepine	0.1/1.0/10/100	*
	$^3\text{H}$ -GABA	GABA		*
	$^3\text{H}$ -Adenosine	[Adenosine Uptake]		*
	$^3\text{H}$ -Prazosin	$\alpha_1$		0
	$^3\text{H}$ -Clonidine	$\alpha_2$		13
	$^3\text{H}$ -DHA	$\beta$		36
	$^3\text{H}$ -5-HT <sub>1</sub>	5-HT <sub>1</sub>		0
	$^3\text{H}$ -Ketanserin	5-HT <sub>2</sub>		0
	$^3\text{H}$ -Doxepin	Histamine-1		0
	$^3\text{H}$ -CMD	Muscarinic agonist		0
BR 58/87 (1987)	$^3\text{H}$ -QNB	Muscarinic antagonist	10	0
	$^3\text{H}$ -CGP 39653	antagonist		0
	$^3\text{H}$ -DCKA	antagonist		0
	$^3\text{H}$ -AMPA	agonist		0
BR 64/94 (1994)	$^3\text{H}$ -Kainic acid	Kainate	10/30/100	0
	$^3\text{H}$ -CGP 39653	antagonist		0
	$^3\text{H}$ -DCKA	antagonist		0
	$^3\text{H}$ -AMPA	agonist		0

\* no binding at the receptor was observed

Ø = no notable effect (10%) was observed

RD-2000-0575 (2000)	Receptor Subtype	Type of Assay	% Stimulation		% Inhibition	
			10 $\mu\text{M}$	100 $\mu\text{M}$	10 $\mu\text{M}$	100 $\mu\text{M}$
mGluR1b	PI hydrolysis		-2	0	22	7
mGluR2	GTP ( $\gamma$ ) <sup>35</sup> S		-7	1	16	8
mGluR4a	GTP ( $\gamma$ ) <sup>35</sup> S		12	-4	0	-35
mGluR5a	PI hydrolysis		1	1	23	61

Binding studies continued:

Study 10847 (2006)		Ligand	% Inhibition	
Receptor	10 $\mu$ M		100 $\mu$ M	
$\alpha_1$			-11	7
$\alpha_{2A}$			14	45
$\alpha_{2B}$			0	25
$\alpha_{2c}$			-1	9
$\beta_1$			-16	-13
$\beta_2$			0	3
$\beta_3$			2	-3
BZD (central)			17	7
CB <sub>1</sub>			4	0
CB <sub>2</sub>			4	-2
D <sub>1</sub>			1	4
D <sub>2S</sub>			0	4
D <sub>3</sub>			-5	21
D <sub>4,4</sub>			1	8
GABA <sub>A</sub>			-12	3
GABA <sub>B(1b)</sub>			-15	-2
M <sub>1</sub>			-2	38
M <sub>2</sub>			4	36
M <sub>3</sub>			-4	12
M <sub>4</sub>			-2	12
M <sub>5</sub>			13	16
N (neuronal)			3	8
N (muscle-type)			2	3
$\delta_2$			5	2
K			-15	10
$\mu$			-5	-11
5-HT <sub>1A</sub>			2	10
5-HT <sub>1B</sub>			-2	10
5-HT <sub>1D</sub>			8	8
5-HT <sub>2A</sub>			11	2

Study 10847 (2006)		Ligand	% Inhibition	
Receptor	10 $\mu$ M		100 $\mu$ M	
5-HT <sub>2B</sub>			-4	13
5-HT <sub>2C</sub>			-4	17
5-HT <sub>3</sub>			-6	-3
5-HT <sub>4c</sub>			-22	9
$\sigma$			-11	9
NE transporter			0	9
DA transporter			0	-11
GABA transporter			4	-10
Choline transporter			14	5
5-HT transporter			-1	-1

\*The results highlighted in light grey are those with 20% to 50% inhibition and may be indicative of weak to moderate effects. No assay exceeded 50% inhibition.

The results for Study 10847 were submitted as amendment to the NDA (May 23, 2006).

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/s/

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CHEMIST  
Sign-off for Deborah Leiderman, M.D., Director Controlled Substance Staff