

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-152

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology Review

NDA:	22-152
Brand Name:	STAVZOR
Generic Name:	Valproic Acid
Type of Dosage Form:	Delayed Release Capsule
Strengths:	125 mg, 250 mg, 500 mg
Indications:	Epilepsy, migraine, mania
Type of Submission:	505(b)(2), new NDA
Sponsor:	Banner
Submission Date:	December 20, 2006 June 1, 2007 July 19, 2007 August 10, 2007 August 22, 2007 August 28, 2007
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
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1 Executive Summary

This NDA review evaluates *in vivo* and *in vitro* data regarding STAVZOR (valproic acid) delayed release capsules (125 mg, 250 mg, and 500 mg) to be indicated for epilepsy, migraine, and mania. The to-be-marketed capsules of the 500 mg strength were used in the pharmacokinetic (BE) study with the reference Depakote (divalproex sodium) delayed release tablets. The difference in the clinical trials capsule and the to-be-marketed 500 mg capsule is a color change that would not be expected to have an effect on performance *in vivo*. 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. Clinical efficacy studies were not conducted.

STAVZOR differs from DEPAKOTE brand of divalproex sodium (delayed release tablets) 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.

A relative bioavailability study comparing the 500 mg strength of STAVZOR with the 500 mg strength of DEPAKOTE met BE criteria. A food effect study with the 500 mg strength capsule demonstrated a food effect on the C_{max} (a 23% decrease) and food resulted in a 2.8 hour delay in median T_{max}.

With respect to the dissolution method and specifications, the sponsor has not justified the use of SDS in the dissolution media and has not shown discriminatory ability of the method to

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detect poorly performing capsules. In addition, since this is a modified release product, dose dumping in alcohol should be evaluated *in vitro*.

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

The Sponsor proposes labeling for STAVZOR for the indication of epilepsy in adults and children down to the age of 10 y.o. The BE study was performed in adults. The label for DEPAKOTE ER (extended release) tablets states that the ER tablets were studied in pediatric patients 10-17 y.o. and had plasma valproic acid concentration time profiles similar to those that have been observed in adults. 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. The Banner product (500 mg delayed release capsule) was BE to Depakote delayed release tablets in adults. Scientifically, we do not expect any significant PK differences in children down to the age of 10.y.o. compared with adults.

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

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology finds that the submitted data in NDA 22-152 is acceptable pending resolution of dissolution issues and information needed to support the biowaiver request for the 125 mg and 250 mg strength capsules.

The Office of Clinical Pharmacology recommends some revisions in the proposed label text. Please refer to Section 5 (page 24).

Please forward the following recommendations regarding dissolution and information required for biowaiver consideration to the Sponsor, along with the labeling comments in *Section 5 (page 24)*. Note that the comments have previously been conveyed to the Sponsor, and the Sponsor is responding to them.

- With respect to the proposed dissolution methodology:
 - The Sponsor has not justified the use of ~~3~~ SDS by showing dissolution data in lower strengths. This should be evaluated at ~~3~~ SDS and in absence of SDS. A request for these dissolution data has been sent to the Sponsor in an email of 7/19/07.
 - The Sponsor has 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 C_{max} 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

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24 months data). The Sponsor was requested in an email of 9/7/07 to discuss the ability of the final proposed method to discriminate poorly performing capsules.

- This information is necessary prior to determining acceptability of the dissolution methodology and specifications.
- 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). This was requested of the sponsor in an email of 7/19/07.
- With respect to the request for biowaiver of the 250 mg and 125 mg strengths:
In order to consider whether a biowaiver of the 250 and 125 mg strengths is possible, the Sponsor has been requested (in an email of 8/23/07) 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. It was further clarified on 8/24/07 that 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).

Clinical Pharmacology Optional Intradivision Briefing:

October 9, 2007

Attendees: Eric Bastings, Silvana Borges, Ramana Uppoor, Mehul Mehta, Sally Yasuda

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Office of Clinical Pharmacology

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

STAVZOR capsules contain valproic acid. STAVZOR therefore differs from DEPAKOTE brand of divalproex sodium (delayed release tablets) 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.

3.2 Current Submission

The present NDA (22-152) has been submitted to support the approval of STAVZOR in the treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure types, and for prophylaxis of migraine headaches. These are the same as the indications for DEPAKOTE. The strengths are 125 mg, 250 mg, and 500 mg. The proposed doses for the three indications are shown in the table below. These are consistent with the labeling for DEPAKOTE tablets.

<i>Indication</i>	<i>Initial Dose</i>	<i>Maximum Recommended Dose</i>
Mania	750 mg daily in divided doses	60 mg/kg/day
Migraine	250 mg twice daily	1000 mg/day
Epilepsy		
• Complex Partial Seizures	10-15 mg/kg/day	60 mg/kg/day
• Simple and Complex Absence Seizures	15 mg/kg/day	60 mg/kg/day

There were no clinical efficacy studies in the present submission. The following clinical pharmacology study has been submitted and reviewed:

- **Study PRACS R05-1643 – Relative** oral bioavailability of STAVZOR 500 mg and DEPAKOTE 500 mg and food effect study on 500 mg strength

The validation and documentation of the bioanalytical methods were acceptable.

The key findings with respect to the clinical pharmacology and biopharmaceutics of STAVZOR are as follows:

- The pharmacokinetic parameters for valproic acid obtained after a single oral 500 mg dose of STAVZOR are in agreement with pharmacokinetic parameters observed following administration of a single 500 mg oral dose of DEPAKOTE.
- A relative bioavailability study comparing the 500 mg strength of STAVZOR with the 500 mg strength of DEPAKOTE met BE criteria.
- The food effect study demonstrated a 23% decrease in C_{max} that fell outside of the BE intervals, but resulted in no change in AUC (extent of exposure). Median T_{max} was delayed by 2.8 hours.
- With respect to the proposed dissolution methodology:
 - The Sponsor has not justified _____ SDS by showing dissolution data in lower strengths. This should be evaluated at 1% and 0.5% SDS and in absence of SDS. A request for these dissolution data has been sent to the Sponsor in an email of 7/19/07.
 - 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). This was requested of the sponsor in an email of 7/19/07.
 - The Sponsor has 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 C_{max} 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). The Sponsor was requested in an email of 9/7/07 to discuss the ability of the final proposed method to discriminate poorly performing capsules.
 - This information is necessary prior to determining acceptability of the dissolution methodology and specifications.
- With respect to the request for biowaiver of the 250 mg and 125 mg strengths:

In order to consider whether a biowaiver of the 250 and 125 mg strengths is possible, the Sponsor has been requested (in an email of 8/23/07) 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. It was further clarified on 8/24/07 that 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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The Division of Scientific Investigations declined the request for inspection of the pivotal BE study. An email of 2/12/07 stated that DSI **did not think they would "be able to do**

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this inspection due to both resource and budget constraints. We have had inspections of PRAC facilities in the past and we may **want to skip it this time**".

The Office of Clinical Pharmacology recommends some revisions in the proposed text. Please refer to Section 5 (*page 25*).

The Office of Clinical Pharmacology finds that the submitted data in NDA 22-152 is acceptable pending resolution of the dissolution issues and request for additional biowaiver information.

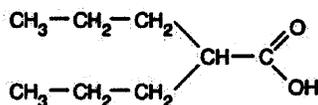
4 Question-Based Review

4.1 General Attributes

4.1.1 *What are the highlights of the chemistry and physical-chemical properties of STAVZOR, and the formulation of the drug product?*

The following information has been extracted from the proposed labeling.

STAVZOR tablets contain valproic acid. The structural formula of valproic acid is:



The empirical formula of valproic acid is C₈H₁₆O₂ and its molecular weight is 144. Valproic acid (pKa 4.8) is a colorless liquid. It is slightly soluble in water and very soluble in organic solvents.

STAVZOR differs from the reference listed drug DEPAKOTE that is divalproex sodium. According to the Sponsor, 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. In addition STAVZOR is formulated as a delayed release capsule whereas DEPAKOTE is a delayed release tablet.

STAVZOR delayed release capsules are clear orange soft gelatin capsules containing a neat fill of 500 mg, 250 mg, or 125 mg valproic acid. The composition of the 125 mg, 250mg, and 500 mg tablets, including inactive ingredients, is shown in the table below from DMF 14194 (provided to the reviewer by Craig Bertha) **and is proprietary information that cannot be shared with the Sponsor.**

4.1.4 What efficacy and safety information contributes to the assessment of clinical pharmacology and biopharmaceutics study data (e.g., can disparate efficacy measurements or adverse events reports be attributed to intrinsic or extrinsic factors that alter drug exposure/response relationships in patients)?

The present submission did not include clinical efficacy trials. According to the labeling for DEPAKOTE, the relationship between valproate plasma concentration and clinical response is not well documented, although the therapeutic range in epilepsy is considered to be 50 to 100 µg/ml. In previous placebo-controlled trials of acute mania, clinical response occurred at trough plasma concentrations between 50 and 125 µg/ml. The present submission did not evaluate dose-dependence of adverse effects. The studies were conducted in healthy volunteers without clinically significant impairment in factors that could alter exposure-response relationships (such as renal or hepatic impairment, congestive heart failure, the extremes of age, or concomitant medications).

4.2 General Clinical Pharmacology

4.2.1 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The present submission did not include studies evaluating pharmacodynamic response to STAVZOR.

4.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moiety, valproic acid, was appropriately identified and measured in the plasma. Please refer to the Bioanalytical Section (4.6).

4.2.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety?

- *Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship for STAVZOR?*

According to the labeling for DEPAKOTE, although the pharmacokinetics of the unbound drug are linear, the relationship between dose and total valproate concentration is nonlinear, with concentration increasing less than proportionally with an increase in dose, due to saturable protein binding. In the present submission for STAVZOR, this was not evaluated.

- *Do PK parameters change with time following chronic dosing?*

There is no data in the label of DEPAKOTE or in the present submission suggesting that PK parameters of valproic acid change with time following chronic dosing.

- *How long is the time to onset and offset of the pharmacological response or clinical endpoint?*

There is no information in either the DEPAKOTE label or in the present submission for STAVZOR regarding time to onset and offset of the response.

- *Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?*

The relationship between dose-concentration-response was not evaluated for STAVZOR. The proposed dosing is in agreement with the dosing regimen for DEPAKOTE.

4.2.4 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

- *What are the basic PK parameters?*

The following table shows the pharmacokinetic parameters for valproic acid obtained from the data submitted in the present NDA (BE study PRACS R05-1643) following single oral doses of STAVZOR (Treatment A fasting, Treatment B fed) or DEPAKOTE (Treatment C fasting) in healthy volunteers.

Pharmacokinetic parameters (arithmetic mean) for Valproic Acid in R05-1643

	Treatment A Test Product Fasting (% CV) n=36	Treatment B Test Product Non- Fasting (% CV) n=36	Treatment C Reference Product Fasting (% CV) n=36
Valproic Acid			
t _{max} (h) ^a	2.0 (0.5-5.00)	4.8 (3.5-12.0)	3.5 (2.00-7.00)
C _{max} (µg/mL)	53.77 (13)	41.5 (18)	55.40 (14)
AUC ₀₋₁ (µg*h/mL)	902.12 (22)	865.3 (22)	932.18 (19)
AUC _{0-inf} (µg*h/mL)	985.80 (21)	947.4 (22)	1014.78 (19)
T _{1/2} (h)	15.12 (18)	15.08 (19)	15.36 (21)

^a median (range)

It can be seen that C_{max}, AUC, and elimination half-life for STAVZOR are in agreement with those parameters for DEPAKOTE. T_{max} for STAVZOR under fasting conditions was slightly earlier than that of DEPAKOTE. (*please refer to individual study reports in Appendix 6.2*).

The pharmacokinetic behavior of STAVZOR has not been evaluated in the target population.

- *Is this a high extraction ratio or a low extraction ratio drug?*

Valproate is considered to have a low hepatic extraction ratio.

- *Does a mass balance study suggest that the major route of elimination is renal or hepatic?*

Valproic acid is extensively metabolized, and the metabolism primarily occurs in the liver. According to the labeling for DEPAKOTE, less than 3% of an administered dose is excreted unchanged in the urine.

4.2.5 What is the inter-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

In healthy volunteers, intersubject variability was approximately 13-18% for C_{max}, 21-22% for AUC, and 18-19% for t_{1/2} after administration of STAVZOR, and this variability was similar to that observed for DEPAKOTE. Pharmacokinetic parameters were not determined in the target population. Potential causes for variability include variability in drug metabolizing enzymes **including uridine 5'-diphosphate-glucuronosyl transferase (UGT)** that is responsible for glucuronidation of valproic acid. Polymorphisms in UGTs have been identified in the literature, but have not been carefully evaluated with respect to valproic acid pharmacokinetics.

4.3 Intrinsic Factors

4.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

The proposed age range is adults and children 10 years of age and older.

The pharmacokinetics of valproate have been previously studied in special populations and the influence of intrinsic factors on exposure can be found in the label for DEPAKOTE (and repeated in the proposed label for STAVZOR) as outlined below.

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4.3.2 *Based upon what is known about exposure-response relationships and their variability, and the groups studied, what dosage regimen adjustments, if any, are recommended for each of these subgroups?*

Elderly – **The labeling of DEPAKOTE states** that initial dosage should be reduced in the elderly. It does not give specific guidelines for dosage adjustment other than suggesting a reduction in starting dose and increasing the dose more slowly. This recommendation is extended to the proposed labeling of STAVZOR . In addition the labeling states that there is insufficient information available to discern the safety and effectiveness for prophylaxis of migraines in patients over 65.

Pediatrics

In epilepsy, specific dosing guidelines for children 10 years of age and older are the same as for adults. In the PRECAUTIONS section of the label as well as in a black box warning, it is stated that when STAVZOR is used in children under the age of 2 years, it should be used with extreme caution and as the sole agent. The label also states in the PEDIATRIC USE section that younger children, especially those receiving enzyme-inducing drugs, will require larger maintenance doses to attain targeted total and unbound valproic acid concentrations. This information is consistent with the DEPAKOTE label.

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Renal Impairment – **There are no recommendations to adjust** dosing in renal impairment in the label of DEPAKOTE or in the proposed STAVZOR label.

Hepatic Impairment – The DEPAKOTE label _____ state that these drugs should not be administered to patients with hepatic disease or significant hepatic dysfunction.

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Pregnancy and Lactation – The proposed STAVZOR label reflects the labeling for DEPAKOTE and states that valproic acid may produce teratogenic effects including neural tube defects. There is a black box warning regarding teratogenicity. It is recommended that antiepilepsy drugs be administered to women of childbearing potential only if they are clearly shown to be essential in the management of their seizures. Consideration should be given to discontinuing nursing when this drug is administered to a nursing woman.

4.4 Extrinsic Factors

4.4.1 *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?*

The label for DEPAKOTE (and extended to STAVZOR) does not refer to extrinsic factors other than drugs that influence exposure/response to valproate.

4.4.2 *Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.*

Discussion of drug-drug interactions can be found in section 4.4.3, below.

4.4.3 Drug-Drug Interactions

4.4.3.1 **Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions with STAVZOR that are mediated by CYP450?**

According to the DEPAKOTE label (extended to the proposed STAVZOR label), *in vitro* studies suggest that valproate is primarily metabolized by mitochondrial β -oxidation and by glucuronidation. P450-dependent oxidation and other pathways are considered to be minor.

Although valproate affects the pharmacokinetics of several drugs that are primarily metabolized by P450s, the effects of valproate on P450s have not been well characterized. The reviewer has identified an *in vitro* study demonstrating inhibition of CYP2C9 in human liver microsomes by valproate at clinically relevant concentrations (Wen et al. Br J Clin Pharmacol 2001; 52:547-53). With a K_i of 600 μ M and plasma concentrations of 100 μ g/ml (694 μ M), the I/K_i value is approximately 1.2 and therefore inhibition of CYP2C9 is likely *in vivo*. The DEPAKOTE label and proposed STAVZOR label state that valproate is a weak inhibitor of some P450 isozymes. The potential for inhibition of phenytoin metabolism is identified in the labeling. Potential for interaction is only identified as *in vitro* protein displacement interactions for CYP2C9 substrates tolbutamide and warfarin.

4.4.3.2 Is valproate an inducer of CYP enzymes?

Valproate is not known to induce P450 enzymes.

4.4.3.3 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Valproate is not known to be a substrate or inhibitor of P-glycoprotein.

4.4.3.4 Are there other metabolic/transporter pathways that may be important in the pharmacokinetics of valproate?

The major elimination pathways for valproate are mitochondrial β -oxidation and glucuronidation.

There is *in vitro* evidence that valproate inhibits glucuronidation of zidovudine in a concentration-dependent manner. (Trapnell CB, Klecker RW, Jamis-Dow C, Collins JM. *Antimicrob. Agents Chemother.* 1998;42: 1592). The DEPAKOTE label and the proposed STAVZOR label refer to a 38% decrease in zidovudine clearance after administration of valproate in humans.

4.4.3.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Valproic acid is indicated for use as monotherapy or as adjunctive therapy in epilepsy. According to the label, in a study of adjunctive therapy for complex partial seizures in which patients were receiving either carbamazepine or phenytoin in addition to DEPAKOTE, no adjustment of carbamazepine or phenytoin dosage was needed. However, the DEPAKOTE and proposed STAVZOR labels (Dosage and Administration) also state that as dosage is titrated upward, concentrations of phenobarbital, carbamazepine, and/or phenytoin may be affected.

Other potential interactions with AEDs that are noted in the label for DEPAKOTE include the following. Concomitant use of valproic acid and clonazepam may induce absence seizures in patients with a history of absence seizures. Valproate increases the free fraction of diazepam, and decreases the plasma clearance and volume of distribution for free diazepam. Valproate inhibits the metabolism of ethosuximide (monitoring is recommended), and increased the elimination half-life of lamotrigine (lamotrigine dosage reduction is recommended), and inhibited the metabolism of Phenobarbital (monitoring for neurological toxicity recommended). Valproate displaces phenytoin from its albumin binding sites and inhibits its hepatic metabolism, resulting in an increase in the free fraction of phenytoin, with a decrease in clearance and apparent volume of distribution of free phenytoin.

In addition, the AEDs phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of valproate, due to increased expression of hepatic enzymes (particularly glucuronosyltransferases).

4.4.3.6 What other co-medications are likely to be administered to the target patient population?

In addition to drugs used to treat epilepsy, these medications could include HIV medications, oral contraceptives, and medications used to treat migraine or mania.

4.4.3.7 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

According to the DEPAKOTE label and proposed STAVZOR label, aspirin decreased protein binding and inhibited metabolism of valproate in children, with a 4-fold increase in valproate free fraction. Felbamate increased valproate peak concentrations. Rifampin increased the oral clearance of valproate. Therefore, according to the label, co-administration with these medications requires caution and possible dosage adjustment.

Valproate increases the elimination half-life of lamotrigine from 26 to 70 hours and the dose of lamotrigine should be reduced when coadministered with valproate. Serious skin reactions such as Stevens - Johnson syndrome and toxic epidermal necrolysis have been reported with concomitant lamotrigine and valproate administration. Valproate decreases clearance of amitriptyline and nortriptyline, and monitoring and consideration of dosage adjustment are recommended. *In vitro* studies suggest the potential for increasing the free fraction of either tolbutamide or warfarin, (both CYP2C9 substrates) and the label recommends monitoring of coagulation tests if valproic acid is given with anticoagulants. Zidovudine clearance was decreased by valproate, with no effect on half-life. Valproate had no effect on the steady-state pharmacokinetics of lithium, and no pharmacokinetic interaction was observed after administration of a single-dose of ethinylestradiol (50 µg)/levonorgestrel (250 µg) in women taking valproate 200 mg bid for 2 months.

4.4.3.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

The label describes severe CNS depression when barbiturate or valproate are co-administered, even without elevations in the concentrations of either drug.

4.4.3.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

There are no unresolved questions in this regard that impact acceptability of data in the present NDA. However, as more information about UGT polymorphisms and UGT-mediated drug interactions becomes available, their role in the pharmacokinetics of valproic acid should be examined.

4.4.4 What issues related to dose, dosing regimen, or administration are unresolved, and represent significant omissions?

There are no significant omissions or issues regarding dosing that affect the acceptability of the data in the present NDA.

4.5 General Biopharmaceutics

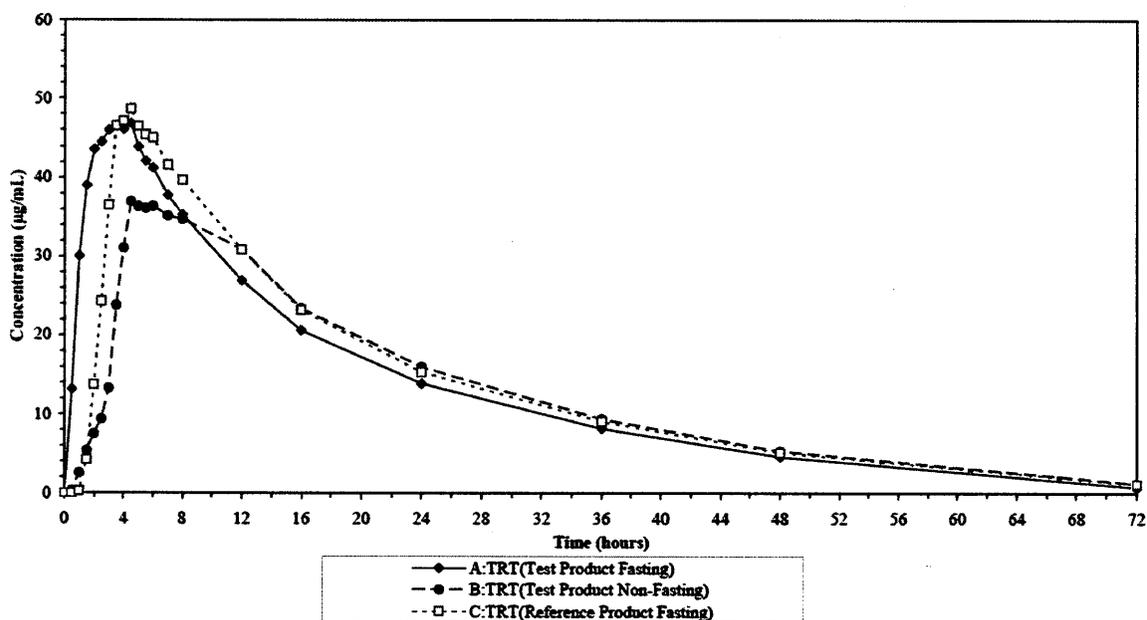
4.5.1 *If the NDA is for a modified release formulation of an approved immediate product without supportive safety/efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

This NDA is for a delayed release product that is compared to the commercially available DEPAKOTE that is also a delayed release product. Although these are given as different drug products (STAVZOR is valproic acid and DEPAKOTE is divalproex sodium), both dissociate in the GI tract to valproate ion, the active moiety, and have the same dosing regimen.

- *What is the bioavailability of STAVZOR relative to DEPAKOTE delayed release tablets?*

Bioequivalence between STAVZOR 500 mg capsules and DEPAKOTE 500 mg tablets under fasting conditions has been demonstrated. Study PRACS R05-1643 evaluated the relative bioavailability of a single dose of STAVZOR 500 mg capsules (test) to DEPAKOTE 500 mg tablets (reference) under fasting conditions in 36 healthy subjects. (The study also included a food effect arm for STAVZOR). For the full study report please refer to the Appendix section 6.2.

The mean plasma concentration time course and pertinent pharmacokinetic parameters for valproic acid are shown in the Figure and Table below.



Pharmacokinetic parameters (arithmetic mean) for Valproic Acid in R05-1643

	Treatment A Test Product Fasting (% CV) n=36	Treatment B Test Product Non- Fasting (% CV) n=36	Treatment C Reference Product Fasting (% CV) n=36
Valproic Acid			
t _{max} (h) ^a	2.0 (0.5-5.00)	4.8 (3.5-12.0)	3.5 (2.00-7.00)
C _{max} (µg/mL)	53.77 (13)	41.5 (18)	55.40 (14)
AUC _{0-t} (µg*h/mL)	902.12 (22)	865.3 (22)	932.18 (19)
AUC _{0-inf} (µg*h/mL)	985.80 (21)	947.4 (22)	1014.78 (19)
T _{1/2} (h)	15.12 (18)	15.08 (19)	15.36 (21)

^a median (range)

The 90% confidence intervals on the geometric means of the C_{max}, AUC_{last}, and AUC_{0-∞} ratios for STAVZOR 500 mg vs DEPAKOTE 500 mg under fasting conditions are within the bioequivalence interval of 0.8 to 1.25 for valproic acid. The median t_{max} for STAVZOR (Treatment A) was 1.5 hr earlier than that for DEPAKOTE (Treatment C). The clinical relevance of this in an individual patient has not been evaluated, although it should be noted that this difference was not accompanied by a statistically significant mean change in exposure as shown above.

The Sponsor has requested biowaivers for the 250 and 125 mg strength STAVZOR capsules. (Please refer to section 4.5.7, page 21 below for a consideration of the request for biowaiver).

- *What dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?*

Single doses of the 500 mg strength of STAVZOR resulted in comparable exposure to the respective strength of DEPAKOTE. Therefore, dosage regimen changes are not expected to be necessary for the 500 mg capsules, although information is not available for the lower strength capsules.

4.5.2 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

BCS-based waivers do not apply in the case of a modified release product.

4.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

This NDA did not include a pivotal clinical trial. The proposed to-be-marketed formulation of the 500 mg capsule is identical to the formulations used in the present submission to evaluate bioavailability relative to DEPAKOTE, except for the _____ and would be expected to result in the same exposure. The 250 mg and 125 mg strengths used in dissolution studies to request the biowaiver are the same as the to-be-marketed except for _____ (like the 500 mg strength), as communicated in the Sponsor's submission of 8/22/07.

b(4)

4.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

Food effect (high fat meal) was included as a third arm of Study PRACS R05-1643, discussed above in Section 4.5.1. The dosage strength used is the highest proposed strength of this product. The results (mean plasma concentration time course and pharmacokinetic parameters) are shown in Section 4.5.1.

When STAVZOR 500 mg capsules are given with a high fat meal, there is a 23% decrease in C_{max} compared to when STAVZOR is given under fasting conditions, although AUC does not change. For C_{max} the 90% confidence interval ratio of geometric means for fed vs fasting is 72.9-80.53% and falls outside of the BE interval. Median t_{max} under fed conditions is 4.8 hours compared to 2 hours under fasting conditions.

According to the labeling for DEPAKOTE, food resulted in an increase in T_{max} from 4 hours to 8 hours for the DEPAKOTE tablets.

- *What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?*

The label should describe the PK differences between fed and fasting.

4.5.5 When would a fed BE study be appropriate and was one conducted?

A fed BE study is not necessary in this case.

4.5.6 How do the dissolution conditions and specifications assure in vivo performance and quality of the product?

Dissolution method development is reviewed in the Appendix, Section 6.2.3. *In vitro* dissolution specifications were based on lots from the clinical trial formulations in the case of the 500 mg strength tablet that was the same lot used in the bioavailability study. The 125 mg and 250 mg strength capsules also used in dissolution method development, as well as the 500 mg strength capsules, are the same as the to-be-marketed except for _____ that would not be expected to have an effect on performance.

b(4)

The Sponsor has proposed the following dissolution method and specifications.

Apparatus:	USP Apparatus 2 (Paddles)
Medium:	Acid Stage: 0.08 N HCl
	Buffer Stage: _____
	_____ pH 7.5
Volume:	900 ml
Temperature:	37 ± 0.5 °C
Rotation Speed:	50 rpm
Sampling time:	1 hour
Specification:	Acid Stage: Not more than _____
	Buffer Stage: Not less than Q _____

b(4)

b(4)

The dissolution profile reasonably reflects the *in vivo* plasma concentration time course where range for tmax is 0.5-5hr and median is 2 hrs.

The Sponsor has been asked (in an email of 7/19/07) to justify the _____ SDS, and evaluate dissolution in the absence of SDS and in the presence of 0.5% and 1%. In addition, the proposed dissolution method has not been evaluated with respect to ability to discriminate poorly performing capsules due to _____

b(4)

The Office of Clinical Pharmacology does not find the proposed dissolution method acceptable without the justification outlined in the paragraph above.

4.5.7 *Are different-strength formulations bioequivalent based on standard criteria? What clinical safety and efficacy data support the approval of the various strengths of the to-be-marketed product?*

There were no bioequivalence studies to compare the 125 mg, 250 mg, and 500 mg dosage strengths of STAVZOR to each other. The Sponsor has requested a biowaiver of the 125 mg and 250 mg strengths. Additional data to be considered include differences in composition of the lower strength capsules and dissolution studies to evaluate similarity of the lower strength capsules to the 500 mg capsules. The results are discussed below.

- *How are the 125 mg, 250 mg, and 500 mg dosage strengths comparable?*

The composition of the three dosage strengths of the commercial formulation of STAVZOR is shown below (_____)

_____ The three strengths are not compositionally proportional as total capsule. The capsule composition is given below from DMF 14194 (provided to the reviewer by Craig Bertha) **and is proprietary information that cannot be shared with the Sponsor.**

Ingredient	Functionality	Weight/capsule			% w/w		
		500 mg	250 mg	125 mg	500 mg	250 mg	125 mg
Capsule Fill							
Valproic Acid, USP	Active	500 mg	250 mg	125 mg			
Capsule shell							
³ Gelatin							
³ Glycerin							
_____ methacrylic acid copolymer							
⁵ Triethyl citrate							
⁴ Ammonium hydroxide							
_____ water							
FD&C yellow #6							
Black Printing Ink							
² Total Dry Shell Weight in mg							
³ Total Dry Capsule Weight in mg							
² Theoretical weight. ⁴ Calculation error of one decimal from previous qualitative composition statement. ⁵ Slight calculation changes due to the above error in calculation of ammonium hydroxide form previous qualitative composition statement.							

b(4)

b(4)

STAVZOR Valproic Acid delayed release capsules have the enteric polymer as an inherent component of the shell matrix, rather than as a coating of the softgel capsule. The three dosage strengths differ in the total weight of the release controlling excipient

b(4)

Based on the quantitative composition, the % difference between the 125 mg capsules and the 500 mg capsule in the total release controlling excipients is _____ and the difference between the 250 mg capsule and the 500 mg capsule is _____. According to the Guidance for Industry SUPAC-MR: Modified Release Solid Oral Dosage Forms, changes in the release controlling excipient are expressed as percentage (w/w) of the total release controlling excipients in the formulation. Changes greater than 10% w/w of total release controlling excipient content in the modified release solid oral dosage form that was the original formulation would be considered a Level 3 change and would require BE documentation. Therefore, the 125 mg capsule would not meet criteria for a biowaiver. A similar situation exists for the 250 mg strength capsule.

b(4)

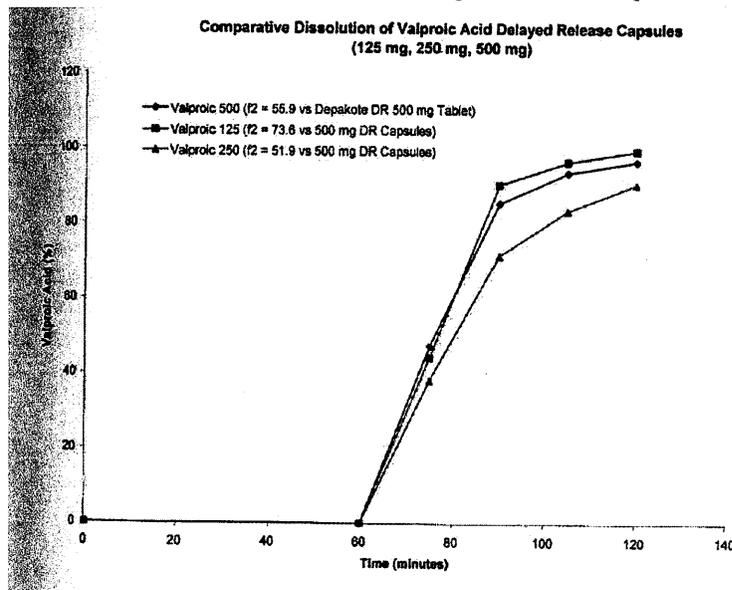
However, other factors can be included in determining whether a request for biowaiver could be considered. The capsule content is neat drug. In this product, the release controlling excipient is a part of the softgel capsule and is present at the same percentage of capsule weight across the strengths. In addition, the thickness of the capsule shell wall is the same across strengths. Therefore, the Office of Clinical Pharmacology believes it is acceptable to consider a biowaiver request.

- *What bioequivalence data supports the approval of the various strengths of STAVZOR?*

There are no BE data to support approval of the 125 mg and 250 mg strengths.

- *What data support granting of the biowaiver for the lower strength capsules?*

The Sponsor has provided dissolution comparisons between the 125 mg and 500 mg strengths and between the 250 mg and 500 mg capsule strengths using the proposed dissolution method. Mean data are shown in the figure below, as provided by the Sponsor.



For similarity comparisons for the 125 mg capsules vs 500 mg capsules, the similarity factor (f2) is 73.6 and the difference factor (f1) is 4.36. For the 250 mg strength capsule, f2 is 51.94 and f1 is 12.15. These values would allow the 125 mg and 250 mg strengths to be considered similar to the 500 mg strength capsule, if the SUPAC guidelines were not applied.

In addition to these data, the Sponsor believes that the biowaiver is justified since the rate determining step for release for valproic acid from the capsule is rupture of the barrier shell _____

_____ The % of shell ingredients that is the release controlling excipient is the same in all strength _____

b(4)

- *Can a biowaiver of the 125 mg and 250 mg strengths be granted?*

At this time, an optimal dissolution method has not been identified for this product. Therefore, data in multiple pH media are necessary. In order to consider whether a biowaiver of the 250 and 125 mg strengths is possible, the Sponsor has been requested (in an email of 8/23/07) to provide dissolution data and comparisons for all 3 strengths (using 12 units of each strength) in multiple media. This should include your 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 _____ 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.

4.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the approved product demonstrated? What is the basis for using either in vitro or in vivo data to evaluate BE?

The only product used was the already approved DEPAKOTE.

4.5.9 What other significant, unresolved issues related to in vitro dissolution or in vivo BA and BE need to be addressed?

- The Sponsor has not justified the _____ SDS by showing dissolution data in lower strengths. This should be evaluated at _____ SDS and in absence of SDS. A request for these dissolution data has been sent to the Sponsor in an email of 7/19/07.
- 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). This was requested of the sponsor in an email of 7/19/07.
- The Sponsor has 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

b(4)

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).

4.5.10 If replicate design studies were conducted and individual BE was analyzed, what were the outcomes with respect to variability and subject-by-formulation interactions?

These studies were not conducted for STAVZOR.

4.6 Bioanalytical Method

4.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Analysis of plasma concentrations of valproic acid was performed using a high performance liquid chromatography with tandem mass spectrometry (LC-MS/MS). A detailed description of the method is found in the Appendix, Section 6.2.2.

4.6.2 Which metabolites have been selected for analysis and why?

Metabolites have not been selected for analysis. This is consistent with other studies of valproic acid.

4.6.3 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Although valproic acid is highly protein bound, the literature and labeling for DEPAKOTE reflect measures of total valproic acid rather than free. Therefore, the assay of total valproic acid in the present submission is consistent with the previous studies of DEPAKOTE, and will allow consistency in evaluation of the data and in the labeling. In addition, in the bioequivalence study each subject was his own control, and therefore the free fraction of valproate would not be expected to differ between the periods of drug administration.

4.6.4 What bioanalytical methods are used to assess concentrations?

- *What is the range of the standard curve and how does it relate to the requirements for the clinical studies?*

For the LC/MS/MS valproic acid assay, linearity was established over the range of _____ μg/ml to _____ g/ml. The highest plasma concentration following administration in the BE study was approximately _____ g/ml, and concentrations were therefore bracketed by the standard curve.

b(4)

Is the bioanalytical method adequately documented and validated?

The bioanalytical method is adequately documented and validated, and the performance of the assays for the clinical pharmacology studies is considered acceptable.

5 Detailed labeling recommendations (only the changed sections are included here)

[*Note from reviewer.* only the highlights, warnings, and sections 2, 3, 4, 5.10, 7, 8, and 12 have been reviewed from a clinical pharmacology perspective. In addition, dosage forms and strengths, dosing, and how supplied, depend on whether the 125 mg and 250 mg strength capsules can be approved.]

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

6 Appendices

- 6.1 *Sponsor Proposed Package Insert With OCP Comments Highlighted (Note: dosage forms and strengths, dosing, and how supplied have not been changed here, but depend on whether 125mg and 250 mg strength capsules can be approved).*

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

6.2 Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

6.2.1 RELATIVE BIOAVAILABILITY OF STAVZOR 500 MG AND DEPAKOTE 500 MG

A RELATIVE BIOAVAILABILITY STUDY OF 500 MG VALPROIC ACID DELAYED RELEASE CAPSULES VS 500 MG DIVALPROEX SODIUM DELAYED-RELEASE TABLETS UNDER FASTING AND NON-FASTING CONDITIONS

Study Investigators and Site:

James D. Carlson, PharmD, Principal Investigator
PRACS Institute, Ltd.
Fargo, ND 58104 and East Grand Forks, MN 56721

Protocol Number: PRACS R05-1643

OBJECTIVE:

To compare the relative bioavailability (rate and extent of absorption) of Valproic Acid Enteric 500 mg Softgel (by Banner Pharmacaps, Inc) with that of Depakote Delayed Release Tablets 500 mg (Abbott) following a single 500 mg oral dose in healthy adult volunteers under fasting conditions. In addition, this study compared differences in serum levels after dosing the test Valproic Acid Enteric 500 mg Softgel with and without food.

FORMULATIONS:

Table 1. Product used in PRACS R05-1643

	Batch Number	Date of Manufacture (Dates of study)
Valproic Acid Enteric 500 mg Softgel Banner Pharmacaps, Inc	XPP0409010	10/04 (3/4/06-3/22/06)
Depakote Delayed Release 500 mg Tablets Abbott Pharmaceuticals PR Ltd.	31269AA21	Exp. Date 10/1/08 (3/4/06-3/22/06)

STUDY DESIGN:

This was a randomized, single-dose, three-way crossover study evaluating the relative bioavailability of Valproic Acid Enteric 500 mg Softgel with that of Depakote Delayed Release Tablets 500 mg following a single oral dose (1x500 mg) under fasting conditions. In addition, the study compared difference in serum levels after dosing the test Valproic Acid Enteric 500 mg Softgel with and without food.

On Day 1 following overnight fast of at least 10 hours, subjects received a single oral dose of either the test Valproic Acid Enteric 500 mg Softgel (Treatment A) or the reference Depakote (Treatment C) with 240 ml water as per the randomization scheme. For subjects dosed with test product under non-fasting conditions (Treatment B), a standardized high fat breakfast (the FDA

high fat breakfast) was served 30 minutes prior to dose administration. All subjects fasted for at least 4.25 hours after dosing, except that at 2 hours post-dose subjects consumed 240 ml of water. Blood samples were collected within 1 hour prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 12, 16, 24, 36, 48, and 72 hours post-dose. Serum was stored at -20° C or colder until transferred for analysis. The Treatment Periods were separated by 7 days.

Inclusion criteria included healthy males or females 18 years of age or older. Females could be included if they were postmenopausal for at least 1 year or surgically sterile for at least 6 months. Exclusion criteria included current use of tobacco products, use of any drug known to induce or inhibit hepatic drug metabolism in the 28 days prior to Period 1 dosing, and volunteers who reported taking any systemic prescription medication in the 14 days prior to Period 1 dosing. Subjects were required to abstain from consuming grapefruit products, caffeine- and or xanthine-containing products, and alcohol for at least 48 hours prior to days on which dosing was scheduled and during the periods when blood samples were collected.

ASSAY:

Serum samples were analyzed at PRACS Institute, Ltd. Bioanalytical Laboratory.

Table 2. Performance of Analytical Method for R05-1643 for Serum Valproic Acid

Analyte	Method	Calibration Standards (µg/ml)	Linearity	LOQ (µg/ml)	QC (µg/ml)	Inter-assay CV (%)	Inter-assay Accuracy (%)
Valproic Acid	LC-MS/MS	2.0-100.0	r > 0.998	2.0	6.0	2.56	-0.5
					25.0	2.17	0.36
					50.0	2.48	-0.56
					80.0	1.94	2.4

Samples were stored at -20 °C and used within the 75-day period for which they are stable at that temperature (sample analysis ended on April 7, 2006). Duplicate calibration curves and four QC samples were analyzed with each batch of study samples for Study R05-1643 for detection of valproic acid in serum. A weighted ($1/x^2$) linear regression was used for the standard curve. Inter-assay accuracy and precision of the calibration standards were acceptable, and all calibration samples were within 15% of the nominal concentration. For the QC samples, only 1 sample was outside of the acceptable range. Inter-assay precision and accuracy for the QC samples are shown above. The performance of the assay is considered acceptable.

RESULTS:

Demographics

Thirty-six subjects were enrolled and completed the study. Demographics of those subjects are shown in the table below, as provided by the Sponsor. There was 1 Asian and there were 35 Caucasians (3 of whom were Hispanic or Latino).

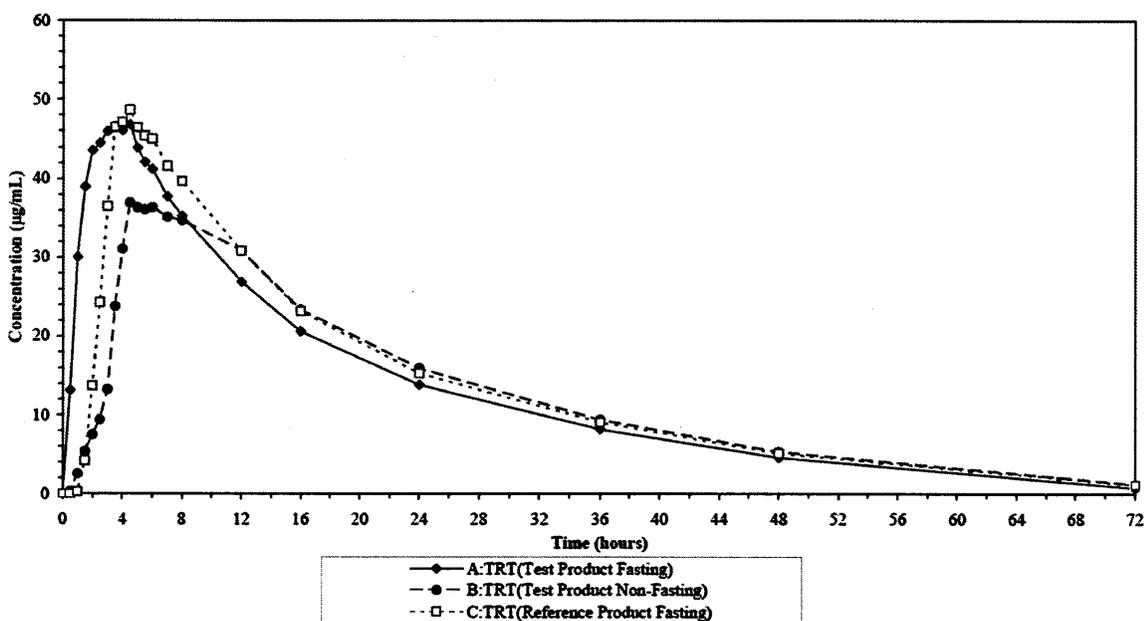
Table 3. Demographics of Subjects Completing Study PRACS R05-1643

	All Subjects (N=36)	Males (N=30)	Females (N=6)
Age	32.1 (±13.7)	28.1 (±11.1)	52.5 (±3.4)
Weight (lbs)	172.8 (±23.5)	175.6 (±22.0)	158.7 (±27.4)
Height (in.)	69.6 (±3.4)	70.6 (±2.6)	64.7 (±2.4)
BMI	25.1 (±2.9)	24.8 (±2.7)	26.6 (±3.6)

The only concomitant medication taken was ibuprofen taken by 1 subject over the course of the study.

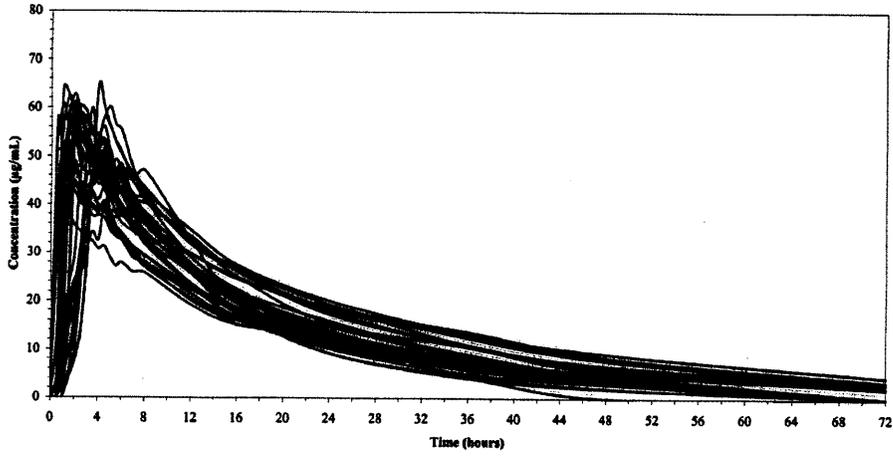
Valproic Acid Serum Concentrations

The mean valproic acid serum concentration time course from each treatment is shown in the figure below, as provided by the Sponsor.

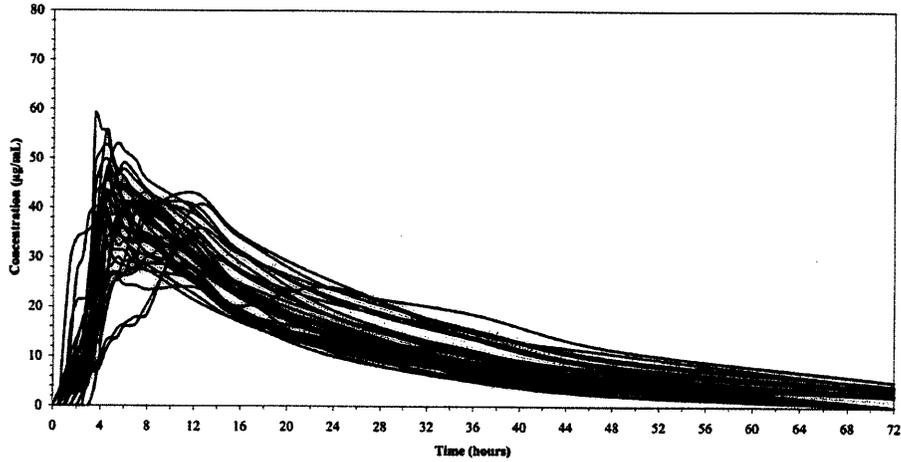


The following plots show concentration time course for each subject for the 3 treatments, as provided by the Sponsor.

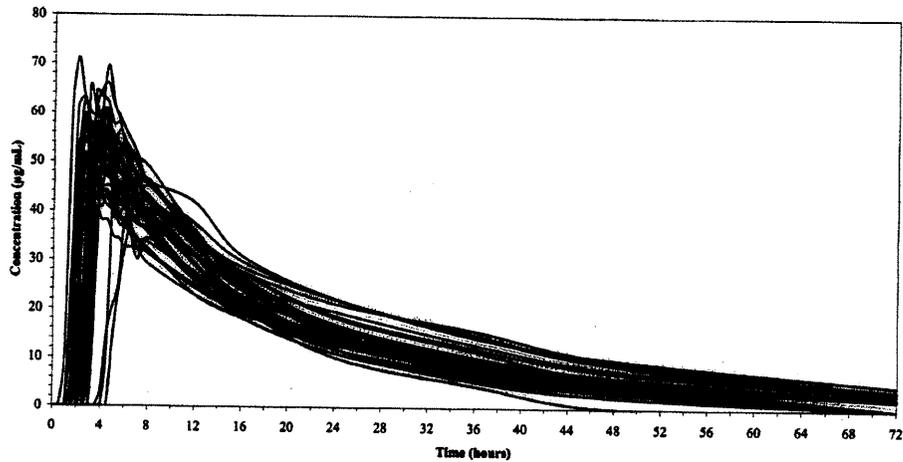
Serum Concentrations (0 - 72 hours) for Each Subject
Treatment A (Test Product Fasting)
N=36



Serum Concentrations (0 - 72 hours) for Each Subject
Treatment B (Test Product Non-Fasting)
N=36



Serum Concentrations (0 - 72 hours) for Each Subject
Treatment C (Reference Product Fasting)
N=36



Pharmacokinetic parameters were determined using noncompartmental analysis. The pertinent pharmacokinetic parameters for valproic acid during each treatment are shown in the table below (as reported by the Sponsor and confirmed by the reviewer).

Table 4. Pharmacokinetic parameters (arithmetic mean) for Valproic Acid in R05-1643

	Treatment A Test Product Fasting (% CV) n=36	Treatment B Test Product Non- Fasting (% CV) n=36	Treatment C Reference Product Fasting (% CV) n=36
Valproic Acid			
t _{max} (h) ^a	2.0 (0.5-5.00)	4.8 (3.5-12.0)	3.5 (2.00-7.00)
C _{max} (µg/mL)	53.77 (13)	41.5 (18)	55.40 (14)
AUC _{0-t} (µg*h/mL)	902.12 (22)	865.3 (22)	932.18 (19)
AUC _{0-inf} (µg*h/mL)	985.80 (21)	947.4 (22)	1014.78 (19)
T _{1/2} (h)	15.12 (18)	15.08 (19)	15.36 (21)

^a median (range)

The bioequivalence comparisons are shown in the tables below.

Table 5. Bioavailability Ratios for Valproic Acid (Treatment A, Test) vs Depakote (Treatment C , Reference) in Study R05-164343

	Geometric Mean		Ratio of Geometric Means (% Reference)	90% CI for the Ratio of Geometric Means
	Treatment C Depakote Product Fasting (REFERENCE)	Treatment A Banner (Test) Product Fasting (TEST)		
Valproic Acid				
C _{max} (µg/ml)	54.86	53.35	96.47	(92.69-100.41%)
AUC _{0-t} (µg*h/ml)	916.05	882.90	96.35	(94.31-98.42%)
AUC _{0-inf} (µg*h/ml)	997.52	966.67	97.31	(95.31-99.34%)

Table 6. Bioavailability Ratios for Valproic Acid Fasting vs With Food in Study R05-1643

	Geometric Mean		Ratio of Geometric Means (% Reference)	90% CI for the Ratio of Geometric Means
	Treatment A Banner (Test) Product Fasting (REFERENCE)	Treatment B Banner (Test) Product With Food (TEST)		
Valproic Acid				
C _{max} (µg/ml)	53.35	40.84	76.64	(72.94-80.53%)
AUC _{0-t} (µg*h/ml)	882.90	845.97	95.88	(93.96-97.85%)
AUC _{0-inf} (µg*h/ml)	966.67	926.80	95.89	(94.10-97.72%)

The bioequivalence comparisons for valproic acid for Test vs Depakote under fasting conditions fall within the BE intervals of 80-125% for C_{max} and AUC. When the test product is given with a high fat meal, there is a 23% decrease in C_{max}, although AUC does not change.

Safety

Eight subjects experienced a total of 10 adverse events (2 subjects receiving Test drug under fasting conditions, 4 receiving test drug under non-fasting conditions, and 2 subjects receiving reference product, resulting in 3, 5, and 2 adverse events in each of those groups, respectively). Adverse events were mild to moderate in severity. Adverse events for the test product under fasting conditions were headache and nausea in test drug fasting; nausea, back pain or pain in extremity, and nasopharyngitis in test drug nonfasting; and dizziness for reference product.

CONCLUSIONS:

The 500 mg strength of the Banner (test) product is bioequivalent to Depakote delayed release tablets given under fasting conditions.

Food delays the median tmax of the Banner product by approximately 2.8 hours and reduces the Cmax by approximately 23%, with no change in the AUC. The Cmax under fed conditions falls outside of the 80-125% BE limits compared to when the capsule is given under fasting conditions.

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

NDA 22-152
STAVZOR

6.3 Consult Reviews (Including Pharmacometric Reviews)

There were no consults in the present OCP review.

6.4 Cover Sheet and OCP Filing/Review Form

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-152	Brand Name		
OCP Division (I, II, III, IV, V)	DCP I	Generic Name	Valproic Acid	
Medical Division	HFD-120	Drug Class	Anticonvulsant	
OCP Reviewer	Sally Usdin Yasuda, MS, PharmD	Indication(s)	Manic episodes associated with bipolar disorder, seizures, migraine	
OCP Team Leader	Ramana Uppoor, PhD	Dosage Form	Delayed Release Capsules, 500 mg and 125 mg	
		Dosing Regimen	Mania: 750 mg qd (divided doses) Epilepsy: Adults and children 10 y.o. and older initiate therapy at 10-15 mg/kg/day Migraine: Starting dose is 250 mg twice daily	
Date of Submission	12/20/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	9/3/07	Sponsor	Banner Pharmacaps, Inc	
PDUFA Due Date	10/22/07	Priority Classification	Standard	
Division Due Date	9/20/07			
<u>Clin. Pharm. and Biopharm. Information</u>				
<p>Summary: This NDA, submitted under section 505 (b)(2) is for valproic acid delayed release capsules. The reference listed drug is Depakote (divalproex sodium) that is available as 500 mg, 250 mg, and 125 mg tablets (NDA 18-723). The pharmacology, toxicology, microbiology, statistical, and clinical portions of this application rely solely on the RLD. The Sponsor has conducted a single BE study comparing the 500 mg capsules to Depakote 500 mg tablets (fasting) and comparing 500 mg capsules fed vs fasted. The clinical study and bioanalytical assay were performed by the CRO, PRACS. A biowaiver is requested for the 125 mg strength product. The Sponsor states that no alternative formulations were investigated. The drug product is a delayed-release soft gelatin capsule containing valproic acid solution. The biobatch (Lot # XPP0409010) is the same as the to-be-marketed capsules except for b(4)</p> <p>_____ that would not be expected to impact performance. Based on the quantitative composition from the DMF, there is more than a 10% change in release controlling excipients for the 125 mg strength compared to the 500 mg strength, and therefore a biowaiver is not possible (see composition in appendix). At the pre-NDA meeting, the Sponsor was told to evaluate dissolution in 3 different media, and that adequate justification of the selected method should be provided. The internal note in the OCP meeting review states that the Sponsor will evaluate other pHs and provide adequate justification of the selected method.</p>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			Only available as paper copy
Reference Bioanalytical and Analytical Methods	X	1		
I. Clinical Pharmacology				
Mass balance:	-	-	-	
Isozyme characterization:	-	-	-	

Blood/plasma ratio:		-	-	
Plasma protein binding:	-	-	-	
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	1	1	Pivotal BE study comparing 500 mg valproic acid (Banner) vs depakote, and fed vs fasting for Banner product
multiple dose:	-	-	-	
<i>Patients-</i>				
single dose:	-	-	-	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	-	-	-	
fasting / non-fasting multiple dose:	-	-	-	
Drug-drug interaction studies -				
In-vivo effects on primary drug:	-	-		
In-vivo effects of primary drug:	-	-		
In-vitro:			-	
Subpopulation studies -				
ethnicity:		-	-	
gender:	-	-	-	
pediatrics:	-	-	-	
geriatrics:	-	-	-	
renal impairment:	-	-	-	
hepatic impairment:	-	-	-	
PD:				
Phase 2:	-	-	-	
Phase 3:	-	-	-	
PK/PD:				
Phase 1 and/or 2, proof of concept:	-	-	-	
Phase 3 clinical trial:	-	-	-	
Population Analyses -				
Data rich:	-	-		
Data sparse:	-	-		
II. Biopharmaceutics				
Absolute bioavailability:	-	-	-	
Relative bioavailability -				
solution as reference:	-	-	-	
alternate formulation as reference:	-	-	-	Depakote as reference
Bioequivalence studies -				
traditional design; single / multi dose:	-	-		
replicate design; single / multi dose:	-	-	-	
Food-drug interaction studies:	X	1	1	See above description of pivotal BE study
Dissolution:	X	1	2	Also requests biowaiver for lower strength capsules
(IVIVC):	-	-		
Bio-waiver request based on BCS	-	-		
BCS class	-			
III. Other CPB Studies				
Genotype/phenotype studies:	-	-	-	
Chronopharmacokinetics	-	-	-	
Pediatric development plan	-	-	-	

Literature References	-	-	-	
Total Number of Studies		3	4	BE/Food effect, dissolution method, bioanalytical assay method; biowaiver request
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	X	Reasons if the application is <u>not</u> filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?		
Comments sent to firm ?		<p>Comments have been sent to firm (or attachment included). FDA letter date if applicable.</p> <p>Please forward to sponsor :</p> <ol style="list-style-type: none"> 1. Please provide raw data and supporting figures to justify the dissolution method development and dissolution specifications. For development of the dissolution method please provide the following: a) the pH solubility profile of valproic acid, b) rationale for selection of paddles, c) dissolution profiles generated at different agitation speeds, d) dissolution profiles in multiple media (e.g. 0.1 N HCl, pH 4.5 buffer, pH 6.8 buffer), d) justification for use of the selected buffers, and c) raw data for dissolution studies. Please provide the dissolution profiles and raw data for both strengths of the product. Please also provide data to show the ability of the proposed method to discriminate poorly performing capsules. 2. Please confirm the temperature at which the freeze-thaw stability was performed in the bioanalytical method development. 3. Please send electronic document (in WORD) with the proposed labeling 4. The 500 and 125 mg strengths are not proportionally similar in composition. There are significant differences in the release controlling excipients of the 500 mg and 125 mg strengths, and therefore a biowaiver could not be granted for the 125 mg strength. A BE study will be required. 		
QBR questions (key issues to be considered)		<p>Is bioequivalence demonstrated between Banner's valproic acid product and Depakote?</p> <p>Is there a food effect on the bioavailability of Banner's valproic acid?</p> <p>Can a biowaiver be granted for the 125 mg strength capsule?</p> <p>Are the bioanalytical methods adequate to assess concentrations?</p> <p>Do the dissolution conditions and specifications assure in vivo performance and quality of the product?</p>		
Other comments or information not included above		<p>Comments to the Project Manager:</p> <p>We request DSI inspection of Study PRACS R05-1643 (pivotal BE study of 500 mg strength capsule vs Depakote). Please convey this request to DSI. Please let DSI know that this study was performed at PRACS Institute, Ltd. Fargo, ND 58104 and East Grand Forks, MN 56721. The bioanalytical assay was performed at PRACS Institute LTD, 4801 Amber Valley Parkway, Fargo, ND 58104</p>		
Primary reviewer Signature and Date				

Secondary reviewer Signature and Date

CC: NDA 22-152, HFD-850(Electronic Entry or Lee), HFD-120(Calder), HFD-860 (R. Uppoor, M. Mehta)

Appendix

Not to be released by FOI

Ingredient	Functionality	Weight/capsule		% w/w	
		500 mg	125 mg	500 mg	125 mg
Valproic Acid, USP	Active	500 mg	125 mg		
Gelatin					
Glycerin					
methacrylic acid copolymer					
Triethyl citrate					
Ammonium hydroxide					
water					
FD&C yellow #6					
⁴ Total Dry Shell Weight					
⁵ Total Dry Capsule Weight					
¹ This part of the gelatin process is proprietary and details have been provided in DMF 14194 on file with FDA.					
²					
³ Theoretical weight					

b(4)

b(4)

b(4)

The _____ is considered to be the release controlling excipient by the Office of New Drug Chemistry. The % change of that excipient in the 125 mg capsule compared to the 500 mg strength capsule is _____

b(4)

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

/s/

Sally Yasuda
10/9/2007 02:27:22 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
10/9/2007 06:19:44 PM
BIOPHARMACEUTICS

NDA 22-152 STAVZOR (Valproic Acid)
Response to Approvable Letter

Clinical Pharmacology Review

NDA:	22-152
Brand Name:	STAVZOR
Generic Name:	Valproic Acid
Type of Dosage Form:	Delayed Release Capsule
Strengths:	125 mg, 250 mg, 500 mg
Indications:	Epilepsy, migraine, mania
Type of Submission:	505(b)(2), Response to Approvable Letter
Sponsor:	Banner
Submission Date:	October 26, 2007, November 16, 2007
OCP Division:	DCP-I
OND Division:	Division of Neurology Drug Products HFD-120
OCP Reviewer:	Sally Usdin Yasuda, MS, PharmD
OCP Team Leader:	Ramana Uppoor, PhD

1 Executive Summary

The NDA for STAVZOR (valproic acid) delayed release capsules (125 mg, 250 mg, and 500 mg) to be indicated for epilepsy, migraine, and mania received an approvable letter dated October 22, 2007. The NDA was 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 Clinical Pharmacology requests to justify the dissolution method, to provide data to support a biowaiver of the lower strength capsules, and to evaluate dose dumping with alcohol have been addressed in the present submission.

1.1 Recommendations and Comments to Sponsor

The Office of Clinical Pharmacology finds that the submitted data in the response to approvable letter for NDA 22-152 is acceptable. The Sponsor's proposed dissolution methodology and specifications are acceptable and a biowaiver for the 250 mg and 125 mg strengths can be granted.

The Sponsor's proposed dissolution method and specifications, below, are acceptable:

Apparatus:	USP Apparatus 2 (Paddles)
Medium:	Acid Stage: 0.08 N HCl Buffer Stage: pH 7.5 Sodium Phosphate Buffer
Volume:	900 ml
Temperature:	37 ± 0.5 °C
Rotation Speed:	50 rpm
Sampling time:	1 hour
Specification:	Acid Stage: Not more than $\frac{1}{2}$ in 60 minutes Buffer Stage: Q $\frac{1}{2}$ in 60 minutes

b(4)

**NDA 22-152 STAVZOR (Valproic Acid)
Response to Approvable Letter**

Based on results of the *in vitro* studies to evaluate dose dumping with alcohol in which early dissolution in the buffer stage is observed compared to the absence of alcohol, the Office of Clinical Pharmacology recommends some revisions in the proposed label text (please refer to pages 8-9 of this review for recommended labeling changes). Please forward the labeling changes to the Sponsor.

In addition, it is noted that although ethanol alters dissolution, it apparently does not alter capsule rupture. Therefore, the Division should consider whether, if ethanol does not alter capsule rupture, the alcohol-induced changes are not product specific but related to valproic acid itself, and would occur with all valproic acid products.

**Sally Usdin Yasuda, MS, PharmD
Senior Reviewer, Neurology Drug Products, DCP I
Office of Clinical Pharmacology**

**Concurrence: Ramana Uppoor, PhD
Team Leader, Neurology Drug Products, DCP I
Deputy Director, DCP I
Office of Clinical Pharmacology**

**cc: HFD-120 NDA 22-152
CSO/L. Chen
/Biopharm/S. Yasuda
/TL Biopharm/R. Uppoor
HFD-860 /DD DCPI/M. Mehta**

NDA 22-152 STAVZOR (Valproic Acid)
Response to Approvable Letter

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3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

3.1 Background

The NDA for STAVZOR (valproic acid) delayed release capsules (125 mg, 250 mg, and 500 mg) to be indicated for epilepsy, migraine, and mania received an approvable letter dated October 22, 2007. The NDA was 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 following Clinical Pharmacology comments were included in the Approvable letter:

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 C_{max} 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 f_2 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).

3.2 Current Submission

The Sponsor's submission of October 26, 2007 provides a response to the Agency's Approvable letter. For detailed review of the responses, please refer to the Appendix of this review. The responses are summarized below:

Dissolution Method Development and Discriminatory Ability of the Method:
(Addresses Clinical Pharmacology Comments 1 and 3)

Dissolution method development is reviewed in the Appendix, Section 4.1.1 The revised *in vitro* dissolution method development was based on lots from the registration stability batch in the case of the 125 mg and 250 mg strength capsules and the scale up batch to the clinical trial batch for the 500 mg strength capsule since the biobatch had expired. These capsules were the same as the to-be-marketed

The originally proposed dissolution method included SLS. The Sponsor evaluated the proposed method in the absence of SLS or in the presence of 0.5%, 1.0%, and 2% SLS, as requested, and found acceptable performance in the absence of SLS. In addition, the discriminatory ability of the method was evaluated

b(4)

The results primarily showed that capsules that rupture in the acid stage could be identified, and also suggest that to some extent slowly dissolving product could be identified.

The Sponsor has proposed the following dissolution method and specifications:

Apparatus: USP Apparatus 2 (Paddles)
Medium: Acid Stage: 0.08 N HCl
Buffer Stage: pH 7.5 Sodium Phosphate Buffer

b(4)

Volume: 900 ml
Temperature: 37 ± 0.5 °C
Rotation Speed: 50 rpm
Sampling time: 1 hour
Specification: Acid Stage: Not more than
Buffer Stage: Q = in 60 minutes

b(4)

The dissolution profile reasonably reflects the *in vivo* plasma concentration time course where range for t_{max} is 0.5-5hr and median is 2 hrs.

The Office of Clinical Pharmacology recommends acceptance of the proposed dissolution method and specifications.

Request for Biowaiver of Lower Strength Capsules

The Sponsor's request for biowaiver of the 250 mg and 125 mg strength capsules is reviewed in the Appendix, Section 4.1.2.

Data regarding the composition of the capsules was reviewed in the OCP review of the original NDA submission. In this product, _____

_____. In addition, _____ is the same across strengths. Therefore, the Office of Clinical Pharmacology believes it is acceptable to consider a biowaiver request.

b(4)

In comparative dissolution studies for a biowaiver request, similarity between 2 strengths is indicated by a similarity factor $f_2 > 50$. The Sponsor has provided dissolution data in 0.08 N HCl for 120 minutes followed by pH 7.5 buffer (the proposed buffer medium), pH 6.8 buffer, and pH 4.5 buffer using multipoint dissolution profiles in the buffer stage with results from 12 capsules per time point. In comparison of the 500 mg vs 250 mg strengths and the 500 mg vs 125 mg strengths in pH 7.5 medium, the f_2 similarity factors were 64 and 63, respectively. In pH 4.5 medium the capsules did not rupture (as expected with the enteric polymer resulting in a delayed release capsule). This resulted in an average % dissolution of up to 8%, and the f_2 similarity factors were 75 and 69 for the 500 mg vs 250 mg strengths and for the 500 mg vs 125 mg strengths, respectively.

In pH 6.8 the f_2 values were < 50 for both 500 mg vs 250 mg and 500 mg vs 125 mg. However, at each time point, there is considerable overlap in the data due to variability at each time point for both comparisons. Therefore, the 3 strengths are similarly poorly performing in this medium.

Because of the similarity in dissolution in 3 different media between 500 mg vs 250 mg and between 500 mg vs 125 mg strength capsules, a biowaiver can be granted for the 250 mg and 125 mg strength capsules.

Dose Dumping with Alcohol (Addresses Clinical Pharmacology Comment 2)

To address dose dumping with alcohol, the Sponsor has performed an *in vitro* study for the 250 mg strength capsules using the proposed dissolution method with either 0%, 5%, 10%, or 20% (v/v) ethanol added to the dissolution media (acid and buffer). The results were reported in a submission of September 28, 2007 and are reviewed in the Appendix, Section 4.1.3.

Adding ethanol to the acid phase did not induce dose dumping. In the buffer stage the % dissolution at 15 minutes was 2.6-3.2x greater in ethanol than in the absence of ethanol and increased as the concentration of alcohol increased. By 30 minutes in ethanol _____ of drug was dissolved compared to _____ in the absence of ethanol.

The *in vivo* plasma concentration time course for the 500 mg strength capsule shows that the median t_{max} for the 500 mg strength is approximately 2 hours (range 0.5-5 hours). Although dose dumping is not observed in the acid phase in the presence of ethanol, the increased dissolution observed at early time points in the buffer stage *in vitro* could result in earlier T_{max} (and potentially higher C_{max}) when this product is used with alcohol *in vivo*. OCP recommends changes to the proposed labeling of this product (see below). In addition, the Division should

**NDA 22-152 STAVZOR (Valproic Acid)
Response to Approvable Letter**

consider whether, if ethanol does not alter capsule rupture, the alcohol-induced changes are not product specific but related to valproic acid itself, and would occur with all valproic acid products.

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_____ Deliberative Process (b5)

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)