

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-152

OTHER ACTION LETTER(s)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-152

Banner Pharmacaps, Inc.
Attention: Dana S. Toops
Director, Regulatory Affairs
4125 Premier Drive
P.O. Box 2210
High Point, NC 27265

Dear Mr. Toops:

Please refer to your new drug application (NDA) dated December 20, 2006, received December 22, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for valproic acid delayed release capsules.

We acknowledge receipt of your submissions dated October 18, 2007, October 26, 2007 and November 16, 2007.

The October 26, 2007 submission constituted a complete response to our October 22, 2007 action letter.

This new drug application provides for the use of valproic acid in the treatment of manic episodes associated with bipolar disorder, monotherapy and adjunctive therapy in multiple seizure types and prophylaxis of migraine headaches.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed upon labeling (enclosed text for the package insert and patient package insert, and immediate container and carton labels submitted October 26, 2007). This determination is contingent upon information available to the Agency at this time (i.e., information in your application and the status of current good manufacturing practices of the facilities used in manufacturing and testing of the drug product) and is, therefore, subject to change on the basis of any new information that may come to our attention.

The referenced listed drug (RLD) product referenced in your application, Depakote of Abbott Laboratories, is subject to periods of patent protection which expire on January 29, 2008 (U.S. Patent No. 4,988,731 [the '731 patent]), and January 29, 2008 (U.S. Patent No. 5,212,326 [the '326 patent]). Your application contains a Paragraph IV Certification to all of these patents under Section 505(b)(2)(A)(iv) of the Act. This certification states that the above listed patents are invalid, unenforceable or would not be infringed by your manufacture, use, or sale of this drug product. Section 505(c)(3)(C) of the Act provides that the approval of a new drug application submitted pursuant to Section 505(b)(2) of the Act shall be made effective immediately, unless an action is brought for infringement of the patents that are the subject of the certification. This action must be taken before the expiration of forty-five days from the date the notice provided under Section

505(b)(3)(A) is received by both the holder of the new drug application (NDA) and the patent owner. You have notified the Agency that Banner Pharmacaps Inc. (Banner) has complied with the requirements of Section 505(c)(3)(C). In addition, you have notified the Agency that the patent owner and/or NDA holder initiated a patent infringement suit against Banner with respect to the '731 and '326 patents in the United States District Court for Delaware (Wilmington) (Abbott Laboratories, an Illinois corporation, vs. Banner Pharmacaps Inc., a Delaware corporation Civil Action Case No. 07-754). Therefore, final approval cannot be granted, with respect to each patent for which a paragraph IV certification was submitted and patent litigation was initiated, until:

1.
 - a) expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3)(A), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,
 - b) the date of a court action described in Section 505(c)(3)(C)(i), (ii), (iii), or (iv) , or,
 - c) the patent has expired, and
2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may effect the final approval. This amendment must provide the following information:

1. Please include updated information related to labeling or chemistry, manufacturing, and controls data, or any other change in the conditions outlined in your application.
2. Please submit a copy of a final order or judgment or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information.

An amendment should be submitted even if no changes were made to the application since the date of this tentative approval. In addition to this amendment, the Agency may request at any time prior to the date of final approval that you submit an additional amendment containing the information described above. Failure to submit either or, if requested, both amendments, may result in rescission of the tentative approval status of your application, or result in a delay in the issuance of the final approval letter.

Timing of Response

Please submit a response to all items listed in this letter and identify changes, if any, in the conditions under which your product was tentatively approved. Your response should include updated labeling, chemistry, manufacturing and controls data, and a safety update. You should respond to this letter no sooner than 60 or 180 days prior to the expiration of Depakote's patent and/or exclusivity (see above). You should determine the timing of your response by referring to resubmission classifications and

associated FDA review times described in the Guidance for Industry: Classifying Resubmissions in Response to Action Letters available at <http://www.fda.gov/cder.guidance/index.htm>.

Failure to submit the response will prompt a review of the application that may result in rescission of this tentative approval letter.

Promotional Materials

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Other

Any significant change in the conditions outlined in this NDA requires our review before final approval may be granted.

Before we issue a final approval letter, this NDA is not deemed approved. If you believe that there are grounds for issuing the final approval letters before the expiration of Depakote's patent and/or exclusivity if granted, has expired, you should amend your application accordingly.

This product may be considered misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before final approval.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

17 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Russell Katz
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NDA 22-152

Banner Pharmacaps, Inc.
Attention: Dana S. Toops
Director, Regulatory Affairs
4125 Premier Drive
P.O. Box 2210
High Point, NC 27265

Dear Mr. Toops:

Please refer to your new drug application (NDA) dated December 20, 2006, received December 22, 2006, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for valproic acid delayed release capsules.

We acknowledge receipt of your submissions dated the following:

January 25, 2007	May 24, 2007	July 20, 2007	September 21, 2007	October 10, 2007
January 31, 2007	June 1, 2007	August 10, 2007	September 28, 2007	October 16, 2007
February 7, 2007	July 2, 2007	August 22, 2007	October 2, 2007	
February 15, 2007	July 19, 2007	August 28, 2007	October 9, 2007	

This new drug application provides for the use of valproic acid in the treatment of manic episodes associated with bipolar disorder, adjunctive therapy in multiple seizure types and prophylaxis of migraine headaches.

We completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to address the issues listed below. Note that some of these issues were already communicated to you during the review cycle, but your response was either not submitted to the NDA in this review cycle, or not yet reviewed by the Agency because of a late submission to the NDA. We also take note that you changed the dissolution method from one containing 0.5% sodium dodecyl sulfate (SDS) in the media to 0.5% SDS, in a September 21, 2007 amendment.

b(4)

Clinical Pharmacology

1. With respect to the proposed dissolution methodology, you have not shown adequate discriminatory ability for poorly performing capsules with respect to the 60 minute time point in buffer for capsules that would release their contents so slowly as to result in a decrease in Cmax or in acid where dose dumping could occur. The discriminatory ability should be shown

in the proposed media with the proposed dissolution method. (The initial data used to justify discriminatory ability was not performed in the same media as the 12 and 24 months data). This information is necessary prior to determining acceptability of the dissolution methodology and specifications.

2. Dose dumping with alcohol should be evaluated in vitro by performing dissolution studies in 0, 5, 10, and 20% alcohol (with alcohol in both the acid and buffer phases).
3. In order to consider whether a biowaiver of the 250 and 125 mg strengths is possible, you need to provide dissolution data and comparisons for all 3 strengths (using 12 units of each strength) in multiple media. This should include the proposed medium (using the optimal strength of SLS following characterization in 0%, 0.5%, 1%, and 2%) as well as in three other conditions (in the absence of SLS). For these 3 other conditions, dissolution tests should be performed in 0.1 N HCl for 2 hours (acid stage) followed by testing in USP buffer media, in the range of pH 4.5- 7.5 (buffer stage). Multipoint dissolution profiles should be obtained during the buffer stage of testing. Profiles for the 250 and 125 mg strengths should be compared to the 500 mg strength, and f2 similarity factor should be calculated. If SLS will not be in the proposed medium, then this testing should be done in the acid phase plus 3 media in the buffer phase (one of these could be the proposed medium without SLS as long as it is a conventional medium).

Chemistry, Manufacturing and Controls

1. In addition to the provision of the new dissolution method that utilizes ~~—~~SDS, and data to support the discriminatory ability of the method to detect "poorly performing capsules," additional data and information will be needed. At a minimum, you must provide the following:
 - a. Data to link the stability of drug product examined for dissolution with the ~~—~~SDS method to that collected with the new non-SDS method, e.g., run the current latest stability samples of each strength (multiple batches) with both methods and compare the results side-by-side. Include an F2 comparison. These data should also be presented in a manner to allow an easy assessment of the comparative variability. **b(4)**
 - b. A justification of the proposed acceptance criteria with the new non-SDS method in place.
 - c. Validation data for the new non-SDS method.
 - d. An explanation of the unexpected behavior of the dissolution data (extent and variability) with respect to the SDS concentration in the range of ~~—~~%. **b(4)**
 - e. Confirmation that the in-process hardness acceptance criterion and test frequency remain as indicated in the revised master batch records included in the July 2, 2007, amendment for the 125 and 500 mg strengths, and as indicated in the master batch record for the 250 mg strength in the July 19, 2007, amendment, i.e. ~~—~~ tested in 4 ± 2 hour intervals. The Quality Overall Summary dated August 10, 2007, did not reflect this revision.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDA (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material.

Additionally, please submit the content of labeling according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format — Content of Labeling (April 2005).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Lana Chen, Regulatory Project Manager, at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Russell Katz

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