

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-152

MEDICAL REVIEW

CLINICAL REVIEW MEMO TO FILE

| | |
|---|---|
| Application Type | NDA |
| Submission Number | 22152 |
| Letter Date | Original Submission Dec 22 2006 Resubmission October 26, 2007 Resubmission May 27, 2008 |
| Reviewer Name | Ramesh Raman, MD |
| Established Name Proposed Trade Name | Valproic Acid Delayed Release Capsules Stavzor (valproic acid) Delayed Release Capsules |
| Applicant | Banner Pharmacaps Inc., NC, USA |
| Formulation | Dipropylacetic Acid, 2-propylpentanoic acid |
| Dosing Regimen | Oral |
| Indication | Mania, Epilepsy, Migraine |
| Intended Population | Adults (and Children ≥ 10 years for Epilepsy indication) |

NDA 022152 for valproic acid (first submitted under IND 71268 in February 2005) was filed on Dec 20th 2006 as a 505 (b)(2) application (under 21 CFR 314.54). PK/bioavailability data from a single study in 36 healthy adult subjects comparing valproic acid (500 mg delayed release capsule- the test drug) to divalproex sodium (500 mg delayed release tablet- the reference listed drug [RLD]- Depakote ®) aiming to establish pharmacokinetic bioequivalence was conducted by the Sponsor to support the 505 (b)(2) application. No significant clinical issues were identified during this cycle 1 review of data that stemmed from a single PK study in healthy adults under fasting and non-fasting conditions in which the relative bioavailability (rate and extent of absorption) of valproic acid 500 mg capsule was compared to Depakote® delayed-release 500 mg tablets. An Approvable action (letter October 22, 2007) was taken by the Agency due to outstanding issues primarily involving Clinical Pharmacology and CMC. There were no clinical issues that precluded approval.

On October 26 2007, the sponsor submitted a response to address these issues (resubmission). No new clinical information was submitted as none was required at that time. A Tentative Approval action was taken on Dec 21, 2007 that was related primarily to issues pertaining patent protection of the referenced listed drug (RLD) in the application, namely Depakote (Abbott Laboratories). The RLD patent protection was due to expire January 29, 2008. In addition, the NDA holder of the RLD had initiated a patent infringement suit against the sponsor (Banner). In the December 21, 2007 letter, the sponsor was informed to provide updated information (related to labeling, chemistry, manufacturing and controls data, etc.,) or of any other change as outlined in the letter in

the response/resubmission. In addition, the sponsor was informed to submit a copy of the final order or judgment or settlement agreement or other relevant information related to the law suit in the response/resubmission. The tentative approval was also dependent on **sponsor's agreement on the recommendations** and amendments that were made to the label by the Agency.

On May 27, 2008, the sponsor submitted a response to the December 21, 2007 Tentative Approval Letter. Since this resubmission does not include clinical information and since there are no outstanding clinical issues, no further clinical comments are made. Reference is made to the cycle 1 and cycle 2 reviews for details and clinical comments.

Clinical Recommendations: None.

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/s/

Ramesh Raman
8/21/2008 01:35:12 PM
MEDICAL OFFICER
Resubmission with no clinical data.

Eric Bastings
8/25/2008 09:12:06 AM
MEDICAL OFFICER

CLINICAL REVIEW MEMO TO FILE

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| Application Type | NDA |
| Submission Number | 22152 |
| Letter Date | Original Submission Dec 22 2006 Resubmission October 26, 2007 |
| Reviewer Name | Ramesh Raman, MD |
| Established Name | Valproic Acid Delayed Release Capsules |
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On October 26 2007, the sponsor submitted a response to these issues (resubmission). No new clinical information was submitted as none was required.

Since this resubmission does not include clinical information and since there are no outstanding clinical issues, no further clinical comments are made. Reference is made to the cycle I review for details and clinical comments on the PK study.

Clinical Recommendations: None.

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/s/

Ramesh Raman

1/7/2008 03:42:43 PM

MEDICAL OFFICER

This resubmission does not contain clinical information. This is the response to the approvable letter of October 22, 2007 in which no outstanding clinical issues were identified. Please refer to the review of the original NDA submission of Dec 2006.

Eric Bastings

2/12/2008 05:20:27 PM

MEDICAL OFFICER

I recommend tentative approval.

Appears This Way
On Original

CLINICAL REVIEW

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|------------------------|--|
| Application Type | NDA |
| Submission Number | 22152 |
| Submission Code | |
| Letter Date | Dec 22 2006 |
| Stamp Date | Dec 27 2006 |
| PDUFA Goal Date | October 22 2007 |
| Reviewer Name | Ramesh Raman, MD |
| Review Completion Date | October 9, 2007 |
| Established Name | Valproic Acid Delayed Release Capsules |
| (Proposed) Trade Name | None |
| Therapeutic Class | |
| Applicant | Banner Pharmacaps Inc., NC, USA |
| Priority Designation | S |
| Formulation | Dipropylacetic Acid, 2- propylpentanoic acid |
| Dosing Regimen | Oral, |
| Indication | Mania, Epilepsy, Migraine |
| Intended Population | Adults (and Children \geq 10 years for Epilepsy indication) |

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Clinical Review
Ramesh Raman, MD
NDA 22152
Valproic Acid Delayed Release Capsules; Dipropylacetic Acid, 2-propylpentanoic acid

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

There are no significant clinical concerns that would preclude approval. However, for reasons alluded to in the review strategy section (4.3), the assessment of this bioequivalence drug development program depends primarily on whether or not the Sponsor has provided PK and **other CMC related data and justifications that meet the Agency's requirements for successful approval** of this 505 (b)(2) application. It is the understanding of this reviewer that at the time of this writing, such information has not been provided and that these outstanding issues are not of great magnitude. The specifics of these deficiencies may be found in the Agency PK/CMC reviews. An approvable action by OCPB and ONDQA has been made.

Secondly, while this 505 (b)(2) application (under 21 CFR 314.54) relies on the yet to be validated comparable data (between valproic acid and the reference listed [RLD]) from Sponsor conducted clinical study in adults, such head to head comparison has not been carried out in the pediatric population. However, the Sponsor, like the RLD, is also seeking pediatric indication for use of valproic acid in children 10 years or older for the epilepsy indication. There is no basis for such a claim other than to assume that because the behavior in adults between valproic acid and the RLD is similar (which is yet to be fully established), then the behavior in pediatric population would also be similar.

The sponsor is seeking a pediatric waiver and whether PREA would be triggered requires further consideration. Under the assumption that bioequivalence is established, the only differences between the RLD (delayed release Depakote) and valproic acid (Stavzor) would be that the RLD is a tablet and Stavzor, a capsule. Delayed release Depakote also exists as a capsule (125mg strength approved under NDA 19,860). Preliminarily, on this basis, such a waiver request may not be required and hence PREA not applicable. However, further clarifications and confirmation before final approval is recommended.

Therefore, an approvable action is recommended.

In order to get approval, the Sponsor needs to carry out the following-

- a) **Meet all the Agency's CMC and PK requirements.**
- b) Agree not to market valproic acid in pediatric population and amend the label accordingly.

1.2 Recommendation on Postmarketing Actions

None.

1.2.1 Risk Management Activity

None.

1.2.2 Required Phase 4 Commitments

None.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Regulatory Background

Valproic acid delayed release was first submitted under IND 71268 in February 2005 with a proposal to conduct bioavailability studies (fasting and non-fasting) (see review by Dr. Philip Sheridan, MD). In the may proceed letter the following information was shared with the sponsor-

“ We also note, as relayed to you in the same phone conversation, that we do not have a preference as to whether you use Depakote or Depakene as the drug to which you compare the Valproic Acid Delayed Release Capsule. However, the Agency’s policy on new drug applications submitted under section 505(b)2 of the Act is evolving. Any reconsideration of our policy could affect a future NDA submission. We note in passing, that a citizen petition has been submitted on behalf of Abbott Laboratories asking that FDA refrain from approving any 505(b)(2) applications that refer to Depakote (2004P-0320/CPI, July 15, 2004). The Agency has not taken any action on the petition, and our drawing your attention to its existence should not be construed as an indication of any action we may take on the petition”.

Reviewer’s Comment

The status of this issue and its potential repercussions in the NDA assessments are unknown. Further clarification is recommended. The out come of this may influence the recommendation.

NDA Related

NDA 022152 for valproic acid (Proposed trade name Stavzor™ [Ref: Aug 28, 2007 submission]) was filed on Dec 20th 2006 as a 505 (b)(2) application (under 21 CFR 314.54). PK/bioavailability data from a single study in 36 healthy adult subjects comparing valproic acid (500 mg delayed release capsule- the test drug) to divalproex sodium (500 mg delayed release

tablet- the reference listed drug [RLD]- Depakote ®) aiming to establish pharmacokinetic bioequivalence was intended to support the 505 (b)(2) application. In the Agency filing letter of March 1, 2007, several issues related to CMC, PPI and waiver request for pediatric studies were identified and the sponsor responded to these on Jun 1, 2007. In addition to responding to the CMC issues and agreeing to the changes recommended to the PPI, the sponsor provided the Agency clarification on the pediatric waiver.

Sponsor is seeking approval to match Stavzor™ labeling with that of Depakote ®. The sought three indications (mania, epilepsy and migraine) are similar to those that the RLD has been approved for. However, the Sponsor, with justification (vol. 1, section 1.9.1), is requesting full waiver for conducting pediatric studies. Specifically, the RLD (Depakote ®) is approved for adults (all three indications) and children 10 years or older (for the epilepsy indication). 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).

Reviewer's Comment

The submitted PK study did not include pediatric subjects but the Sponsor is claiming a pediatric indication.

Scientific Rationale for a 505 (b)(2) application

According to the Sponsor, the rationale for pursuing a 505 (b)(2) application that is based on PK/bioavailability comparability, is that equivalent doses of Depakote® (divalproex sodium) and **Stavzor™ (valproic acid) deliver equivalent quantities of valproate ion systemically. Although Depakote® has a different active ingredient (divalproex sodium) from Stavzor™ (valproic acid),** both medications dissociate to the valproate ion following oral administration so that the active moiety is the same. Following oral administration, divalproex sodium is rapidly converted to valproate ion in the GI tract. Valproate is rapidly and almost completely absorbed from the GI tract.

The Study

This sponsor conducted single PK study assessed the bioavailability of 500 mg valproic acid delayed-release capsules (the test drug from Banner Pharmacaps, Inc.) vs. 500 mg divalproex sodium delayed-release tablets (Depakote ®- the reference listed drug [RLD]) in healthy adults under fasting and non-fasting conditions. Specifically, the objective of this study was to compare the relative bioavailability (rate and extent of absorption) of valproic acid 500 mg capsule (by Banner Pharmacaps, Inc.) with that of Depakote® delayed-release 500 mg tablets (by Abbott Laboratories) following a single, oral dose (1 x 500 mg) in healthy adult volunteers administered under fasting conditions. In addition this study compared the differences in serum levels after dosing the test drug (valproic acid 500 mg capsule by Banner Pharmacaps, Inc.) with and without food.

This was a single dose, open-labeled, randomized, single-dose, three-way crossover Phase 1 study under fed and fasted conditions. The main inclusion criteria were: Subjects were healthy male and female (of non-childbearing potential) volunteers 18 years of age and older. They did not exceed \pm 20% of their Ideal Body Weight (IBW) as per the *Table of Desirable Weights of Adults* (1983, Metropolitan Life Insurance Company). All volunteers were judged to be healthy on the basis of a pre-study physical examination, an electrocardiogram, and clinical laboratory tests.

36 healthy volunteers (30 males and 6 females), mean age of 32.1 years (\pm 13.7), mean weight of 172.8 lbs (\pm 23.5), mean height of 69.6 (\pm 3.4) and mean BMI of 25.1 (\pm 2.9) were enrolled in this study. All 36 subjects received treatment and all 36 subjects successfully completed the study. PK and safety data from all 36 subjects were collected and used in the statistical analyses.

There were three study periods with at least a seven day washout between study periods. Subjects were treated based on the randomized treatment codes.

Three treatment codes A, B and C (resulting in 6 randomization sequences ABC, ACB, BAC, BCA, CAB and CBA), were designated to indicate the following-

Treatment A= Test Product (500 mg Valproic Acid Delayed Release Capsule- Sponsor's) after an overnight fast;
Treatment B= Test Product (500 mg Valproic Acid Delayed Release Capsule- Sponsor's) 30 minutes after high fat breakfast (preceded by an overnight fast);
Treatment C= Reference Product (500 mg Divalproex sodium Delayed Release Tablets by Abbott Labs) after an overnight fast.

Subjects were confined ~ 10.5 hours prior to and until at least 24 hours after dosing during each treatment period. All subjects fasted overnight. Subjects were dosed at the 0 hour, sequentially, in groups of three at 1-minute intervals. The actual time of dosing was recorded for each subject. Each drug (1 x 500 mg) administration was assisted with 240 mL of ambient temperature water consumed under direct observation. Immediately after dose administration, each subject's oral cavity was checked to confirm medication and fluid consumption. Dose administration was completed as scheduled.

During the confinement study hours, when fluids were not restricted, subjects were allowed water *ad lib.*, if requested. No fluid, except that given with drug administration and the standardized breakfast (dependent on randomization), was allowed from 1 hour prior to dose administration until 1 hour after dosing. At 2 hours post-dose, subjects consumed 240 mL of ambient temperature water. At 4.25, 10.5, and 14.5 hours after dose administration during all three study periods, standardized meals and beverages were provided to each subject. All meals were free from grapefruit, xanthine-, and caffeine-containing products. Meals were identical during all three study periods. Subjects refrained from engaging in strenuous activities at any time during the confinement period. Subjects were to generally remain seated, in an upright position for four hours on hardback chairs following drug administration to ensure proper stomach emptying, except for brief periods when they were permitted to leave their seats under

close supervision (e.g., to use the restroom). Subjects were not allowed to use prescription or non-prescription medications during the 14 days and 3 days, respectively, preceding the study and throughout the entire study. Subjects were queried regarding concomitant medications prior to each study period and at each ambulatory visit.

This was an open-label study; the clinical investigators and the subjects were not blinded to the treatment assignments. However, the bio-analytical facility was blinded to the randomization code to prevent bias during analysis. Each sample tube was labeled with study number, study period, subject number, sampling time point, sample number, date collected, and matrix but did not include any reference to treatment regimen.

Assessments and Variables are shown in the Study Schema table below.

| TABLE 1.3.1 [#] : STUDY SCHEMA | | | | |
|--|--|---|--------------------|---|
| Trial Phase (Each Treatment Period) | Screening Day -28 to Day -2 (Performed Once) | Confinement at Clinical Research Unit (Each Treatment Period) | | Early Discontinuation or End of Study/ Discharge |
| | | Check-in Day -1 | Treatment Day 1 | |
| Informed Consent | X | X ^a | | |
| Eligibility (Inclusion/Exclusion) | X | X | | |
| Prior Medication Assessment | X | X ^b | | |
| Medical History | X | X ^b | | |
| Vital Signs | X | | X ^c | X |
| Physical Exam | X | | | X |
| <u>Clinical Laboratory Tests</u> | | | | |
| CBC with differential | | | | |
| Clinical Chemistry | | | | |
| HIV Antibody Screen | X | | | X ^e |
| Hepatitis B Screen | | | | |
| Hepatitis C Screen | | | | |
| Urinalysis | | | | |
| Pregnancy Screen (females only) | X | X | | X |
| FSH (females only) | X | | | |
| Urine Drug Screen | X | | | |
| Safety 12-lead ECG | X | | | |
| Study Drug Administration | | | X | |
| Pharmacokinetic Sampling | | | X ^d | |
| Adverse Events | | | X | X |
| Concomitant Medication | | | X | X |
| # Ref- Modified Sponsor's Table 9.1 (Page 19 of 2152- Full Final Report). Same as Table 10.1.1. | | | | |
| Note: | | | | |
| a = Period I only; | | | | |
| b = Updated; | | | | |
| c = Vital signs were collected predose, 12 and 24 hours after dose administration; | | | | |
| d = Pharmacokinetic samples collected: predose and 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 after dose administration; | | | | |

e = CBC with differential and Clinical Chemistry

Results

The PK results are as shown in the two tables below. According to the sponsor, the results of this study indicated that the test Valproic Acid Enteric 500 mg Softgel was bioequivalent to the reference Depakote® Delayed-Release Tablets 500 mg under fasting conditions. Further, administration of the test Valproic Acid Enteric 500 mg Softgel under non-fasting conditions resulted in a significant decrease in C_{max} , but did not affect the extent of absorption ($AUC_{(0-t)}$ and $AUC_{0-\infty}$).

Reviewer's Comment

Reference is made to the Agency PK review on the acceptance of the results establishing such PK comparability (between the 500 mg test valproic acid delayed release capsule and the 500 mg RLD [Depakote®]).

| TABLE 1.3.2 [#] : PK RESULTS | | | | |
|---|--------------------------|--------------------------|---------|----------------|
| TEST PRODUCT NON-FASTING (TREATMENT B [^]) VS. TEST PRODUCT FASTING (TREATMENT A [^]) | | | | |
| Geometric Means, Ratio of Means, and 90% Confidence Intervals- Ln-Transformed Data | | | | |
| Valproic Acid (N=36) | | | | |
| Parameter | Treatment B [^] | Treatment A [^] | % Ratio | 90% CI |
| AUC _{0-t} (µg-hr/mL) | 845.97 | 882.90 | 95.82 | (93.79, 97.89) |
| AUC _{0-∞} (µg-hr/mL) | 926.80 | 966.67 | 95.88 | (93.92, 97.87) |
| C _{max} (µg/mL) | 40.84 | 53.35 | 76.56 | (73.29, 79.9) |
| # Ref Modified Sponsor's Table 11.2 ((Page 27 of 2152- Full Final Report). Same as Table 10.1.4. | | | | |
| ^ A= 500mg Valproic acid l Delayed Release Softgel (Fasting), B= 500mg Valproic acid Delayed Release Softgel (Non-fasting- after fatty meal), C= 500mg Depakote® Delayed Release Tablet (Fasting) | | | | |

| TABLE 1.3.3 [#] : PK RESULTS | | | | |
|---|--------------------------|--------------------------|---------|----------------|
| TEST PRODUCT FASTING (TREATMENT A [^]) VS. REF PRODUCT FASTING (TREATMENT C [^]) | | | | |
| Geometric Means, Ratio of Means, and 90% Confidence Intervals- Ln-Transformed Data | | | | |
| Valproic Acid (N=36) | | | | |
| Parameter | Treatment A [^] | Treatment C [^] | % Ratio | 90% CI |
| AUC _{0-t} (µg-hr/mL) | 882.90 | 916.05 | 96.38 | (94.34, 98.47) |
| AUC _{0-∞} (µg-hr/mL) | 966.67 | 997.51 | 96.91 | (94.93, 98.93) |
| C _{max} (µg/mL) | 53.35 | 54.86 | 97.24 | (93.1, 101.57) |
| # Ref Modified Sponsor's Table 11.3 (Page 27 of 2152- Full Final Report). Same as Table 10.1.5. | | | | |
| ^ A= 500mg Valproic acid Delayed Release Softgel (Fasting), C= 500mg Depakote® Delayed Release Tablet (Fasting) | | | | |

The total exposure for each of the 36 subjects who completed the study was 1500mg (3 treatment doses; each dose = 1 x 500 mg).

No deaths or serious adverse events (AE) or other significant adverse events were reported. There were a total of 10 adverse events reported by 8 subjects over the course of the study. Three AEs, 5 AEs and 2 AEs occurred with treatments A, B and C respectively. Eight AEs (in 6 subjects) occurred with the administration of the test drug regardless of the condition (fast vs.

fed) and 2 AEs (in 2 subjects) occurred with the administration of the RLD. There were 2 adverse events (nausea and headache) considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under fasting conditions (treatment arm A). There were 3 adverse events (back pain, extremity pain and nasopharyngitis) considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under non-fasting conditions (treatment arm B). None of the AEs were considered related to the RLD (Depakote®). In concurrence with the Sponsor, the clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product.

Overall, valproic acid was well tolerated as a single, oral dose of 500 mg administered under fasting and fed conditions in healthy adults.

1.3.2 Efficacy

Not applicable. The Sponsor made reference to the Agency's findings of safety and efficacy for a referenced listed drug (RLD), Depakote® Tablets (500mg, 250mg, 125mg) under NDA 18723 held by Abbott Pharmaceuticals PR Ltd. Therefore, this application relied on the data from the RLD. There was no data that was referenced from the literature.

1.3.3 Safety

The Sponsor made reference to the Agency's findings of safety and efficacy for a referenced listed drug (RLD), Depakote® Tablets (500mg, 250mg, 125mg) under NDA 18723 held by Abbott Pharmaceuticals PR Ltd. Therefore, this application relied on the data from the RLD. There was no data that was referenced from the literature.

The safety findings from the single PK study in 36 healthy adult volunteers that is discussed in detail in Appendix [10.1] under individual study reports did not raise any specific safety concerns.

1.3.4 Dosing Regimen and Administration

The following is from the PPI (Aug 28, 2007 submission)-

7
b(4)
)

[REDACTED] b(4)

1.3.5 Drug-Drug Interactions

Not applicable. Please refer to the Agency PK review.

1.3.6 Special Populations

Not applicable. Please refer to the Agency PK review.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

2.2 Currently Available Treatment for Indications

2.3 Availability of Proposed Active Ingredient in the United States

Valproic acid- Depakene ® (Abbott- NDA 18-082); Depakote ® (Abbott- NDA 18723 [RLD]) and others. In the section 1.9.1, vol. 1, p. 3, the sponsor has provided a table that lists at least 16 NDA application numbers from 12 different companies (including Banner- the Sponsor for this NDA) under which valproic acid is available in different dosage forms (syrup, solution, capsule, and tablet).

2.4 Important Issues With Pharmacologically Related Products

2.5 Presubmission Regulatory Activity

See Regulatory background under section 1.3.1.

2.6 Other Relevant Background Information

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please refer to Agency CMC review.

3.2 Animal Pharmacology/Toxicology

Not relevant.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Sponsor conducted a single biopharmaceutical/bioavailability study in healthy adult subjects under protocol # PRACS R05-1643 which formed the sole data source for clinical review. The **Sponsor made reference to the Agency's findings** of safety and efficacy for a referenced listed drug (RLD), Depakote® Tablets (500mg, 250mg, 125mg) under NDA 18723 held by Abbott Pharmaceuticals PR Ltd. Therefore, the pharmacology, toxicology, microbiology, statistical and clinical aspects of safety and efficacy of this application relied on the data from the RLD. There was no data that was referenced from the literature.

This sponsor conducted a single PK study that assessed the bioavailability of 500 mg valproic acid delayed-release capsules (the test drug from Banner Pharmacaps, Inc.) vs. 500 mg divalproex sodium delayed-release tablets (Depakote ®- the reference listed drug [RLD] by Abbott Laboratories) under fasting and non-fasting conditions. Specifically, the objective of this study was to compare the relative bioavailability (rate and extent of absorption) of valproic acid 500 mg capsule with that of Depakote® delayed-release tablets 500 mg following a single, oral dose (1 x 500 mg) in healthy adult volunteers administered under fasting conditions. In addition this study compared the differences in serum levels after dosing the test drug (valproic acid 500 mg capsule by Banner Pharmacaps, Inc.) with and without food.

4.2 Tables of Clinical Studies

Not relevant. Only a single bioavailability study was performed under this NDA. See Appendix (10.1) under individual study reports.

4.3 Review Strategy

The clinical (safety) aspects from the single PK/bioavailability study in healthy adult subjects and the resulting safety profile was the focus of this review. Further, comparison of this safety profile with those of the approved comparable drugs, in particular to the referenced listed drug (RLD), Depakote® Tablets, was undertaken. Reliance on the Agency CMC and Clinical of the submitted CMC and PK data establishing equivalence (PK) to the RLD was critical since no other efficacy or safety data was required to be submitted under the provisions of a 505 (b)(2) application (under 21 CFR 314.54).

While in this single bioavailability study the 500 mg valproic acid delayed release capsule was compared head to head with the 500 mg divalproex sodium delayed release tablet (the RLD Depakote ®) with the aim of establishing PK equivalence between them, the sponsor in addition to seeking claim to market the 500 mg strength, is also requesting to market the 125mg and 250 mg strengths but without such PK data. The sponsor is seeking biowaiver for the 125 mg and the 250 mg strength. Reliance on the Agency CMC and Clinical **Pharmacologist's acceptance and**

validation of the information sufficient to grant such a waiver was critical in the inclusion of the 125 mg and the 250 mg strengths in the label.

This bioavailability study included only healthy adults and did not include pediatric subjects. However, the indication for epilepsy includes ages 10 years and above. Therefore, there was no head to head comparison for the sought pediatric epilepsy indication between Valproic acid and the RLD. According to the Agency PK reviewer, such PK data exist for the RLD. In this situation, acceptance of bioequivalence to the RLD for the pediatric age group would be based on an assumption that if there was PK comparability in adults between Valproic acid and the RLD (that would be based on a head to head comparison via a study), then there would also be PK comparability in pediatric population.

It is clear from the table (4.3) that in the absence of significant clinical safety concerns, regulatory decisions and the basis for approvability would depend on PK assessments. In short, all clinical comments and assessments were made under the assumption that there were no CMC or PK concerns either with respect to the adult and or pediatric populations or for the sought strengths.

| TABLE 4.3: BASIS FOR APPROVABILITY | | |
|---|-----------------------------|-------------------------|
| | Valproic Acid (NDA) vs. RLD | Basis for Approvability |
| Adult PK Data - Comparison | Yes | PK Bioequivalence |
| Pediatric PK Data - Comparison | No | ? |
| 500 mg - Compared | Yes (adult only) | PK Bioequivalence |
| 250 mg - Compared | No | Biowaiver for 250 mg |
| 125 mg - Compared | No | Biowaiver for 125 mg |
| Same Adult Indications (Mania, Epilepsy and Migraine) | Yes | PK Bioequivalence |
| Same Pediatric Indication (Epilepsy) | Yes | ? |

A third aspect that was also the focus for this review was on the proposed label (PPI- Proposed Package Insert) and its format. Specifically, while the bulk of the contents under the various sections of the PPI, by and large, were the same from the label of the RLD (Approved Depakote ® PI of 10/13/06 [Ref: vol. 1, section 1.14.3.1]), whether the format of the PPI and its conformation to the new Agency **“requirements on content and format of labeling for human prescription drug and biological products” (Physician’s Labeling Rule [PLR]) were met was the focus.**

General comments to the reader

It should be noted that throughout the submission (including the earlier versions of the proposed label) the sponsor has used the terms **“softgel” and “delayed release capsule” interchangeably. However, based on the Agency’s recommendation during the review cycle, the term softgel was deleted and the later version of the label was amended accordingly (ref- Aug 28th 2007 submission).** Further, the sponsor has proposed the trade name **“Stavzor™” (ref- Aug 28th 2007 submission).** This trade name proposal is currently under review.

NDA documents were not submitted with consistency either electronically or as hard copies. This caused difficulty in reviewing both at the level of being aware of a submission or in its identification and location. Even for those documents that were submitted electronically, there were no covering letters. The lack of consistency in a methodological approach to the submission of the documents whether as hard copies or as electronic copies, therefore brought arduousness to the review process.

4.4 Data Quality and Integrity

Please refer to Agency CMC and PK review.

4.5 Compliance with Good Clinical Practices

The Sponsor states that this study was performed in compliance with Good Clinical Practice (GCP) regulations.

4.6 Financial Disclosures

In vol. 1.1 of the submission, under section 1.3.4 (financial certification), the sponsor has completed the OMB 0910-0396 form and has selected option 1.

5 CLINICAL PHARMACOLOGY

Please refer to the Agency PK review. A summary of the PK study is presented in Appendix (10.1) under individual study reports.

5.1 Pharmacokinetics

Please refer to the Agency PK review. A summary of the PK study is presented in Appendix (10.1) under individual study reports.

5.2 Pharmacodynamics

Please refer to the Agency PK review. A summary of the PK study is presented in Appendix (10.1) under individual study reports.

5.3 Exposure-Response Relationships

Please refer to the Agency PK review. A summary of the PK study is presented in Appendix (10.1) under individual study reports.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Divalproex Sodium Delayed-Release tablets are indicated for the treatment of certain types of seizures caused by epilepsy. It is also used to treat manic depressive illness and help prevent migraine headaches.

6.1.1 Methods

Not applicable.

6.1.2 General Discussion of Endpoints

Not applicable.

6.1.3 Study Design

Not applicable.

6.1.4 Efficacy Findings

Not applicable.

6.1.5 Clinical Microbiology

Not applicable.

6.1.6 Efficacy Conclusions

Not applicable.

7 INTEGRATED REVIEW OF SAFETY

Not applicable. The safety findings are discussed in the PK study (presented in Appendix [10.1] under individual study reports).

7.1 Methods and Findings

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.1 Deaths

None.

7.1.2 Other Serious Adverse Events

None.

7.1.3 Dropouts and Other Significant Adverse Events

None.

7.1.3.1 Overall profile of dropouts

None.

7.1.3.2 Adverse events associated with dropouts

None.

7.1.3.3 Other significant adverse events

None.

7.1.4 Other Search Strategies

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5 Common Adverse Events

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.1 Eliciting adverse events data in the development program

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.3 Incidence of common adverse events

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.4 Common adverse event tables

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.5 Identifying common and drug-related adverse events

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.5.6 Additional analyses and explorations

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.6 Less Common Adverse Events

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.7 Laboratory Findings

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

Not Applicable.

7.1.11 Human Carcinogenicity

Not Applicable.

7.1.12 Special Safety Studies

Not Applicable.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not Applicable.

7.1.14 Human Reproduction and Pregnancy Data

Not Applicable.

7.1.15 Assessment of Effect on Growth

Not Applicable.

7.1.16 Overdose Experience

Not Applicable.

7.1.17 Postmarketing Experience

Not Applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.2.1.1 Study type and design/patient enumeration

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.2.1.2 Demographics

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.2.1.3 Extent of exposure (dose/duration)

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Not applicable.

7.2.2.1 Other studies

Not applicable.

7.2.2.2 Postmarketing experience

Not applicable.

7.2.2.3 Literature

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

Not applicable.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Not applicable.

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.4 General Methodology

Not applicable. These are discussed in the PK study presented in Appendix [10.1] under individual study reports.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

Not applicable.

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

None. Not applicable.

8.1 Dosing Regimen and Administration

8.2 Drug-Drug Interactions

8.3 Special Populations

8.4 Pediatrics

8.5 Advisory Committee Meeting

8.6 Literature Review

8.7 Postmarketing Risk Management Plan

8.8 Other Relevant Materials

9 OVERALL ASSESSMENT

See executive summary.

9.1 Conclusions

9.2 Recommendation on Regulatory Action

9.3 Recommendation on Postmarketing Actions

None. Not applicable.

9.3.1 Risk Management Activity

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

The Sponsor chose Depakote® as the RLD and its October 13, 2006 version of the label as the prototype for valproic acid label. Sponsor has provided annotated label versions of the RLD and valproic acid (section 1.14.3.1, vol. 1) in which the differences have been highlighted. These broadly include to reflect-a) changes and substitutions in name (trade vs. established), b) changes and substitutions in active and inactive moieties [salt vs. acid], c) changes in format as required - **conformation of the PPI to the new Agency “requirements on content and format of labeling for human prescription drug and biological products” (Physician’s Labeling Rule [PLR]), d) changes and substitutions in formulation (tablets vs. capsule), e) changes and substitutions in strength, f) changes in PK properties, f) omission of other Trade names, products and alternate formulations, g) changes and substitutions in manufacturer’s names.**

In addition, the sponsor has submitted (vol. 1, section 1.14.1.3) a version of PPI that aims to meet the format and content of the required PPL according to 21 CFR 201.56(d) and 201.57 (formerly under 201.56(e) and 201.80) and additionally incorporates the changes and substitutions as mentioned above.

While broadly, the PPI appears to match the new format and contents of the required PLR, the following discrepancies and comments require attention-

1. **In the annotated version of the PPI, “somnolence in the elderly” under the Warnings and Precautions section (5.4) has not been numbered (page 29 of 88, vol. 1.1).** As a result, the

subsequently listed items under this Warnings and Precautions section in the annotated version of the label do not bear the same numbers as the draft text version of the PPI. These are appropriately numbered in the text version of the PPI.

2. The information under Pharmacokinetics section of the PPI (under section 12) compared to the RLD (Section 1.14.3.1, Vol. 1.1, pp. 6-7 of 88) is meant to reflect findings consistent with data derived from the sponsor conducted PK study (PRACS R05-1643). Reference is made to the comments from the Agency PK review on its acceptability.
3. Acceptability of inclusion of the 250 mg and 125 mg strengths in the PPI would depend on the Agency PK review.
4. Since there is no pediatric data with valproic acid, the inclusion of pediatric patients down to the age of 10 years (page 3 of 16, PPI, text version) under the epilepsy dosage and administration section (2.2) is not justified.

9.5 Comments to Applicant

None.

10 APPENDICES

10.1 Review of Individual Study Reports

Study PRACS R05-1643

Study Title

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.

Name of Test Drug/Investigational Product

Valproic Acid Enteric 500 mg Softgel (Lot No.: XPP0409010; Mfg. Date: October 2004);
Cumulative maximum dose 1000mg.

Active Ingredient of Investigation Product

Valproic acid.

Name of Reference Drug

Depakote® Delayed-Release Tablets 500 mg (Abbott Pharmaceuticals PR Ltd. [for Abbott Laboratories]; Lot No.: 31269AA21; Expiration Date: 01 October 2008); Cumulative maximum dose 500mg.

Active Ingredient of Reference Drug

Divalproex sodium.

Indications

Divalproex Sodium Delayed-Release tablets are indicated for the treatment of certain types of seizures caused by epilepsy. It is also used to treat manic depressive illness and help prevent migraine headaches.

Study Initiation and Completion Date

The protocol and consent form dated 25 January 2006 were approved by the PRACS Institute, Ltd. Institutional Review Board (IRB) on 08 February 2006. Revisions to the consent form dated 08 February 2006 were approved by the IRB on 10 February 2006. All subjects checked into the clinical facility for study Period I on 04 March 2006. The study was completed (date of

last blood sample collection) on 22 March 2006. The first dose was administered on March 5, 2006 and the date of the last subject visit was April 13, 2006.

Ethical Conduct of the Study

According to the Sponsor, this study was conducted in accordance with the guidelines set forth by the *International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH), the *U.S. Code of Federal Regulations* (21 CFR Part 50 and 56) and the *Declaration of Helsinki* (provided in Appendix 16.1.3) regarding the treatment of human subjects in a study.

Subject Information and Consent

All subjects who agreed to participate in the study were required to provide the investigator with documented, fully executed (signed by all parties) informed consent.

At the screening visit, subjects signed the PRACS Institute, Ltd. Screening Consent and HIPAA Disclosure Form (*Consent-To-Be-Screened Form No. 136*) approved by the PRACS Institute, Ltd. Institutional Review Board. During the screening visit the study specific ICF for PRACS R05-1643 was reviewed with each subject. Study staff emphasized the nature of the study, the drug product tested, potential adverse events, the conduct of the study, dates of confinement and ambulatory procedures. At Period I check-in, all subjects signed the study-specific ICF to give consent to participate in the study and were allowed to ask and have answered questions regarding the conduct of the study prior to enrollment. A copy of the Screening Consent Form and HIPAA Disclosure Form (*Consent-To-Be-Screened Form No. 136*) and the study specific ICF was submitted (Appendix 16.1.3).

Subjects were advised that they were free to withdraw from the study at any time. Subjects were also informed that they could be withdrawn from the study by the clinical investigator(s) and/or Sponsor in the case of unnecessary risk, adverse events or noncompliance.

Study Objectives

The objective of this study was 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 (by Abbott Laboratories) following a single, oral dose (1 x 500 mg) in healthy adult volunteers administered under fasting conditions. In addition, this study compared the differences in serum levels after dosing the test Valproic Acid Enteric 500 mg Softgel (by Banner Pharmacaps, Inc.) with and without food.

Study Design and Phase of Development

According to the Sponsor, this study was designed to comply with FDA guidelines on the conduct of bioavailability and bioequivalence studies.

This was a single dose, open-labeled, randomized, single-dose, three-way crossover Phase 1 study under fed and fasted conditions. There were three study periods with at least a seven day washout between study periods. The randomization code was available for statistical analysis and preparation of the final report. The randomization scheme was computer generated by PRACS Institute, Ltd., and the subjects were randomized prior to Period I dose administration.

Main Criteria for Inclusion

Subjects who met the following criteria were included in the study-

1. Subjects were selected from non-institutionalized volunteers.
2. Age: 18 years and older.
3. Sex: Male and or females.
 - a. If female and:
 - (1) was postmenopausal for at least 1 year with postmenopausal status defined as: > 60 years of age and amenorrheic for at least one year; if 60 years of age or younger, had a serum FSH level > 30 IU/L; or
 - (2) was surgically sterile for at least 6 months (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy)
4. Weight: Subjects did not exceed **± 20% of their Ideal Body Weight (IBW) (Sponsor's reference by the Table of Desirable Weights of Adults [1983, Metropolitan Height and Weight Table])**.
5. All subjects were judged normal and healthy during a pre-study medical evaluation (general observations, physical examination, demographics, medical and medication history, an electrocardiogram, sitting blood pressure and heart rate, respiratory rate and temperature. Laboratory screening procedures included: Hepatitis B and Hepatitis C tests, HIV test, urine drug screen, including ethyl alcohol, amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, opiates and phencyclidine, serum pregnancy screen (females only), and follicle stimulating hormone (FSH; females 60 years of age or younger), performed within 28 days of the initial dose of study medication. According to the sponsor, because divalproex sodium and valproic acid are pregnancy category D drugs, only males, postmenopausal women or surgically sterile women were eligible to participate in this study.

Main Exclusion Criteria

Subjects who met any of the following criteria were excluded from the study-

1. Volunteers who reported a recent history of drug or alcohol addiction or abuse.
2. Volunteers who reported the presence of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine, or neurologic system(s) or psychiatric disease (as determined by the clinical investigators).
3. Volunteers whose clinical laboratory test values were outside the accepted reference range and when confirmed on re-examination were deemed to be clinically significant.

4. Volunteers who demonstrated a reactive screen for hepatitis B surface antigen, hepatitis C antibody or HIV antibody.
5. Volunteers who demonstrated a positive drug abuse screen when screened for this study.
6. Female volunteers who demonstrated a positive pregnancy screen.
7. Female volunteers who were currently breastfeeding.
8. Volunteers who reported a history of allergic response(s) to divalproex sodium, valproic acid or related drugs.
9. Volunteers who reported a history of clinically significant allergies including drug allergies.
10. Volunteers who reported a clinically significant illness during the 4 weeks prior to Period I dosing (as determined by the clinical investigators).
11. Volunteers who currently used tobacco products.
12. Volunteers who had taken any drug known to induce or inhibit hepatic drug metabolism in the 28 days prior to Period I dosing.
13. Volunteers who reported donating greater than 150 mL of blood within 28 days prior to Period I dosing. All subjects were advised not to donate blood for four weeks after completing the study.
14. Volunteers who had donated plasma (e.g. plasmapheresis) within 14 days prior to Period I dosing. All subjects will be advised not to donate plasma for four weeks after completing the study.
15. Volunteers who reported receiving any investigational drug within 28 days prior to Period I dosing.
16. Volunteers who reported taking any systemic prescription medication in the 14 days prior to Period I dosing.

Number of Subjects (planned and analyzed)

Thirty-six (36) volunteers enrolled in the study and completed the study. Serum concentration data from all 36 subjects were used in the statistical analyses. These included 30 males and 6 females.

Treatments, Randomization and Procedures

There were three study periods (with a washout of at least 7 days between each period) at which time subjects were treated based on the randomized treatment codes.

Three treatment codes A, B and C designated to indicate the following-

Treatment A= Test Product (500 mg Valproic Acid Delayed Release Capsule- Sponsor's) after an overnight fast

Treatment B= Test Product (500 mg Valproic Acid Delayed Release Capsule- Sponsor's) 30 minutes after high fat breakfast (preceded by an overnight fast)

Treatment C= Reference Product (500 mg Divalproex sodium Delayed Release Tablets by Abbott Labs) after an overnight fast

The randomization scheme (Appendix 16.1.7 of the submission) was generated by PRACS Institute, Ltd., and treatment sequences were randomly assigned to each subject number. This resulted in 6 randomization sequences based on the treatment codes. These were Sequence 1 = ABC, Sequence 2 = ACB, Sequence 3 = BAC, Sequence 4 = BCA, Sequence 5 = CAB and Sequence 6 = CBA.

Subjects were confined ~ 10.5 hours prior to and until at least 24 hours after dosing during each treatment period. The subjects fasted overnight. Subjects were dosed sequentially at one minute intervals. Subjects were dosed at the 0 hour, sequentially, in groups of three at 1-minute intervals with dosing beginning at 0730 (Subjects 01-03) and ending at 0741 (Subjects 34-36). The actual time of dosing was recorded for each subject. Each drug (1 x 500 mg) administration was assisted with 240 mL of ambient temperature water consumed under direct observation. **Immediately after dose administration, each subject's oral cavity was checked to confirm medication and fluid consumption.** Dose administration was completed as scheduled.

During the confinement study hours, when fluids were not restricted, subjects were allowed water *ad lib.*, if requested. No fluid, except that given with drug administration and the standardized breakfast (dependent on randomization), was allowed from 1 hour prior to dose administration until 1 hour after dosing. At 2 hours post-dose, subjects consumed 240 mL of ambient temperature water.

At 4.25, 10.5, and 14.5 hours after dose administration during all three study periods, standardized meals and beverages were provided to each subject. All meals were free from grapefruit, xanthine-, and caffeine-containing products. Meals were identical during all three study periods.

Subjects refrained from engaging in strenuous activities at any time during the confinement period. Subjects were to generally remain seated, in an upright position for four hours on hardback chairs following drug administration to ensure proper stomach emptying, except for brief periods when they were permitted to leave their seats under close supervision (e.g., to use the restroom).

Subjects were specifically queried by the staff at PRACS Institute, Ltd., on all restrictions as outlined in the protocol (see inclusion/exclusion criteria). Subjects were required to abstain from consuming grapefruit products, caffeine- and/or xanthine-containing products, and alcohol at least 48 hours prior to days on which dosing was scheduled and during the periods when blood samples were collected.

During the first four hours after dose administration, subjects remained in an upright position. They were permitted to lie down if symptoms of dizziness or lightheadedness occurred, secondary to phlebotomy or investigational products. The subjects were encouraged to remain in a sitting or supine position until the symptoms resolved. After four hours, subjects were permitted to engage in normal activity avoiding vigorous exertion.

Subjects were not allowed to use prescription or non-prescription medications during the 14 days and 3 days, respectively, preceding the study and throughout the entire study. Subjects were queried regarding concomitant medications prior to each study period and at each ambulatory visit.

This was an open-label study; the clinical investigators and the subjects were not blinded to the treatment assignments. However, the bio-analytical facility was blinded to the randomization code to prevent bias during analysis. Each sample tube was labeled with study number, study period, subject number, sampling time point, sample number, date collected, and matrix but did not include any reference to treatment regimen.

Assessments and Variables (see Study Schema Table)

The study schema table summarizes several aspects of the study, design and assessments.

| Trial Phase (Each Treatment Period) | Screening Day -28 to Day -2 (Performed Once) | Confinement at Clinical Research Unit (Each Treatment Period) | | Early Discontinuation or End of Study/ Discharge |
|---|--|---|--------------------|---|
| | | Check-in Day -1 | Treatment Day 1 | |
| Informed Consent | X | X ^a | | |
| Eligibility (Inclusion/Exclusion) | X | X | | |
| Prior Medication Assessment | X | X ^b | | |
| Medical History | X | X ^b | | |
| Vital Signs | X | | X ^c | X |
| Physical Exam | X | | | X |
| <u>Clinical Laboratory Tests</u> | | | | |
| CBC with differential | | | | |
| Clinical Chemistry | | | | |
| HIV Antibody Screen | X | | | X ^e |
| Hepatitis B Screen | | | | |
| Hepatitis C Screen | | | | |
| Urinalysis | | | | |
| Pregnancy Screen (females only) | X | X | | X |
| FSH (females only) | X | | | |
| Urine Drug Screen | X | | | |
| Safety 12-lead ECG | X | | | |
| Study Drug Administration | | | X | |
| Pharmacokinetic Sampling | | | X ^d | |
| Adverse Events | | | X | X |
| Concomitant Medication | | | X | X |
| # Ref- Modified Sponsor's Table 9.1 (Page 19 of 2152- Full Final Report) | | | | |
| Note: | | | | |
| a = Period I only; | | | | |
| b = Updated; | | | | |

| |
|--|
| c = Vital signs were collected predose, 12 and 24 hours after dose administration; d = Pharmacokinetic samples collected: predose and 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 after dose administration; e = CBC with differential and Clinical Chemistry |
|--|

Pre-Study

During screening, the following assessments were completed: medical and medication history, physical examination, sitting blood pressure and heart rate, oral temperature, respiratory rate, electrocardiogram, clinical laboratory evaluations, screens for HIV antibody, hepatitis B surface antigen, hepatitis C antibody, drugs of abuse, pregnancy (females only), and FSH (females 60 years of age or younger) within 28 days prior to Period I dose administration. All subjects gave written informed consent.

Demographic data (including height, weight, age, gender, race, and ethnicity) were collected for each subject. This information was presented in Section 14.1 for all subjects. The summary of the mean demographic data of the exposed subjects is presented in the table below.

Study Check-in

At study check-in, the subjects were briefly evaluated to assess if they continued to meet the study inclusion/exclusion criteria. In addition, a blood sample was collected for a pregnancy screen (females only).

Vital Signs Measurement

Sitting blood pressure and radial heart rate were measured prior to dosing and at 12 and 24 hours after each dose of study medication.

ECG (12-Lead) Recording and Evaluation

A 12-lead ECG was recorded during the screening visit.

Post-Study

Study exit procedures were completed within 14 days after the last blood sample collection. The exit procedures included general observations, a physical examination, blood pressure, heart rate and temperature evaluations, clinical laboratory tests and a pregnancy screen (females only).

Serum Valproic Acid Concentration Measurements and Blood Draw Time Points

The measurements of this study were the serum concentrations of valproic acid.

During each study period, 21 blood samples (7 mL each) were collected from each subject (via venipuncture) at the following time points: within one hour prior to dosing (0 hour) and after

dose administration 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. Approximately 441 mL of blood was collected from each subject for pharmacokinetic samples over the course of the study.

Analysis

An analysis of variance (ANOVA) was performed on each of the pharmacokinetic parameters using SAS® software. The ANOVA model containing factors for sequence of products, subjects within sequence, periods and products was utilized in comparing the effects between the test and reference products. Differences were declared statistically significant at the 5% level. A 90% confidence interval about the ratio of the mean test value to mean reference value was calculated for all of the pharmacokinetic parameters for each test product. The calculation for the confidence intervals used the least squares means (LSMEANS) and the standard error of the estimate, both generated by the SAS® software. The ratio of the geometric means for the ln-transformed data and the corresponding 90% confidence intervals were calculated for AUC_{0-t}, AUC_{0-∞}, and C_{max}, as well. The statistical analysis was done using SAS®, Version 8.2 for Windows, using code based on Chow and Liu pp. 559-562. The lower limit of quantitation for valproic acid was 2.00 µg/mL. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero. The documentation of statistical methods employed for this study was presented in Appendix 16.1.9 of the submission

Study Subjects

Demographics

The summary of the mean demographic data of the exposed subjects is presented in the table below.

| TABLE 10.1.2 [#] : SUMMARY OF MEAN DEMOGRAPHIC DATA (±SD) | | | |
|---|---------------------|---------------|---------------|
| | 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) |
| # Ref: Modified Sponsor's Table 11.1 (Pages 25, 40 of 2152- Full Final Report) | | | |
| Race: Caucasian (White) = 32 subjects (88.89%); Asian = 1 subject (2.78%); Hispanic = 3 subjects (8.3%) | | | |

Disposition

All subjects checked in the day prior to dose administration at the clinical facility at specified dates for each of the three periods and remained confined at the clinical facility until after the 24 hour post-dose blood sample collection. At study hours 36, 48, and 72, the subjects returned to the clinical facility for the scheduled blood sample collections.

| TABLE 10.1.3 [#] : SUBJECT DISPOSITION (N) | |
|---|----|
| Subjects Randomized | 36 |

| | |
|--|----|
| Subjects Who Received Treatment | 36 |
| Subjects Successfully Completed | 36 |
| Subjects Who Withdrew Consent | 0 |
| Subjects Dropped by Investigator/Sponsor | 0 |
| Subjects Discontinued | 0 |
| Subjects Who Withdrew or were Dismissed due to AEs | 0 |
| # Ref- Modified Sponsor's Table 10.2 (Page 24 of 2152- Full Final Report) | |

Exposure and Extent

The total exposure for each of the 36 subjects who completed the study was 1500mg (3 treatment doses; each dose = 1 x 500 mg).

Summary of the PK Results

The administration of valproic acid 500 mg softgel capsules with food significantly decreased the ln-transformed C_{max} (23.44%). However, food did not significantly decrease the ln-transformed AUC_{0-t} (4.18%) and ln-transformed AUC_{0-∞} (4.12%). The 90% confidence intervals about the ratio of Treatment B (Test Product Non-Fasting) geometric mean to Treatment A (Test Product Fasting) geometric mean were within the 80% and 125% limits for the pharmacokinetic parameters AUC_{0-t}, and AUC_{0-∞}, but not for C_{max}, of the ln-transformed data. The 90% confidence intervals about the ratio of Treatment A (Test Product Fasting) geometric mean to Treatment C (Reference Product Fasting) geometric mean were within the 80% and 125% limits for the pharmacokinetic parameters C_{max}, AUC_{0-t}, and AUC_{0-∞} of the ln-transformed data.

The two tables shown below summarize these results.

| TABLE 10.1.4[#]: PK RESULTS | | | | |
|---|--------------------------------|--------------------------------|----------------|----------------|
| TEST PRODUCT NON-FASTING (TREATMENT B[^]) VS. TEST PRODUCT FASTING (TREATMENT A[^]) | | | | |
| Geometric Means, Ratio of Means, and 90% Confidence Intervals- Ln-Transformed Data | | | | |
| Valproic Acid (N=36) | | | | |
| Parameter | Treatment B[^] | Treatment A[^] | % Ratio | 90% CI |
| AUC_{0-t} (µg-hr/mL) | 845.97 | 882.90 | 95.82 | (93.79, 97.89) |
| AUC_{0-∞} (µg-hr/mL) | 926.80 | 966.67 | 95.88 | (93.92, 97.87) |
| C_{max} (µg/mL) | 40.84 | 53.35 | 76.56 | (73.29, 79.9) |
| # Ref Modified Sponsor's Table 11.2 ((Page 27 of 2152- Full Final Report) | | | | |
| [^] A= 500mg Valproic acid I Delayed Release Softgel (Fasting), B= 500mg Valproic acid Delayed Release Softgel (Non-fasting- after fatty meal), C= 500mg Depakote® Delayed Release Tablet (Fasting) | | | | |

| TABLE 10.1.5[#]: PK RESULTS | | | | |
|---|--------------------------------|--------------------------------|----------------|----------------|
| TEST PRODUCT FASTING (TREATMENT A[^]) VS. REF PRODUCT FASTING (TREATMENT C[^]) | | | | |
| Geometric Means, Ratio of Means, and 90% Confidence Intervals- Ln-Transformed Data | | | | |
| Valproic Acid (N=36) | | | | |
| Parameter | Treatment A[^] | Treatment C[^] | % Ratio | 90% CI |
| AUC_{0-t} (µg-hr/mL) | 882.90 | 916.05 | 96.38 | (94.34, 98.47) |
| AUC_{0-∞} (µg-hr/mL) | 966.67 | 997.51 | 96.91 | (94.93, 98.93) |
| C_{max} (µg/mL) | 53.35 | 54.86 | 97.24 | (93.1, 101.57) |
| # Ref Modified Sponsor's Table 11.3 (Page 27 of 2152- Full Final Report) | | | | |
| [^] A= 500mg Valproic acid Delayed Release Softgel (Fasting), C= 500mg Depakote® Delayed Release Tablet (Fasting) | | | | |

Safety Overview & Adverse Events

There were no deaths or serious AEs or other significant AEs. There were 10 AEs that occurred in 8 subjects as shown in the table below. Of these, 3 AEs, 5 AEs and 2 AEs occurred with treatments A, B and C respectively. Eight AEs (in 6 subjects) occurred with the administration of the test drug regardless of the condition (fast vs. fed) and 2 AEs (in 2 subjects) occurred with the administration of the RLD. All AEs were mild to moderate in severity. The breakdown of these AEs using MedDRA (Version 9.0) by treatment is shown in the table below. Subjects 05 and 22 each experienced two AEs (subject 05 experienced pain in the extremity and back pain and subject 22 experienced nausea and headache). There were 2 adverse events considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under fasting conditions. There were 3 adverse events considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under non-fasting conditions. All AEs were reported resolved without treatment except for subject 22, whose headache eventually resolved with intervention. There were 2 AEs in 2 subjects with Treatment C (RLD- Depakote®) and none of these were considered related.

| | Total | TREATMENT [^] | | |
|--|-------|--------------------------------|------------------------------------|-------------------------------|
| | | A [^] (Test, Fast) | B [^] (Test, Non-fast) | C [^] (Ref, Fast) |
| Deaths (Subject N) | 0 | 0 | 0 | 0 |
| Serious AE (Subject N) | 0 | 0 | 0 | 0 |
| Subjects Who Withdrew or Were Dismissed Due to AEs | 0 | 0 | 0 | 0 |
| Other Significant Adverse Events (Subject N) | 0 | 0 | 0 | 0 |
| Common Adverse Events (Subject N) | 8 | 2 | 4 | 2 |
| Common Adverse Events (Events N) | 10 | 3 | 5 | 2 |

Ref: Modified Sponsor's Table 12.2 (Page 29 of 2152- Full Final Report), 16.2.7 (Page. 480 of 2152- Full Final Report)
[^] A= 500mg Valproic acid Softgel Delayed Release (Fasting), B= 500mg Valproic acid Softgel Delayed Release (Non-fasting- after fatty meal), C= 500mg Depakote® Delayed Release Tablet (Fasting)

| Subject # | Body System* | Event | Intensity | Relation | Outcome | Treatment [^] |
|-----------|---------------------|-----------------|-----------|-----------|-----------|------------------------|
| 02 | Nervous | Dizziness | Mild | Unrelated | Resolved | C |
| 03 | Mus. Skeletal & CT | Back Pain | Mild | Unrelated | Resolved | B |
| 05 | Mus. Skeletal & CT | Extremity pain | Mild | Probable | Resolved | B |
| 05 | Mus. Skeletal & CT | Back pain | Mild | Probable | Resolved | B |
| 15 | Nervous | Dizziness | Mild | Unrelated | Resolved | C |
| 21 | Nervous | Headache | Mild | Unrelated | Resolved | A |
| 22 | GI | Nausea | Mild | Probable | Resolved | A |
| 22 | Nervous | Headache | Moderate | Probable | Resolved+ | A |
| 23 | GI | Nausea | Mild | Unrelated | Resolved | B |
| 34 | Resp, Thoracic, Med | Nasopharyngitis | Mild | Remote | Resolved | B |

Ref: Modified Sponsor's Tables 12.3, 12.4, 12.5 (pp. 31-34 of 2152-Full Final Report)

* MedDRA Version 9.0; + Required therapy; ^ A= 500mg Valproic acid Softgel Delayed Release (Fasting), B= 500mg Valproic acid Softgel Delayed Release (Non-fasting- after fatty meal), C= 500mg Depakote® Delayed Release Tablet (Fasting)

The following was the frequency for each of the AEs for the 36 subjects by treatment-

- **Treatment A – headache 2 (5.56%), nausea 1 (2.78%)**
- **Treatment B – nausea 1 (2.78%), back pain 2 (5.56%), extremity pain 1 (2.78%), nasopharyngitis 1 (2.78%)**
- **Treatment C - dizziness 2 (5.56%)**

Labs

Results from screening and exit hematology tests, clinical chemistry tests, urinalysis (screening only), urine drug screen (screening only), HIV antibody screen (screening only), hepatitis B surface antigen screen (screening only), hepatitis C antibody screen (screening only) and serum pregnancy screens (females only) were presented in Appendix 16.4; page 481 of 2152 (Full Final Report).

All results were reviewed by the clinical investigators. Those values outside the reported **reference range were either designated as ‘NCS’ (not clinically significant) or follow-up testing** was requested. There were no clinically significant changes in the clinical laboratory measurements over the course of the study which could be reasonably associated with the test formulation.

Vital Signs, Physical Findings and Other Observations Related to Safety

Individual vital signs, physical examination, and electrocardiograms collected at screening were presented in the section entitled *Individual Subject Data Listings* in (see Appendix 16.4). The results of the physical examination done at study exit were also presented in Appendix 16.4.

Summary Conclusions

According to the sponsor, the results of this study indicated that the test Valproic Acid Enteric 500 mg Softgel was bioequivalent to the reference Depakote® Delayed-Release Tablets 500 mg under fasting conditions. Further, administration of the test Valproic Acid Enteric 500 mg Softgel under non-fasting conditions resulted in a significant decrease in C_{max} , but did not affect the extent of absorption ($AUC_{(0-t)}$ and $AUC_{(0-\infty)}$). Reference is made to the Agency PK review on the acceptance of the results establishing such PK comparability (between the 500 mg test valproic acid delayed release capsule and the 500 mg RLD [Depakote®]).

No deaths or serious adverse events (AE) or other significant adverse events were reported. There were a total of 10 adverse events reported by 8 subjects over the course of the study. Three AEs, 5 AEs and 2 AEs occurred with treatments A, B and C respectively. Eight AEs (in 6 subjects) occurred with the administration of the test drug regardless of the condition (fast vs.

fed) and 2 AEs (in 2 subjects) occurred with the administration of the RLD. There were 2 adverse events considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under fasting conditions. There were 3 adverse events considered to be related to the oral administration of the test Valproic Acid Enteric 500 mg Softgel under non-fasting conditions. None of the AEs were considered related to the RLD (Depakote®). In concurrence with the sponsor, the clinical laboratory values were considered unremarkable and none of the values outside of the reference range at study exit were considered directly attributable to the product.

Overall, valproic acid was well tolerated as a single, oral dose of 500 mg administered under fasting and fed conditions.

10.2 Line-by-Line Labeling Review

See 9.4 label review.

Clinical Review
Ramesh Raman, MD
NDA 22152
Valproic Acid Delayed Release Capsules; Dipropylacetic Acid, 2-propylpentanoic acid

REFERENCES

None.

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this page is the manifestation of the electronic signature.**

/s/

Ramesh Raman

10/22/2007 02:35:07 PM

MEDICAL OFFICER

Clinical Review for NDA 22152 505(b)(2) PK/bioavailability application. See
attached review document for details.

Eric Bastings

10/26/2007 09:00:21 AM

MEDICAL OFFICER

Please refer to my memorandum for discussion of topics
where my opinion may be different from that
of Dr. Raman.

Review and Evaluation of Clinical Data

CONSULT: #10983

FROM: HFD-120

NAME OF DRUG: Valproic acid delayed release capsules

SPONSOR: Banner Pharmacaps

DATE ASSIGNED: 1/9/07

DESIRED COMPLETION 10/22/07

LETTER DATE: December 20, 2006

MATERIAL RECEIVED: Original 505(b)(2) NDA
Valproic Acid Delayed Release Capsules,
500 mg, 125 mg

I. Review:

HFD-130 has been consulted to verify the mania sections in labeling for this NDA.

BACKGROUND:

Banner Pharmacaps Inc. (BPI) is submitting a **New Drug Application (“NDA”) for Valproic Acid Delayed Release Capsules, 500 mg, 125 mg**, in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. BPI is seeking FDA approval for Prescription marketing of this drug product.

The enclosed application relies on the Agency’s finding of safety and effectiveness for the reference listed drug (RLD), Depakote® Tablets, 500 mg, 250 mg, 125 mg, the subject of NDA 18-723, held by Abbott Pharmaceuticals PR Ltd. Therefore, the pharmacology, toxicology, microbiology, statistical and clinical portions of this application rely solely on the RLD, and no further literature references are provided herein.

The proposed drug product, Valproic Acid Capsules, 500mg, 125 mg, differs from the 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. **BPI’s proposed drug product is bioequivalent** to Depakote®, as demonstrated by the bioequivalence studies performed by the contract research organization (CRO), PRACS, and provided herein in accordance with 21 CFR 314.54(a). No further clinical studies on the proposed drug product have been performed. A biowaiver is requested herein for the proposed 125 mg strength product.

There is no unexpired exclusivities applicable to the RLD and two patents with expiration date of Jan 29, 2008. BPI is not infringing any RLD patent claims which refer to molar ratios **of active moiety, which is different for BPI’s product** (valproic acid vs. divalproex sodium). **BPI’s proposed product has no relevant** patents or marketing exclusivity to claim at this time. Form FDA 3397, the PDUFA user fee cover sheet is not being submitted as it is not applicable for a 505(b) (2) application.

The current Depakote® Tablets labeling contains directions for adults and children 10 years and older. BPI seeks to match the RLD labeling for marketing of this prescription product. However, in accordance with the Pediatric Research Equity Act of 2003, a pediatric assessment is required for NDA products that seek approval of a new dosage form. BPI is submitting herein a waiver from the pediatric assessment for children under age 10.

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BPI manufactures the proposed drug product at its facilities in High Point, North Carolina, and stability packaging is also performed by BPI. The finished product will be shipped to repackagers distributed by repackagers, in **accordance with BPI's** approved 505(b)(2) NDA.

MANIA LABELING:

The changes in the mania sections are limited to 3 types.

- New labeling format
- Replaced Depakote with valproate
- Trade name vs. Established name

Please see the sections reproduced below.

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15 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

II. RECOMMENDATIONS:

I believe the mania sections in this labeling are acceptable as provided by the sponsor. There are only three types of changes. These are the new labeling format, replacing depakote with valproate and the trade name vs. the established name. The content of the mania sections are accurate and compare directly with the approved RLD Depakote label. I have not reviewed the other sections of the label.

Earl Hearst, M.D.

HFD-130

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this page is the manifestation of the electronic signature.**

/s/

Earl Hearst
4/18/2007 04:50:11 PM
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Ni Aye Khin
4/18/2007 06:47:47 PM
MEDICAL OFFICER

Thomas Laughren
4/20/2007 08:19:28 AM
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