HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BANZEL® safely and effectively. See full prescribing information for BANZEL®.

BANZEL® **(rufinamide) Tablet, Film Coated for Oral Use**
Initial U.S. Approval: 2008

----------INDICATIONS AND USAGE----------

BANZEL **(rufinamide)** is an anti-epileptic drug indicated for:

- Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years and older and adults. (1)

----------DOSAGE AND ADMINISTRATION----------

BANZEL should be given with food. Tablets can be administered whole, as half tablets, or crushed. (2)

- **Children four years and older with LGS:** Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less, administered in two equally divided doses. (2.1)
- **Adults with LGS:** Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg every other day until a maximum dose of 3200 mg/day, administered in two equally divided doses is reached. (2.1)
- See Full Prescribing Information for dosing in patients with renal impairment, (2.2), hemodialysis (2.3), hepatic impairment, (2.4), and for those patients on valproate. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

- 200 mg (pink), 400 mg (pink), film-coated tablets with a score on both sides. (3)

----------CONTRAINDICATIONS----------

- BANZEL is contraindicated in patients with Familial Short QT syndrome. (4)

----------WARNINGS AND PRECAUTIONS----------

- Suicidal behavior and ideation. (5.1)
- Patients should be advised that BANZEL can cause Central Nervous System Reactions (5.2)
- Caution should be used when administering BANZEL with other drugs that shorten the QT interval. (5.3)
- Multi-organ Hypersensitivity Reactions have occurred in association with BANZEL. If this reaction is suspected, BANZEL should be discontinued and alternative treatment started. (5.4)
- Withdrawal of AEDs. BANZEL should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. (5.5)
- Status Epilepticus (5.6)

----------ADVERSE REACTIONS----------

- In all patients with epilepsy treated with BANZEL in double-blind, adjunctive therapy studies, the most commonly observed adverse reactions (≥ 10% and greater than placebo) were headache, dizziness, fatigue, somnolence, and nausea (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eisai, Inc. at 1-888-274-2378 or www.banzel.com or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

----------DRUG INTERACTIONS----------

See Full Prescribing Information for effects of BANZEL on other AEDs (7.1), effects of other AEDs on BANZEL (7.2), and effects of BANZEL on other medication (7.3)

- Based on a population pharmacokinetic analysis, rufinamide clearance was decreased by valproate. In children, valproate administration may lead to elevated levels of rufinamide by up to 70 %. Patients on valproate should begin at a BANZEL dose lower than 10 mg/kg/day (children) or 400 mg/day (adults). (7.2)
- Other AEDs can influence rufinamide concentrations. This effect is more pronounced in children than adults (7.1)
- Concurrent use of BANZEL with hormonal contraceptives may render this method of contraception less effective. Additional non-hormonal forms of contraception are recommended when using BANZEL. (7.3)

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** To enroll in the North American Antiepileptic Drug Pregnancy Registry call 1-888-233-2334, toll free (8.1)
- **Renal impairment:** Renally impaired patients (creatinine clearance less than 30 mL/min) do not require any specific dosage change. (2.2) Adjusting the BANZEL dose for the loss of drug upon dialysis should be considered. (8.6)
- **Hepatic impairment:** Use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and MEDICATION GUIDE

Revised: October 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

BANZEL (rufinamide) is indicated for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years and older and adults.

2 DOSAGE AND ADMINISTRATION

BANZEL should be given with food. Tablets can be administered whole, as half tablets or crushed, for dosing flexibility.

2.1 Patient with Lennox-Gastaut Syndrome

Children four years and older with Lennox-Gastaut syndrome: Treatment should be initiated at a daily dose of approximately 10 mg/kg/day administered in two equally divided doses. The dose should be increased by approximately 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less, administered in two equally divided doses. It is not known whether doses lower than the target doses are effective.

Adults with Lennox-Gastaut syndrome: Treatment should be initiated at a daily dose of 400-800 mg/day administered in two equally divided doses. The dose should be increased by 400-800 mg every other day until a maximum daily dose of 3200 mg/day, administered in two equally divided doses is reached. It is not known whether doses lower than 3200 mg are effective.

2.2 Patients with Renal Impairment

Renally impaired patients (creatinine clearance less than 30 mL/min) do not require any special dosage change when taking BANZEL [*see Clinical Pharmacology (12.3)*]

2.3 Patients Undergoing Hemodialysis

Hemodialysis may reduce exposure to a limited (about 30%) extent. Accordingly, adjusting the BANZEL dose during the dialysis process should be considered [see *Clinical Pharmacology (12.3)]*

2.4 Patients with Hepatic Disease

Use of BANZEL in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment [see *Use in Specific Population, (8.7)*].

2.5 Patients on AEDs

Patients on valproate should begin at a BANZEL dose lower than 10 mg/kg/day (children) or 400 mg/day (adults). For effects of other AEDs on BANZEL see *Drug Interactions (7.2)*.

3 DOSAGE FORMS AND STRENGTHS

200 mg (pink) and 400 mg (pink) film-coated tablets. Tablets are scored on both sides.

4 CONTRAINDICATIONS

BANZEL is contraindicated in patients with Familial Short QT syndrome [see *Warnings and Precautions, QT Shortening (5.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including Banzel, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1: Absolute and Relative Risk of Suicidal Behavior and Ideation

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing Banzel or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.2 Central Nervous System Reactions

Use of BANZEL has been associated with central nervous system-related adverse reactions. The most significant of these can be classified into two general categories:
1) somnolence or fatigue, and 2) coordination abnormalities, dizziness, gait disturbances, and ataxia [see *Adverse Reactions* (6.1)].

5.3 QT Shortening

Formal cardiac ECG studies demonstrated shortening of the QT interval (mean = 20 msec, for doses $\geq$ 2400 mg twice daily) with BANZEL treatment. In a placebo-controlled study of the QT interval, a higher percentage of BANZEL-treated subjects (46% at 2400 mg, 46% at 3200 mg, and 65% at 4800 mg) had a QT shortening of greater than 20 msec at T_{max} compared to placebo (5 – 10%).

Reductions of the QT interval below 300 msec were not observed in the formal QT studies with doses up to 7200 mg/day. Moreover, there was no signal for drug-induced sudden death or ventricular arrhythmias.

The degree of QT shortening induced by BANZEL is without any known clinical risk. Familial Short QT syndrome is associated with an increased risk of sudden death and ventricular arrhythmias, particularly ventricular fibrillation. Such events in this syndrome are believed to occur primarily when the corrected QT interval falls below 300 msec. Non-clinical data also indicate that QT shortening is associated with ventricular fibrillation.

Patients with Familial Short QT syndrome should not be treated with BANZEL. Caution should be used when administering BANZEL with other drugs that shorten the QT interval [see *Contraindications* (4)].

5.4 Multi-organ Hypersensitivity Reactions

Multi-organ hypersensitivity syndrome, a serious condition sometimes induced by antiepileptic drugs, has occurred in association with BANZEL therapy in clinical trials. One patient experienced rash, urticaria, facial edema, fever, elevated eosinophils, stuperous state, and severe hepatitis, beginning on day 29 of BANZEL therapy and extending over a course of 30 days of continued BANZEL therapy with resolution 11 days after discontinuation. Additional possible cases presented with rash and one or more of the following: fever, elevated liver function studies, hematuria, and lymphadenopathy. These cases occurred in children less than 12 years of age, within four weeks of treatment initiation, and were noted to resolve and/or improve upon BANZEL discontinuation. This

syndrome has been reported with other anticonvulsants and typically, although not exclusively, presents with fever and rash associated with other organ system involvement. Because this disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. If this reaction is suspected, BANZEL should be discontinued and alternative treatment started.

All patients who develop a rash while taking BANZEL must be closely supervised.

5.5 Withdrawal of AEDs

As with all antiepileptic drugs, BANZEL should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus. If abrupt discontinuation of the drug is medically necessary, the transition to another AED should be made under close medical supervision. In clinical trials, BANZEL discontinuation was achieved by reducing the dose by approximately 25% every two days.

5.6 Status Epilepticus

Estimates of the incidence of treatment emergent status epilepticus among patients treated with BANZEL are difficult because standard definitions were not employed. In a controlled Lennox-Gastaut syndrome trial, 3 of 74 (4.1 %) BANZEL-treated patients had episodes that could be described as status epilepticus in the BANZEL-treated patients compared with none of the 64 patients in the placebo-treated patients. In all controlled trials that included patients with different epilepsies, 11 of 1240 (0.9%) BANZEL-treated patients had episodes that could be described as status epilepticus compared with none of 635 patients in the placebo-treated patients.

5.7 Laboratory Tests

Leucopenia (white cell count < $3X10^9$ L) was more commonly observed in BANZEL-treated patients (43 of 1171, 3.7%) than placebo-treated patients (7 of 579, 1.2%) in all controlled trials.

6 ADVERSE REACTIONS

6.1 Controlled Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-controlled double-blind studies were performed in adults and in pediatric patients, down to age of 4, in other forms of epilepsy, in addition to the trial in Lennox-Gastaut syndrome. Data on CNS Reactions [see *Warnings and Precautions (5.2)]* from the Lennox-Gastaut study are presented first. Because there is no reason to suspect that adverse reactions would substantially differ between these patient populations, safety data from all of these controlled studies are then presented. Most of these adverse reactions were mild to moderate and transient in nature.

Common central nervous system reactions in the controlled trial of patients 4 years or older with Lennox-Gastaut syndrome treated with BANZEL as adjunctive therapy [see *Warnings and Precautions (5.2)]*

Somnolence was reported in 24.3% of BANZEL-treated patients compared to 12.5% of placebo patients and led to study discontinuation in 2.7% of treated patients compared to 0% of placebo

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