CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-911

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF NEUROLOGY PRODUCTS

MEMORANDUM

DATE: September 29, 2008

FROM: Robert Temple M.D., Director, Office of Drug Evaluation I

SUBJECT: Risk Evaluation and Mitigation Strategy (REMS) Requirements for Banzel (rufinamide) Tablets (NDA 22-911)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)). Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug
(F) Whether the drug is a new molecular entity.

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary to ensure that the benefits of Banzel (rufinamide) outweigh the increased risk of suicidal thoughts and behavior associated with the class of antiepileptic drugs (AEDs) that includes Banzel (rufinamide). In reaching this determination, we considered the following:

A. It is not possible to precisely estimate the size of the population likely to use antiepileptic drugs, including Banzel (rufinamide). The age-adjusted prevalence of epilepsy in developed countries is 4 to 8 per 1,000. It is estimated that approximately three million people in the United States have epilepsy. Many antiepileptic drugs are also approved for the treatment of other illnesses including bipolar disorder,

trigeminal neuralgia, migraine, postherpetic neuralgia, pain from diabetic peripheral neuropathy, and fibromyalgia. The total number of patients receiving a prescription for any of the 11 antiepileptic drugs included in a recent meta-analysis of the risk for suicidal thoughts and behavior with antiepileptic drugs in outpatient retail pharmacies in the United States was over 11 million in 2007.

B. Patients with epilepsy have approximately two to three times the risk of death from any cause compared with persons without epilepsy. Many of the deaths in persons with epilepsy are directly related to seizures, accidents and injuries arising from seizures, and the underlying condition resulting in seizures. Antiepileptic drugs are also approved for a variety of other treatment indications (Attachment 1). Many of these illnesses are also associated with substantial morbidity and an increased risk of mortality.

C. Antiepileptic drugs have a demonstrated ability to reduce frequency of seizures when used for treatment of epilepsy. Since many deaths in persons with epilepsy are directly related to seizures, antiepileptic drugs reduce mortality in this population of patients. Some antiepileptic drugs also are approved for the treatment of conditions other than epilepsy (Attachment 1 describes approved indications other than epilepsy for the antiepileptic drugs that were studied in the meta-analysis [described below]).

D. Antiepileptic drugs are used as chronic therapy in patients with epilepsy. Duration of treatment may vary for other treatment indications.

E. A known serious risk of antiepileptic drugs as a therapeutic class is an increased risk of suicidal thoughts and behavior (which are risk factors for completed suicide). The increased risk of suicidal thoughts and behavior were demonstrated in a meta-analysis of randomized, parallel-arm, placebo-controlled clinical trial data for 11 approved AEDs.[1] Rufinamide was not approved at the time that this meta-analysis was performed.

In the meta-analysis, the odds ratio for suicidal behavior or ideation for all AEDs studied was 1.80 (95% CI: 1.24, 2.66); 0.37% of all drug-treated patients and 0.24% of placebo-treated patients had an event of suicidal behavior or ideation. This finding was generally consistent among drugs in the data analyzed. It was shared by drugs with varying mechanisms of action and was observed for all indications studied; this observation suggests that the risk applies to all antiepileptic drugs regardless of indication of use.

The background incidence of suicide in patients with epilepsy is estimated as being higher than the incidence of suicide in the general population. Estimates of the

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[1]Statistical review and evaluation: Antiepileptic drugs and suicidality. (Accessed September 24, 2008, at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf.)

incidence of suicide in patients with epilepsy vary widely, but studies have consistently indicated a higher incidence of suicide (and suicide attempts) in patients with epilepsy. The background incidence of suicide is also estimated as being higher in other conditions for which antiepileptic drugs are indicated, including bipolar disorder. In patients with bipolar disorder, the estimated rate of suicide is 0.40% per year (compared to the international general population average of 0.017% per year); the standardized mortality ratio is estimated to be 22.

F. Banzel (rufinamide) is a new molecular entity (NME).

In accordance with section 505-1 of the FDCA, as one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Banzel (rufinamide) poses a serious and significant public health concern requiring distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Banzel (rufinamide). FDA has determined that Banzel (rufinamide) has serious risks of which patients should be made aware because information concerning the risks could affect patients' decisions to use Banzel (rufinamide). In addition, patient labeling could help prevent serious adverse effects related to the use of Banzel (rufinamide).

The only elements of the REMS will be a Medication Guide and a timetable for submission of assessments of the REMS.

Attachment 1

FDA-approved non-epilepsy treatment indications of antiepileptic drugs (AEDs) with data in the FDA analysis of AEDs and suicidality

Drug	Treatment Indications
Carbamazepine	trigeminal neuralgia
Gabapentin	postherpetic neuralgia
Lamotrigine	bipolar disorder (maintenance)
Pregabalin	neuropathic pain from diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia
Topiramate	migraine
Divalproex sodium	mania, migraine

Attachment 2

Total number of unique patients receiving a prescription for any of 11* antiepileptic drugs in U.S. outpatient retail pharmacies, 2002-2007

year	2002	2003	2004	2005	2006	2007
# patients						

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*11 drugs included: carbamazepine, divalproex sodium, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide.

Source: Verispan, Vector One Total Patient Tracker

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/s/

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