CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-152

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Date:	October 12, 2007
From:	Eric Bastings, MD.
To:	Russell Katz, MD
Subject:	——— Valproic Acid delayed release capsules b(4)

NDA ——— is a 505 (b)(2) application received on December 20, 2006 for Valproic Acid Delayed Release Capsules (Stavzor), 500 mg, 250 mg, and 125 mg. This NDA is entirely based on a single bioequivalence study for the 500 mg strength with a request for biowaiver for the 125 and 250 mg strengths. The Stavzor 500 mg capsules strength were used in the pharmacokinetic (BE) study with the reference Depakote (divalproex sodium) delayed release tablets. The proposed drug product differs from the reference listed drug (RLD) in dosage form (capsule vs. tablet), active ingredient (valproic acid vs. divalproex sodium) and is otherwise similar with respect to route of administration, strength and indications. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. Clinical efficacy studies were not conducted. b(4)

For this application, Dr. Craig Bertha provided the CMC review, Dr. Sally Yasuda provided the OCPB review, Dr. Ramesh Raman and Dr. Earl Hearst provided the clinical review. The tradename Stavzor was submitted late in the review cycle, and is under review by DMETS at the time of redaction of this memorandum. I will use it in the rest of this document, without any implication regarding its ultimate acceptability.

CMC

ONDQA recommends an approvable action.

Dr. Bertha filed 4 review documents in DFS, the first one concerning the original application, and the subsequent ones addressing the responses provided by the sponsor to the various issues that he identified, and which ONDQA communicated to the sponsor. I refer the reader to Dr. Bertha's reviews in DFS for the issues which were resolved, and which I will not discuss further.

I will comment here below on the outstanding issues, identified in the fourth review document of Dr. Bertha. The main remaining CMC issue is that the sponsor changed the dissolution method from one containing ——— sodium dodecyl sulfate (SDS) in the media to ———SDS, in a September 21, 2007 amendment. The bulk of the stability dissolution data for the high strength product (after 9 months to 24 months), and all of the stability dissolution data for the low and middle strengths were collected with the method using the media with ———SDS. Thus, Dr. Bertha notes that there is no longer a link to the b(4) b(4)

stability data for the quality control method being proposed, and that the applicability of the previous acceptance criteria for dissolution is also in question. Dr. Bertha recommends that the new method should be demonstrated to be suitably validated. In addition, Dr. Bertha noted that the dissolution profile with 0% SDS is somewhat unexpected given the dissolution behavior with 0.5, 1, and 2% SDS, which he wants the sponsor to address. Dr. Bertha already forwarded comments regarding these issues to the sponsor in an email message on September 25, 2007, but the sponsor's response was pending at the time of completion of his review.

Finally, Dr. Bertha noted that approvability is also dependent on a satisfactory recommendation from the Office of Compliance regarding the inspection of the various sites.

OCPB

OCPB recommends an approvable action.

Dr. Yasuda notes that Stavzor differs from Depakote in the active ingredient. However, both valproic acid and divalproex sodium dissociate to the valproate ion *in vivo* in the GI tract following oral administration, resulting in exposure to the same active moiety.

Dr. Yasuda notes that the relative bioavailability study comparing the 500 mg strength of STAVZOR with the 500 mg strength of DEPAKOTE met bioequivalence (BE) criteria. A food effect study with the 500 mg strength capsule demonstrated a food effect on the Cmax (a 23% decrease) with a 2.8 hour delay in median Tmax, similar to that seen with Depakote.

Dr. Yasuda notes that with respect to the dissolution method and specifications, the sponsor has not justified the use of —% SDS in the dissolution media, but this issue is moot since the sponsor submitted a revised dissolution method using ——SDS. Dr. Yasuda also comments that the sponsor has not shown discriminatory ability of the method to detect poorly performing capsules. In addition, since this is a modified release product, dose dumping in alcohol should be evaluated in vitro. b(4)

In addition, the Sponsor has requested a biowaiver for the 125 mg and 250 mg strength capsules. In order to consider this request, Dr. Yasuda is requesting further data regarding comparative dissolution using the optimal methodology, as well as dissolution in three other media.

Finally, the Sponsor proposes labeling for Stavzor for the indication of epilepsy in adults and children down to the age of 10. Dr. Yasuda notes that the BE study was performed in adults. She further notes that the label for Depakote ER (extended release) tablets states that the ER tablets were studied in pediatric patients age 10-17 and had plasma valproic acid concentration time profiles similar to those that have been observed in adults. She adds that the labeling of Depakote delayed release tablets, the reference product for this application, states that children over the age of 10 years have PK parameters that approximate those of adults. Since Stavzor (500 mg delayed release capsule) was

bioequivalent to Depakote delayed release tablets in adults, Dr. Yasuda does not expect any significant PK differences in children down to the age of 10 compared with adults. I agree, and I do not believe that pediatric studies are needed to support using a pediatric use of Stavzor identical to that described in the Depakote labeling.

A separate questions is to determine if PREA is triggered by this application. The only difference between Depakote used as comparator in this NDA and Stavzor is that Depakote Delayed Release was a tablet dosage form, and Stavzor as capsule. However, Depakote Delayed Release also exists as a capsule (approved under NDA 19,860), although only in the 125mg strength. Therefore, I believe that PREA does not apply to this application, but this will need to be confirmed before final approval is considered.

Clinical

Because this application is based on bioequivalence, there were very limited clinical data included in the application. Dr. Raman did not identify any significant safety issue in the pivotal bioequivalence study, which was conducted in 36 healthy volunteers.

Dr. Raman also comments that the Sponsor is seeking pediatric waiver as follows based on the indications- Mania (up to 16 years of age), Migraine (up to 16 years of age) and Epilepsy (up to 10 years of age). The RLD, Depakote, is approved for adults (all three indications) and children 10 years or older (for the epilepsy indication).

DSI

The Division of Scientific Investigations declined the request for inspection of the pivotal BE study.

Patent

According to the Orange book, there is no unexpired exclusivities applicable to the RLD and two patents with expiration date of Jan 29, 2008. This issue will need to be revisited if final approval is considered.

Recommendation

I recommend an approvable action. The issues described above must be addressed to support approval, and a satisfactory recommendation from the Office of Compliance regarding the inspection of the various sites is needed.

The following comments should be attached to the action letter:

CMC

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: b(4)

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 F_2 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., ———— ested in 4 ± 2 hour intervals. The Quality Overall Summary dated August 10, 2007, did not reflect this revision. b(4)

OCPB

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).

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Team leader, Neurology

epb
cc:
HFD-120

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

/s/

Eric Bastings
10/26/2007 08:56:07 AM
MEDICAL OFFICER