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RESEARCH**

APPLICATION NUMBER:
201367Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross Discipline Team Leader Review

Date	3/1/11
From	Angela Men, MD, PhD
Subject	Cross Discipline Team Leader Review
NDA/BLA #	201367
Supplement#	
Applicant	Eisai Co., Ltd.
Date of Submission	April 30, 2010
PDUFA Goal Date	March 3, 2011
Proprietary Name / Established (USAN) names	Banzel/rufinamide
Dosage forms / Strength	Oral Suspension (40 mg/ml)
Proposed Indication(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS)
Recommended:	(Approval vs. Approvable vs. Not Approvable vs. Complete Response)

1. Introduction/Background

Rufinamide (BANZEL), a triazole derivative, was first approved in the United States on November 14, 2008 as a tablet formulation (200 and 400 mg film-coated tablets) for adjunctive treatment of seizures associated with Lennox Gastaut Syndrome in patients 4 years and older. The sponsor developed BANZEL Oral Suspension, which is intended to be used for treatment of the same indication and at the same dose amounts as tablets (in mg) but affords a more convenient presentation for administration to young children. The oral suspension is also expected to address the needs of older patients who are unable to or would prefer not to swallow a solid oral dosage form.

The BANZEL Oral Suspension formulation has a single strength of 40 mg/mL. One 5 mL spoonful of suspension is equivalent to one 200 mg tablet. This dosage form affords compliance and flexibility of dosing from 100 mg (2.5 mL) administered by a graduated oral syringe to [REDACTED] (b) (4). The marketing approval is based upon bioequivalence of the oral suspension with that of the marketed tablets (Study E2080-E044-003). There is no clinical efficacy trial in this submission.

2. CMC/Device

Initial chemistry review (initial review 12/16/10 conducted by CMC primary reviewer: Akm Khairuzzaman, Ph.D; CMC Branch Chief: Ramesh K Sood) did not find the application as approvable.

During NDA discussions with the sponsor for Banzel Oral Suspension, [REDACTED] (b) (4) the maximum dosage is 80mL and the

minimum dosage is 2.5mL. The FDA/DNP and Eisai agreed to include two 20mL dosing syringes to assist the patient in administering Banzel Oral Suspension to the patient. The 20 mL syringe is able to maintain the low dose, but still able to adequately provide larger doses. In addition, Eisai proved accuracy of the new 20mL syringe to (+/-)10% and the its readability following 90-day multiple washings. Based on these updated information, the non-approvable issues have been resolved and approval is recommended in an updated review (2/23/11) by CMC. No post-approval commitments are recommended.

3. Clinical Pharmacology/Biopharmaceutics

As noted above, approval is based upon the demonstration of bioequivalence. This application contains data from a primary relative bioavailability study in healthy volunteers (E2080E044- 003) entitled "A randomized, open label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide administered as the marketed tablet with three suspension formulations manufactured using different homogeneity speeds (1800, 2100 and 3000 rpm)." The three rufinamide oral suspension formulations manufactured using different homogeneity speeds (1800, 2100 and 3000 rpm) are bioequivalent to the highest strength of the rufinamide tablets (400 mg) under fed conditions (N = 21). Rufinamide is recommended to be taken under fed conditions. Rufinamide oral suspension formulations [REDACTED] ^{(b) (4)} was chosen as the to-be marketed formulation. Clinical pharmacology review team (reviewer: Dr. Veneeta Tandon; team leader: Dr. Angela Men) has agreed that the study is adequate and justifies approval. There is no post-approval commitment recommended.

4. Clinical/Statistical- Efficacy

There is no clinical efficacy study. Efficacy is based upon prior studies and the present bridging bioequivalent study E2080E044- 003 (see above Section 4).

5. Safety

The clinical review team (medical officer: Dr Steven Dinsmore; clinical team leader: Dr. Norman Hershkowitz) performed the safety evaluation for study E2080-E044-003. No deaths or serious adverse events were observed. While there were some adverse events which are not a part of the present label (paraesthesia, chest discomfort, palpitations, arthralgia and ocular hyperemia), these were mild and there was not adequate evidence to attribute these to drug as a causal factor. Some minor laboratory abnormalities were noted, but again could not be attributed to the drug. Of interest there were 2 cases of urinary track infections, but two such isolated cases, in the background of a previous absence of signal could not be used to determine drug causality. There were no other safety issues that needed to be resolved before recommending approval. The clinical review team recommends approval. The clinical reviewer does not recommend any post-approval commitments or recommendations.

6. Inspections and Financial Disclosure

Inspections for primary study proved satisfactory. Financial disclosure was found acceptable.

7. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action Approval

Risk/Benefit Assessment

There were no new safety issues that needed to be resolved before recommending approval. Efficacy is based upon prior studies and the present bridging bioequivalent study, which demonstrated that the to-be-marketed rufinamide oral suspension formulation is bioequivalent to the highest strength of the rufinamide tablets (400 mg) under fed conditions. After review, all of the involved review divisions recommend approval and there are no recommended post-approval commitments or recommendations.

8. Labeling

The FDA/DNP negotiated the wording of the label and REMS with the sponsor during the review of this submission. The final label and REMS are attached below, as well as to the approval letter.

28 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS)
immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YUXIN MEN
03/02/2011