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RESEARCH**

*APPLICATION NUMBER:*

**22-152**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	July 29, 2008
<b>From</b>	Eric Bastings, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA #</b>	22152
<b>Supplement#</b>	
<b>Applicant</b>	Banner Pharmacaps, Inc.
<b>Date of Submission</b>	May 27, 2008
<b>PDUFA Goal Date</b>	July 29, 2008
<b>Proprietary Name / Established (USAN) names</b>	Stavzor/valproic acid
<b>Dosage forms / Strength</b>	125, 250, and 500 mg capsule
<b>Proposed Indication(s)</b>	<ol style="list-style-type: none"> <li>1. Mania</li> <li>2. Epilepsy</li> <li>3. Migraine</li> </ol>
<b>Recommended:</b>	Approval

### Purpose of Cross-Discipline Team Leader (CDTL) Review

## 1. Introduction

Stavzor was issued a tentative approval letter on December 21, 2007. At that time, the referenced listed drug (RLD), Depakote, was subject to patent protection, to expire on July 29, 2008. This submission is a response to the tentative approval letter.

## 2. Background

The Stavzor 505(b)(2) new drug application (NDA) was originally received on December 22, 2006. I described in an October 12, 2007 memorandum to the file the various issues identified by the review team in that original submission, for which an approvable letter was sent to the sponsor on October 22, 2007. The issues concerned dissolution methods and data, as described in the action letter.

The sponsor submitted on October 26, 2007 a complete response to our October 22, 2007 action letter. In that response, the sponsor adequately addressed the issues described in the approvable letter, and was issued on December 21, 2007 a tentative approval letter, pending resolution of patent protection for the reference listed drug, Depakote.

### **3. CMC/Device**

Dr. Craig Bertha recommends approval on a CMC perspective. Dr. Bertha recommends the following labeling changes for the “INGREDIENTS” portion of the Drug Listing Data elements (DLDE) table:

- Remove the “black imprinting ink” entry.
- Revise “ammonium hydroxide” to “ammonia solution, strong.”:

### **4. Nonclinical Pharmacology/Toxicology**

No outstanding nonclinical issue.

### **5. Clinical Pharmacology/Biopharmaceutics**

No outstanding Pharmacology/Biopharmaceutics issue.

### **6. Clinical Microbiology**

Not applicable.

### **7. Clinical/Statistical- Efficacy**

Not applicable. This is a 505(b)(2) application, based on bioequivalence to a reference listed drug, Depakote Delayed Release.

### **8. Safety**

No outstanding clinical issue. There was no ongoing clinical trial at the time of tentative approval, and there are no new clinical safety data.

### **9. Advisory Committee Meeting**

No advisory committee meeting was held.

### **10. Pediatrics**

Under the Pediatric Research Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of

administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. I have the following recommendations for the proposed indications:

**Prophylaxis of Migraine Headache**

Age 12-17: waiver because a previous study in that age group failed to demonstrate effectiveness for this indication.

Age 6-11: waiver because, in light of the previous negative study in the 12-17 age group, the necessary studies are impossible or highly impracticable (the critical design elements for adequate studies in this age group for this drug are unknown) .

Age 0-5: waiver because the necessary studies are impossible or highly impracticable (migraine is difficult to diagnose in children under age 6 years and the critical design elements for adequate studies in this age group for this drug are unknown).

**Acute treatment of manic episodes associated with bipolar disorder**

Age 10-17: waiver because a previous study in that age group failed to demonstrate effectiveness for this indication.

Age 0-9: waiver because the necessary studies are impossible or highly impracticable (this disease does not exist in children under age 10).

**Treatment of simple & complex absence seizures**

This product is appropriately labeled for use in ages birth up to 17 years for this indication. Therefore, no additional studies are needed in this pediatric group.

**Monotherapy and adjunctive therapy of complex partial seizures**

Age 10-17: product is appropriately labeled.

Age 0-9: waiver, because the necessary studies are impossible or highly impracticable (prior attempts of recruiting patients of that age group into a study have not been successful).

## **11. Other Relevant Regulatory Issues**

Patent protection for the RLD, Depakote, expires today, i.e. on July 29, 2008.

## **12. Labeling**

Labeling was updated from the tentative approval version to include the following:

- New Warning/Precaution on hypothermia
- New Warning/Precaution on drug-drug interaction with carbapenem antibiotics
- New information on pediatric use

Proprietary name and labeling were reviewed by the Division of Medication Error Prevention (DMEP). DMEP found that the proposed name does not appear to be

vulnerable to name confusion that could lead to medication errors. Thus, DMEP does not object to the use of the proprietary name Stavzor for this product.

DMEP recommends the following labeling change: delete or relocate the graphic circular 'V' logo from immediately in front of the proprietary name. DMEP believes that the placement of the logo may lend itself to misinterpretation of the proprietary name (i.e. UStavzor or VStavzor).

### **13. Recommendations/Risk Benefit Assessment**

I recommend approval.

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/s/

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Eric Bastings  
7/29/2008 01:28:30 PM  
MEDICAL OFFICER