

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 BANZEL should be withdrawn gradually to minimize the risk of precipitating seizures, seizure exacerbation, or status epilepticus.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 ($\geq 10\%$ 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

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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, stuporous 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 $< 3 \times 10^9$ 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

patients. Fatigue was reported in 9.5% of BANZEL-treated patients compared to 7.8% of placebo patients. It led to study discontinuation in 1.4% of treated patients and 0% of placebo patients.

Dizziness was reported in 2.7% of BANZEL-treated patients compared to 0% of placebo patients, and did not lead to study discontinuation.

Ataxia and gait disturbance were reported in 5.4% and 1.4% of BANZEL-treated patients, respectively, and in no placebo patients. Balance disorder and abnormal coordination were each reported in 0% of BANZEL-treated patients and 1.6% of placebo patients. None of these reactions led to study discontinuation.

All Adverse Reactions for All Treated Patients with Epilepsy, Double-blind Adjunctive Therapy Studies: The most commonly observed ($\geq 10\%$) adverse reactions in BANZEL-treated patients, when used as adjunctive therapy at all doses studied (200 to 3200 mg/day) with a higher frequency than in placebo were: headache, dizziness, fatigue, somnolence, and nausea.

Table 2 lists treatment-emergent adverse reactions that occurred in at least 3% of pediatric patients with epilepsy treated with BANZEL in controlled adjunctive studies and were numerically more common in patients treated with BANZEL than placebo.

At the target dose of 45 mg/kg/day for adjunctive therapy in children, the most commonly observed ($\geq 3\%$) adverse reactions with an incidence greater than in placebo, for BANZEL were somnolence, vomiting and headache.

Table 2: Incidence (%) of Treatment-Emergent Adverse Reactions in all Pediatric Double-Blind Adjunctive Trials by Preferred Term at the Recommended Dose of 45 mg/kg/day (Adverse Reactions occurred in at least 3% of BANZEL-treated patients and occurred more frequently than in Placebo Patients)

Preferred Term	BANZEL (N=187) %	Placebo (N=182) %
Somnolence	17	9
Vomiting	17	7
Headache	16	8
Fatigue	9	8
Dizziness	8	6
Nausea	7	3
Influenza	5	4
Nasopharyngitis	5	3
Decreased Appetite	5	2
Rash	4	2
Ataxia	4	1
Diplopia	4	1
Bronchitis	3	2
Sinusitis	3	2
Psychomotor Hyperactivity	3	1
Abdominal Pain Upper	3	2
Aggression	3	2
Ear Infection	3	1

Disturbance in Attention	3	1
Pruritis	3	0

Table 3 lists treatment-emergent adverse reactions that occurred in at least 3% of adult patients with epilepsy treated with BANZEL (up to 3200mg/day) in adjunctive controlled studies and were numerically more common in patients treated with BANZEL than placebo. In these studies, either BANZEL or placebo was added to current AED therapy.

At all doses studied of up to 3200 mg/day given as adjunctive therapy in adults, the most commonly observed ($\geq 3\%$) adverse reactions, and with the greatest increase in incidence compared to placebo, for BANZEL were dizziness, fatigue, nausea, diplopia, vision blurred, and ataxia.

Table 3: Incidence (%) of Treatment-Emergent Adverse Reactions in all Adult Double-Blind Adjunctive Trials (up to 3200mg/day) by Preferred Term (Adverse Reactions occurred in at least 3% of BANZEL-treated patients and occurred more frequently than in Placebo Patients)

Preferred Term	BANZEL (N=823) %	Placebo (N=376) %
Headache	27	26
Dizziness	19	12
Fatigue	16	10
Nausea	12	9
Somnolence	11	9
Diplopia	9	3
Tremor	6	5
Nystagmus	6	5
Vision Blurred	6	2
Vomiting	5	4
Ataxia	4	0
Abdominal Pain Upper	3	2
Anxiety	3	2
Constipation	3	2
Dyspepsia	3	2
Back Pain	3	1
Gait Disturbance	3	1
Vertigo	3	1

Discontinuation in Controlled Clinical Studies

In controlled double-blind adjunctive clinical studies, 9.0% of patients receiving BANZEL as adjunctive therapy and 4.4% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL ($>1\%$) used as adjunctive therapy were generally similar in adults and children.

In pediatric double-blind adjunctive clinical studies, 8.0% of patients receiving BANZEL as adjunctive therapy and 2.2% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL ($>1\%$) used as adjunctive therapy are presented in Table 4.

Table 4: Adverse Reactions Most Commonly Leading to Discontinuation in Double-Blind Adjunctive Trials (At The Recommended Dose of 45mg/kg/day) in Pediatric Patients

Preferred Term	BANZEL (N=187) %	Placebo (N=182) %
Convulsion	2	1
Rash	2	1
Fatigue	2	0
Vomiting	1	0

In adult double-blind adjunctive clinical studies (up to 3200 mg/day), 9.5% of patients receiving BANZEL as adjunctive therapy and 5.9% receiving placebo discontinued as a result of an adverse reaction. The adverse reactions most commonly leading to discontinuation of BANZEL (>1%) used as adjunctive therapy are presented in Table 5.

Table 5: Adverse Reactions Most Commonly Leading to Discontinuation in Double-Blind Adjunctive Trials (up to 3200 mg/day) in Adult Patients

Preferred Term	BANZEL (N=823) %	Placebo (N=376) %
Dizziness	3	1
Fatigue	2	1
Headache	2	1
Nausea	1	0
Ataxia	1	0

Other Adverse Events Observed During Clinical Trials:

BANZEL has been administered to 1978 individuals during all epilepsy clinical trials (placebo-controlled and open-label). Adverse events occurring during these studies were recorded by the investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of patients having adverse events, these events were grouped into standardized categories using the MedDRA dictionary. Adverse events occurring at least three times and considered possibly related to treatment are included in the System Organ Class listings below. Terms not included in the listings are those already included in the tables above, those too general to be informative, those related to procedures and terms describing events common in the population. Some events occurring fewer than 3 times are also included based on their medical significance. Because the reports include events observed in open-label, uncontrolled observations, the role of BANZEL in their causation cannot be reliably determined.

Events are classified by body system and listed in order of decreasing frequency as follows: *frequent adverse events*- those occurring in at least 1/100 patients; *infrequent adverse events*- those occurring in 1/100 to 1/1000 patients; *rare*- those occurring in fewer than 1/1000 patients.

Blood and Lymphatic System Disorders: *Frequent*: anemia. *Infrequent*: lymphadenopathy, leukopenia, neutropenia, iron deficiency anemia, thrombocytopenia.

Cardiac Disorders: *Infrequent*: bundle branch block right, atrioventricular block first degree.

Metabolic and Nutritional Disorders: *Frequent*: decreased appetite, increased appetite.

Renal and Urinary Disorders: *Frequent*: pollakiuria. *Infrequent*: urinary incontinence, dysuria, hematuria, nephrolithiasis, polyuria, enuresis, nocturia, incontinence.

7 DRUG INTERACTIONS

Based on *in vitro* studies, rufinamide shows little or no inhibition of most cytochrome P450 enzymes at clinically relevant concentrations, with weak inhibition of CYP 2E1. Drugs that are substrates of CYP 2E1 (e.g. chlorzoxazone) may have increased plasma levels in the presence of rufinamide, but this has not been studied.

Based on *in vivo* drug interaction studies with triazolam and oral contraceptives, rufinamide is a weak inducer of the CYP 3A4 enzyme and can decrease exposure of drugs that are substrates of CYP 3A4 [see *Drug Interactions* (7.3)].

Rufinamide is metabolized by carboxylesterases. Drugs that may induce the activity of carboxylesterases may increase the clearance of rufinamide. Broad-spectrum inducers such as carbamazepine and phenobarbital may have minor effects on rufinamide metabolism via this mechanism. Drugs that are inhibitors of carboxylesterases may decrease metabolism of rufinamide.

7.1 Effects of BANZEL on other AEDs

Population pharmacokinetic analysis of average concentration at steady state of carbamazepine, lamotrigine, phenobarbital, phenytoin, topiramate, and valproate showed that typical rufinamide C_{avss} levels had little effect on the pharmacokinetics of other AEDs. Any effects, when they occur, have been more marked in the pediatric population.

Table 6 summarizes the drug-drug interactions of BANZEL with other AEDs.

Table 6: Summary of drug-drug interactions of BANZEL with other antiepileptic drugs

AED Co-administered	Influence of Rufinamide on AED concentration ^{a)}	Influence of AED on Rufinamide concentration
Carbamazepine	Decrease by 7 to 13% ^{b)}	Decrease by 19 to 26% Dependent on dose of carbamazepine
Lamotrigine	Decrease by 7 to 13% ^{b)}	No Effect
Phenobarbital	Increase by 8 to 13% ^{b)}	Decrease by 25 to 46% ^{c), d)} Independent of dose or concentration of phenobarbital
Phenytoin	Increase by 7 to 21% ^{b)}	Decrease by 25 to 46% ^{c), d)} Independent of dose or concentration of phenytoin
Topiramate	No Effect	No Effect
Valproate	No Effect	Increase by <16 to 70% ^{c)} Dependent on concentration of valproate
Primidone	Not Investigated	Decrease by 25 to 46% ^{c), d)} Independent of dose or concentration of primidone
Benzodiazepines ^{e)}	Not Investigated	No Effect

- a) Predictions are based on BANZEL concentrations at the maximum recommended dose of BANZEL.
- b) Maximum changes predicted to be in children and in patients who achieve significantly higher levels of BANZEL, as the effect of rufinamide on these AEDs is concentration-dependent.
- c) Larger effects in children at high doses/concentrations of AEDs.
- d) Phenobarbital, primidone and phenytoin were treated as a single covariate (phenobarbital-type inducers) to examine the effect of these agents on BANZEL clearance.
- e) All compounds of the benzodiazepine class were pooled to examine for ‘class effect’ on BANZEL clearance.

Phenytoin: The decrease in clearance of phenytoin estimated at typical levels of rufinamide (C_{avss} 15 $\mu\text{g/mL}$) is predicted to increase plasma levels of phenytoin by 7 to 21%. As phenytoin is known to have non-linear pharmacokinetics (clearance becomes saturated at higher doses), it is possible that exposure will be greater than the model prediction.

7.2 Effects of Other AEDs on BANZEL

Potent cytochrome P450 enzyme inducers, such as carbamazepine, phenytoin, primidone, and phenobarbital appear to increase the clearance of BANZEL (see Table 6). Given that the majority of clearance of BANZEL is via a non-CYP-dependent route, the observed decreases in blood levels seen with carbamazepine, phenytoin, phenobarbital, and primidone are unlikely to be entirely attributable to induction of a P450 enzyme. Other factors explaining this interaction are not understood. Any effects, where they occurred were likely to be more marked in the pediatric population.

Valproate: 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 stabilized on BANZEL before being prescribed valproate should begin valproate therapy at a low dose, and titrate to a clinically effective dose. Similarly, patients on valproate should begin at a BANZEL dose lower than 10 mg/kg/day (children) or 400 mg/day (adults) [see *Dosage and Administration* (2.5)].

7.3 Effects of BANZEL on other Medications

Hormonal contraceptives: Co-administration of BANZEL (800 mg BID for 14 days) and Ortho-Novum 1/35[®] resulted in a mean decrease in the ethinyl estradiol AUC_{0-24} of 22% and C_{max} by 31% and norethindrone AUC_{0-24} by 14% and C_{max} by 18%, respectively. The clinical significance of this decrease is unknown. Female patients of childbearing age should be warned that the 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 [see *Information for Patients* (17)].

Triazolam: Co-administration and pre-treatment with BANZEL (400 mg bid) resulted in a 37% decrease in AUC and a 23% decrease in C_{max} of triazolam, a CYP 3A4 substrate.

Olanzapine: Co-administration and pre-treatment with BANZEL (400mg bid) resulted in no change in AUC and C_{max} of olanzapine, a CYP 1A2 substrate.

8 USE IN SPECIFIC POPULATIONS

8.1 PREGNANCY

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. BANZEL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Rufinamide produced developmental toxicity when administered orally to pregnant animals at clinically relevant doses.

Rufinamide was administered orally to rats at doses of 20, 100, and 300 mg/kg/day and to rabbits at doses of 30, 200, and 1000 mg/kg/day during the period of organogenesis (implantation to closure of the hard palate); the high doses are associated with plasma AUCs \approx 2 times the human plasma AUC at the maximum recommended human dose (MRHD, 3200 mg/day). Decreased fetal weights and increased incidences of fetal skeletal abnormalities were observed in rats at doses associated with

maternal toxicity. In rabbits, embryo-fetal death, decreased fetal body weights, and increased incidences of fetal visceral and skeletal abnormalities occurred at all but the low dose. The highest dose tested in rabbits was associated with abortion. The no-effect doses for adverse effects on rat and rabbit embryo-fetal development (20 and 30 mg/kg/day, respectively) were associated with plasma AUCs \approx 0.2 times that in humans at the MRHD.

In a rat pre- and post-natal development study (dosing from implantation through weaning) conducted at oral doses of 5, 30, and 150 mg/kg/day (associated with plasma AUCs up to \approx 1.5 times that in humans at the MRHD), decreased offspring growth and survival were observed at all doses tested. A no-effect dose for adverse effects on pre- and post-natal development was not established. The lowest dose tested was associated with plasma AUC $<$ 0.1 times that in humans at the MRHD.

Pregnancy Registry

To provide information regarding the effects of in utero exposure to BANZEL physicians are advised to recommend that pregnant patients taking BANZEL enroll in the North American Antiepileptic Drug Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>.

8.2 Labor and Delivery

The effect of BANZEL on labor and delivery in humans is not known.

8.3 Nursing Mothers

Rufinamide is likely to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from BANZEL, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness in patients with Lennox-Gastaut syndrome have not been established in children less than 4 years. The pharmacokinetics of rufinamide in the pediatric population (age 4-17 years) is similar to that in the adults [*see Clinical Pharmacology (12.3)*]

8.5 Geriatric Use

Clinical studies of BANZEL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pharmacokinetics of rufinamide in the elderly is similar to that in the young subjects [*see Clinical Pharmacology (12.3)*]

8.6 Renal Impairment: Rufinamide pharmacokinetics in patients with severe renal impairment (creatinine clearance $<$ 30 mL/min) was similar to that of healthy subjects. Dose adjustment in patients undergoing dialysis should be considered [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment: There have been no specific studies investigating the effect of hepatic impairment on the pharmacokinetics of rufinamide. 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 Dosage and Administration (2.4)*].

9 DRUG ABUSE AND DEPENDENCE

The abuse and dependence potential of BANZEL has not been evaluated in human studies.

10 OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Certified Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.

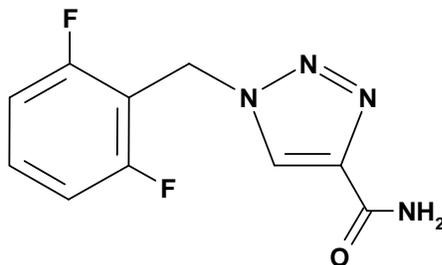
One overdose of 7200 mg/day BANZEL was reported in an adult during the clinical trials. The overdose was associated with no major signs or symptoms, no medical intervention was required, and the patient continued in the study at the target dose.

Treatment or Management of Overdose: There is no specific antidote for overdose with BANZEL. If clinically indicated, elimination of unabsorbed drug should be attempted by induction of emesis or gastric lavage. Usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Hemodialysis: Standard hemodialysis procedures may result in limited clearance of rufinamide. Although there is no experience to date in treating overdose with hemodialysis, the procedure may be considered when indicated by the patient's clinical state.

11 DESCRIPTION

BANZEL (rufinamide) is a triazole derivative structurally unrelated to currently marketed antiepileptic drugs (AEDs). Rufinamide has the chemical name 1-[(2,6-difluorophenyl)methyl]-1H-1,2,3-triazole-4 carboxamide. It has an empirical formula of $C_{10}H_8F_2N_4O$ and a molecular weight of 238.2. The drug substance is a white, crystalline, odorless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and in acetonitrile.



BANZEL is available for oral administration in film-coated tablets, scored on both sides, containing 200 and 400 mg of rufinamide. Inactive ingredients are colloidal silicon dioxide, corn starch crosscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulphate. The film coating contains hypromellose, iron oxide red, polyethylene glycol, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which rufinamide exerts its antiepileptic effect is unknown. The results of *in vitro* studies suggest that the principal mechanism of action of rufinamide is modulation of the activity of sodium channels and, in particular, prolongation of the inactive state of the channel. Rufinamide ($\geq 1 \mu\text{M}$) significantly slowed sodium channel recovery from inactivation after a prolonged prepulse in cultured cortical neurons, and limited sustained repetitive firing of sodium-dependent action potentials (EC_{50} of $3.8 \mu\text{M}$).

12.3 Pharmacokinetics

Overview

BANZEL is well absorbed after oral administration. However, the rate of absorption is relatively slow and the extent of absorption is decreased as dose is increased. The pharmacokinetics does not change with multiple dosing. Most elimination of rufinamide is via metabolism, with the primary metabolite resulting from enzymatic hydrolysis of the carboxamide moiety to form the carboxylic acid. This metabolic route is not cytochrome P450 dependent. There are no known active metabolites. Plasma half-life of rufinamide is approximately 6-10 hours.

Absorption and Distribution

Following oral administration of BANZEL, peak plasma concentrations occur between 4 and 6 hours (T_{max}) both under fed and fasted conditions. BANZEL tablets display decreasing bioavailability with increasing dose after single and multiple dose administration. Based on urinary excretion, the extent of absorption was at least 85% following oral administration of a single dose of 600 mg rufinamide under fed conditions.

Multiple dose pharmacokinetics can be predicted from single dose data for both rufinamide and its metabolite. Given the dosing frequency of every 12 hours and the half-life of 6 to 10 hours, the observed steady-state peak concentration of about two to three times the peak concentration after a single dose is expected.

Food increased the extent of absorption of rufinamide in healthy volunteers by 34% and increased peak exposure by 56% after a single dose of 400 mg, although the T_{max} was not elevated. Clinical trials were performed under fed conditions and dosing is recommended with food [see *Dosage and Administration* (2)].

Only a small fraction of rufinamide (34%) is bound to human serum proteins, predominantly to albumin (27%), giving little risk of displacement drug-drug interactions. Rufinamide was evenly distributed between erythrocytes and plasma. The apparent volume of distribution is dependent upon dose and varies with body surface area. The apparent volume of distribution was about 50 L at 3200 mg/day.

Metabolism

Rufinamide is extensively metabolized but has no active metabolites. Following a radiolabeled dose of rufinamide, less than 2% of the dose was recovered unchanged in urine. The primary biotransformation pathway is carboxylesterase(s) mediated hydrolysis of the carboxamide group to the acid derivative CGP 47292. A few minor additional metabolites were detected in urine, which

appeared to be acyl-glucuronides of CGP 47292. There is no involvement of oxidizing cytochrome P450 enzymes or glutathione in the biotransformation process.

Rufinamide is a weak inhibitor of CYP 2E1. It did not show significant inhibition of other CYP enzymes. Rufinamide is a weak inducer of CYP 3A4 enzymes.

Rufinamide did not show any significant inhibition of P-glycoprotein in an *in-vitro* study.

Elimination/Excretion

Renal excretion is the predominant route of elimination for drug related material, accounting for 85% of the dose based on a radiolabeled study. Of the metabolites identified in urine, at least 66% of the rufinamide dose was excreted as the acid metabolite CGP 47292, with 2% of the dose excreted as rufinamide.

The plasma elimination half-life is approximately 6-10 hours in healthy subjects and patients with epilepsy.

Special Populations

Gender: Population pharmacokinetic analyses of females show a 6-14% lower apparent clearance of rufinamide compared to males. This effect is not clinically important.

Race: In a population pharmacokinetic analysis of clinical studies, no difference in clearance or volume of distribution of rufinamide was observed between the black and Caucasian subjects, after controlling for body size. Information on other races could not be obtained because of smaller numbers of these subjects.

Pediatrics: Based on a population analysis in 117 children (age 4-11 years) and 99 adolescents (age 12-17 years), the pharmacokinetics of rufinamide in these patients is similar to the pharmacokinetics in adults.

Elderly: The results of a study evaluating single-dose (400 mg) and multiple dose (800 mg/day for 6 days) pharmacokinetics of rufinamide in 8 healthy elderly subjects (65-80 years old) and 7 younger healthy subjects (18-45 years old) found no significant age-related differences in the pharmacokinetics of rufinamide.

Renal Impairment: Rufinamide pharmacokinetics in 9 patients with severe renal impairment (creatinine clearance <30 mL/min) was similar to that of healthy subjects. Patients undergoing dialysis 3 hours post rufinamide dosing showed a reduction in AUC and C_{max} by 29% and 16% respectively. Adjusting rufinamide dose for the loss of drug upon dialysis should be considered.

Hepatic Impairment: There have been no specific studies investigating the effect of hepatic impairment on the pharmacokinetics of rufinamide. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Rufinamide was given in the diet to mice at 40, 120, and 400 mg/kg/day and to rats at 20, 60, and 200 mg/kg/day for two years. The doses in mice were associated with plasma AUCs 0.1 to 1 times the human plasma AUC at the maximum recommended human dose (MRHD, 3200

mg/day). Increased incidences of tumors (benign bone tumors (osteomas) and/or hepatocellular adenomas and carcinomas) were observed in mice at all doses. Increased incidences of thyroid follicular adenomas were observed in rats at all but the low dose; the low dose is <0.1 times the MRHD on a mg/m² basis.

Mutagenesis: Rufinamide was not mutagenic in the *in vitro* bacterial reverse mutation (Ames) assay or the *in vitro* mammalian cell point mutation assay. Rufinamide was not clastogenic in the *in vitro* mammalian cell chromosomal aberration assay or the *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility: Oral administration of rufinamide (doses of 20, 60, 200, and 600 mg/kg/day) to male and female rats prior to mating and throughout mating, and continuing in females up to day 6 of gestation resulted in impairment of fertility (decreased conception rates and mating and fertility indices; decreased numbers of corpora lutea, implantations, and live embryos; increased preimplantation loss; decreased sperm count and motility) at all doses tested. Therefore, a no-effect dose was not established. The lowest dose tested was associated with a plasma AUC \approx 0.2 times the human plasma AUC at the MRHD.

14 CLINICAL STUDIES

The effectiveness of BANZEL as adjunctive treatment for the seizures associated with Lennox-Gastaut syndrome (LGS) was established in a single multicenter, double-blind, placebo-controlled, randomized, parallel-group study (n=138). 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 1 to 3 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 on stable therapy, patients were randomized to have BANZEL or placebo added to their ongoing therapy during the 12 week Double-blind Phase. The Double-blind Phase consisted of 2 periods: the Titration Period (1 to 2 weeks) and the Maintenance Period (10 weeks). During the Titration Period, the dose was increased to a target dosage of approximately 45 mg/kg/day (3200 mg in adults of \geq 70kg), given on a b.i.d. schedule. Dosage reductions were permitted during titration if problems in tolerability were encountered. Final doses at titration were to remain stable during the maintenance period. Target dosage was achieved in 88% of the BANZEL-treated patients. The majority of these patients reached the target dose within 7 days, with the remaining patients achieving the target dose within 14 days.

The primary efficacy variables were:

- The percent change in total seizure frequency per 28 days;
- The percent change in tonic-atonic (drop attacks) seizure frequency per 28 days;
- Seizure severity from the Parent/Guardian Global Evaluation of the patient's condition. This was a 7-point assessment performed at the end of the Double-blind Phase. A score of +3 indicated that the patient's seizure severity was very much improved, a score of 0 that the seizure severity was unchanged, and a score of -3 that the seizure severity was very much worse.

The results of the three primary endpoints are shown in Table 7 below.

Table 7: Lennox -Gastaut Syndrome Trial Seizure Frequency Primary Efficacy Variable Results

Variable	Placebo	Rufinamide
Median percent change in total seizure frequency per 28 days	-11.7	-32.7 (p=0.0015)
Median percent change in tonic-atonic seizure frequency per 28 days	1.4	-42.5 (p<0.0001)
Improvement in Seizure Severity Rating from Global Evaluation	30.6	53.4 (p=0.0041)

16 HOW SUPPLIED/STORAGE AND HANDLING

BANZEL 200 mg tablets (containing 200 mg rufinamide) are pink in color, film-coated, oblong-shape tablets, with a score on both sides, imprinted with “€ 262” on one side. They are available in bottles of 30 (NDC 62856-582-30).

BANZEL 400 mg tablets (containing 400 mg rufinamide) are pink in color, film-coated, oblong-shape tablets, with a score on both sides, imprinted with “€ 263” on one side. They are available in bottles of 120 (NDC 62856-583-52).

Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°F - 86°F). Protect from moisture. Replace cap securely after opening.

17 PATIENT COUNSELING INFORMATION

Patients should be informed of the availability of a Medication guide and they should be instructed to read the Medication Guide prior to taking BANZEL.

Patients should be instructed to take BANZEL only as prescribed.

17.1 Suicidal Thinking and Behavior - Patients, their caregivers, and families should be informed that antiepileptic drugs 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.

As with all centrally acting medications, alcohol in combination with BANZEL may cause additive central nervous system effects.

Patients should be advised to notify their physician if they experience a rash associated with fever.

BANZEL should be taken with food.

Patients should be advised about the potential for somnolence or dizziness and advised not to drive or operate machinery until they have gained sufficient experience on BANZEL to gauge whether it adversely affects their mental and/or motor performance.

Female patients of childbearing age should be warned that the concurrent use of BANZEL with hormonal contraceptives may render this method of contraception less effective [see *Drug Interactions (7.3)*]. Additional non-hormonal forms of contraception are recommended when using BANZEL.

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. They should also be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry if they become pregnant. To enroll, patients can call the toll free number 1-888-233-2334 [see *Use in Specific Populations (8.1)*].

Patients should be advised to notify their physician if they are breast-feeding or intend to breast-feed.