CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-152

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-152
From: Ramesh Sood, Branch Chief, ONDQA
Date: 8-Jul-2008
Drug name: Stavzor (valproic acid) delayed release capsules, 125 mg, 250 mg, and 500 mg
Applicant: Banner Pharmacaps, Inc.
Subject: Approval recommendation for NDA 22-152

Introduction: The Stavzor (valproic acid) delayed release capsules are indicated for seizure disorders, manic episodes and migraine prophylaxis. The capsules are available in 125 mg, 250 mg and 500 mg strengths. The capsules are orange soft gelatin capsules and the gelatin formulation is modified so that the drug product has enteric or delayed release properties. The fill of the capsules is neat valproic acid. The capsule imprinting for the 125, 250, and 500 mg strengths is "NVN", "NVN1", and NVN2", respectively, in black print. The currently approved immediate release forms of the drug have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects. All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with ——— caps as well as in ——— corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. The details of the drug substance manufacturing and controls were reviewed and found to be acceptable in the first cycle review.

Application history and information reviewed in the this cycle: The original application (125 and 500 mg strengths) was reviewed and a discipline review letter dated 08-MAR-2007, was forwarded by electronic mail to the applicant. The amendments dated 01-JUN-2007, (labeling) and 02-JUL-2007, (CMC) were submitted in response and were the subject of the chemistry review #2. An information request letter dated 31-JUL-2007, was forwarded to the applicant and the response of 10-AUG-2007, was evaluated in chemistry review #4.

The unsolicited 19-JUL-2007, amendment added the 250 mg strength to the application. This amendment also proposed a proprietary name for the product and proposed the elimination of ——— leaving the FD&C Yellow #6. Also the ——— was replaced by black imprinting ink. For details, refer to chemistry review #3. As a result of that review, a second information request letter dated 08-AUG, 2007, was forwarded to the applicant. The response of 28-AUG-2007, to this IR was also evaluated in chemistry review #4. b(4)

An approval recommendation could have been made from the CMC perspective had not the applicant submitted the 21-SEP-2007, clinical pharmacology amendment. In response to inquiries made by the clinical pharmacology team, the applicant altered the dissolution method

such that the SDS content of the buffer stage dissolution medium was reduced from 2% to 0%. As a result, from the CMC perspective, this led to questions regarding the applicability of the previous dissolution data and the evaluation of drug product stability, the appropriateness of the proposed dissolution buffer stage acceptance criterion, and the potential necessity for additional validation data for the methodology. And finally, the data presented in the 21-SEP-2007, amendment were collected with dissolution media containing_____ SDS. The differences seen between the plot of typical dissolution profiles with these varying SDS levels were somewhat unexpected upon initial examination. The applicant was asked to provide an explanation and to address the other issues raised above, via the CMC IR comments sent by the PM in an electronic mail message of 25-SEP-2007. The response was requested to be submitted by 02-OCT-2007. However, the response was not received to allow sufficient time prior to the finalization of the final review of the 1st review cycle, chemistry review #4 (dated 04-OCT-2007). The response to the 25-SEP-2007, CMC IR request was sent in two parts on 10-OCT-2007, and 16-OCT-2007. These amendments were not reviewed prior to the first AE action. As a result, the comments in the CMC IR request of 25-SEP-2007, were again included in the AE letter dated 22-OCT-2007. However, the response to the AE letter dated 26-OCT-2007, makes reference to these earlier amendments and also includes the same information/data submitted in the two earlier amendments. The fifth review evaluated the 26-OCT-2007, response to the AE letter and also the 09-OCT-2007, labeling amendment, which contained a revised package insert. There were no changes made to the DESCRIPTION or the HOW SUPPLIED/STORAGE AND HANDLING sections so no further comment was needed regarding the 09-OCT-2007, amendment.

b(4)

The applicant received a tentative approval letter dated 21-DEC-2007, and the current amendment dated 27-MAY-2008, is submitted in response to this tentative approval letter and is the subject of the CMC review #6. This amendment contains some minor labeling changes related to the carton labels, imprint on the capsules and change in the marketing partner from JDS pharmaceuticals to Noven Therapeutics. The product imprint change is also reflected in the revised drug product specification. The applicant has submitted additional stability data that has resulted in our assignment of 21, 21 and 36 month expiration dates for the 125 mg, 250 mg and 500 mg capsules, respectively, as requested by the applicant.

All manufacturing sites have been found acceptable by Office of Compliance during the first review cycle and an "Acceptable" recommendation by made by the Ofiice of compliance on 18-Oct-2007 is still valid.

Recommended action: The application is recommended as "Approval" from CMC perspective pending agreement on the following changes to the Drug Listing Data Elements (DLDE) recommended in the review.

- *Remove the "black imprinting ink" entry from the ingredient list.*
- *Revise "ammonium hydroxide" to "ammonia solution, strong."*

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/s/

Ramesh Sood
7/8/2008 09:03:55 AM
CHEMIST

CHEMISTRY REVIEW

NDA 22-152

Stavzor™ (valproic acid) Delayed Release Capsules, 125, 250, and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 6

3. REVIEW DATE: 17-JUN-2008

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)
Amendment	01-JUN-2007 (assigned 21-JUN-2007)
Amendment	02-JUL-2007 (assigned 10-JUL-2007)
Amendment	19-JUL-2007 (assigned 30-JUL-2007)
Amendment	10-AUG-2007 (assigned 24-AUG-2007)
Amendment	28-AUG-2007 (assigned 11-SEP-2007)
Amendment	21-SEP-2007 (clinical pharm. amendment)
Amendment	09-OCT-2007 (labeling amendment, assigned 19-OCT-2007)
Amendment	10-OCT-2007 (partial response to 25-SEP-2005, CMC IR[1])
Amendment	16-OCT-2007 (partial response to 25-SEP-2005, CMC IR[1])
Amendment	26-OCT-2007 (response to AE letter, assigned 20-NOV-2007)

6. SUBMISSION(S) BEING REVIEWED:

[1] Reviewed via resubmission of information/data in 26-OCT-2007, amendment.

Submission(s) Reviewed	Document Date
Amendment	27-MAY-2008 (response to tentative approval)

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.[2]
Address:	4125 Premier Drive High Point, NC 27265
Representative:	Dale A. Kruep, Ph.D., Director, Regulatory Affairs
Telephone:	(336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE (620)

12. STRENGTH/POTENCY: 125, 250, and 500 mg per capsule

13. ROUTE OF ADMINISTRATION: ORAL (001)

[2] Banner Pharmacaps Inc. has Noven Therapeutics LLC as a marketing partner for this drug product.

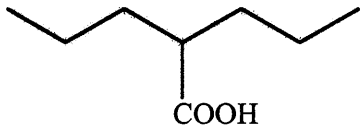
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:[3] (reproduced from 3.2.S.1.2)

Valproic acid is 2-propylpentanoic acid and has the following structure:



Molecular formula: $C_8H_{16}O_2$
Molecular weight: 144.22

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
					Adequate	07-JUL-2006	
14194	4	Banner Pharmacaps, Inc.	Gelatin Masses (Soflet and Softgel Formulations)	1	Adequate	30-APR-2007 02-AUG-2007	Information on new 250mg strength added in 17-JUL-2007, amendment. See CR#3.
					Adequate	02-AUG-2007 (black ink)	
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms.

b(4)

b(4)

[3] Note: RLD is Depakote Tablets, which contain divalproex sodium, a stable coordination complex comprised of sodium valproate and valproic acid in a 1:1 molar ratio.

							See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Reference to location in most recent CMC review
[4] The applicant has withdrawn the ——— that had been proposed for use in packaging the 500 mg strength with a——— from the application. See p. 12 of chemistry review #4.
[5] ———

b(4)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
ANDA	73,484	Banner Pharmacaps	Application referenced for drug substance information. Valproic Acid Capsules AP 29-JUN-1993

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not needed; for details see P.8 evaluation in CR#1; p. 18 of CR#3; p. 12 of CR#6.
EES	PAI Inspection	01-FEB-2007	Completed 18-OCT-2007	Acceptable recommendation from Office of Compliance (see memorandum dated 18-OCT-

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
				2007)
Pharm/Tox				Not needed
Biopharm				
Methods Validation				There are no particularly novel or complex chromatography methods nor any particular single methods deemed critical to the assessment of the drug product performance. As such, no request will be forwarded to the Agency laboratory for methodological assessment.
DMETS/DDMAC	Trade name consult	08-JAN-2007	Completed 18-OCT-2007	See p. 11 of CR#5.
EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the application is recommended for **approval (AP)**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Stavzor (valproic acid) Delayed Release Capsules and it is manufactured in three strengths, 125, 250, and 500 mg/capsule. The capsules are orange soft gelatin capsules and the gelatin formulation is modified so that the drug product has enteric or delayed release properties. The fill of the capsules is neat valproic acid. The capsule imprinting for the 125, 250, and 500 mg strengths is "NVN", "NVN1", and NVN2", respectively, in black print. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with ——— caps as well as in ——————corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. The expiration dating periods for the 125, 250, and 500 mg strengths of 21, 21, and 36 months, respectively, are supported by stability data. b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. There are immediate release forms of the drug approved that have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

The manufacturing is typical for the production of soft gelatin capsules, but with the ——————————— b(4)
——————————— the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. Upon exposure to higher pH ——————————— ——— the capsule shells rupture and the drug is released. ——————— b(4)

[redacted] b(4)

The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2).

B. Description of How the Drug Product is Intended to be Used

The 125 mg, 250 mg, and 500 mg strengths of the product are to be packaged in 100 ct HDPE bottles (50/60, 100, and 150 cc, respectively). The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/6/17/08
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

LChen/DNP/Regulatory PM
MHeimann/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I
AAl-Hakim/ONDQA/DIV I/Branch Chief

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Craig Bertha
6/17/2008 08:14:21 AM
CHEMIST

Hardcopy of amendment is in your mailbox for reference if necessary.

Ramesh Sood
6/18/2008 10:28:47 AM
CHEMIST

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-152
From: Ramesh Sood, Branch Chief, ONDQA
Date: 27-Nov-2007
Subject: Approval recommendation for NDA 22-152

Introduction: The Stavzor (valproic acid) delayed release capsules are indicated for seizure disorders, manic episodes and migraine prophylaxis. The capsules are available in 125 mg, 250 mg and 500 mg strengths. . All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with [redacted] caps as well as in [redacted] corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. The review #5 addresses the responses submitted by the applicant in their resubmission in response to the pending CMC issues from the first cycle. b(4)

Drug Substance: The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. The details of the drug substance manufacturing and controls were reviewed and found to be acceptable in the first cycle review.

Drug Product: The currently approved immediate release forms of the drug have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

The pending issues addressed in this cycle related to the change in the dissolution media. The company has submitted adequate data to support the deletion of [redacted] SDS from the dissolution media. The product manufacturing is typical for the production of soft gelatin capsules, but with the [redacted] during the production of the soft gelatin mass, the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. Upon exposure to higher pH [redacted], the capsule shells rupture and the drug is released. [redacted] The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. All other CMC related information was found to be acceptable in first cycle CMC reviews. b(4) b(4)

All manufacturing sites have been found acceptable by Office of Compliance during the first review cycle.

Recommended action: The application is recommended as "Approval" from CMC perspective pending agreement on the labeling issues raised in the review.

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/s/

Ramesh Sood
11/27/2007 02:12:07 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-152

Stavzor™ (valproic acid) Delayed Release Capsules, 125, 250, and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 5

3. REVIEW DATE: 27-NOV-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)
Amendment	01-JUN-2007 (assigned 21-JUN-2007)
Amendment	02-JUL-2007 (assigned 10-JUL-2007)
Amendment	19-JUL-2007 (assigned 30-JUL-2007)
Amendment	10-AUG-2007 (assigned 24-AUG-2007)
Amendment	28-AUG-2007 (assigned 11-SEP-2007)
Amendment	21-SEP-2007 (clinical pharm. amendment)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	09-OCT-2007 (labeling amendment, assigned 19-OCT-2007)
Amendment	10-OCT-2007 (partial response to 25-SEP-2005, CMC IR[1])
Amendment	16-OCT-2007 (partial response to 25-SEP-2005, CMC IR[1])
Amendment	26-OCT-2007 (response to AE letter, assigned 20-NOV-2007)

[1] Reviewed via resubmission of information/data in 26-OCT-2007, amendment.

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.[2]
Address:	4125 Premier Drive High Point, NC 27265
Representative:	Dale A. Kruep, Ph.D., Director, Regulatory Affairs
Telephone:	(336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE (620)

12. STRENGTH/POTENCY: 125, 250, and 500 mg per capsule

13. ROUTE OF ADMINISTRATION: ORAL (001)

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

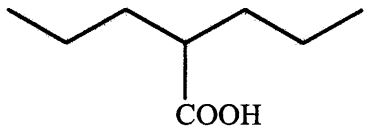
[2] Banner Pharmacaps Inc. has JDS Pharmaceuticals LLC (JDS) as a marketing partner for this drug product.

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:[3] (reproduced from 3.2.S.1.2)

Valproic acid is 2-propylpentanoic acid and has the following structure:



Molecular formula: $C_8H_{16}O_2$
Molecular weight: 144.22

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
					Adequate	07-JUL-2006	
14194	4	Banner Pharmacaps, Inc.	Gelatin Masses (Soflet and Softgel Formulations)	1	Adequate	30-APR-2007 02-AUG-2007	Information on new 250mg strength added in 17-JUL-2007, amendment. See CR#3.
					dequate	02-AUG-2007 (black ink)	
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for

b(4)

b(4)

b(4)

[3] Note: RLD is Depakote Tablets, which contain divalproex sodium, a stable coordination complex comprised of sodium valproate and valproic acid in a 1:1 molar ratio.

							solid oral dosage forms. See P.7 of CR#1
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Reference to location in most recent CMC review
[4] The applicant has withdrawn the [redacted] that had been proposed for use in packaging the 500 mg strength with a [redacted] from the application. See p. 12 of chemistry review #4.

b(4)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
ANDA	73,484	Banner Pharmacaps	Application referenced for drug substance information. Valproic Acid Capsules AP 29-JUN-1993

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not needed; for details see P.8 evaluation in CR#1 and p. 18 of CR#3.
EES	PAI Inspection	01-FEB-2007	Completed 18-OCT-2007	Acceptable recommendation from Office of Compliance (see memorandum dated 18-OCT-2007)
Pharm/Tox				Not needed
Biopharm				
Methods Validation				There are no particularly novel or complex chromatography methods nor any particular single methods deemed critical to the assessment of the drug product performance.

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
				As such, no request will be forwarded to the Agency laboratory for methodological assessment.
DMETS/DDMAC	Trade name consult	08-JAN-2007	Completed 18-OCT-2007	See p. 11 of this review.
EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the application is recommended for **approval (AP)**.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Stavzor (valproic acid) Delayed Release Capsules and it is manufactured in three strengths, 125, 250, and 500 mg/capsule. The capsules are orange soft gelatin capsules and the gelatin formulation is modified so that the drug product has enteric or delayed release properties.[4] The fill of the capsules is neat valproic acid. The capsule imprinting for the 125, 250, and 500 mg strengths is "JDS", "JDS1", and JDS2", respectively. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with [redacted] caps as well as in [redacted] corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. There are immediate release forms of the drug approved that have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

The manufacturing is typical for the production of soft gelatin capsules, but with the [redacted] b(4)
[redacted], the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. Upon exposure to higher pH [redacted] b(4)

[4] For a more detailed discussion of the [redacted] and proposed changes see the 2nd paragraph on p. 10. b(4)

[redacted], the capsule shells rupture and the drug is released. [redacted]

[redacted] b(4)

[redacted] The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2).

B. Description of How the Drug Product is Intended to be Used

The 125 mg, 250 mg, and 500 mg strengths of the product are to be packaged in 100 ct HDPE bottles (50/60, 100, and 150 cc, respectively). The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/11/27/07
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

LChen/DNP/Regulatory PM
MHeimann/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I

10 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Craig Bertha
11/27/2007 08:10:57 AM
CHEMIST

Ramesh Sood
11/27/2007 01:41:30 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-152

Stavzor™ (valproic acid) Delayed Release Capsules, 125, 250, and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 4

3. REVIEW DATE: 04-OCT-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)
Amendment	01-JUN-2007 (assigned 21-JUN-2007)
Amendment	02-JUL-2007 (assigned 10-JUL-2007)
Amendment	19-JUL-2007 (assigned 30-JUL-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	10-AUG-2007 (assigned 24-AUG-2007)
Amendment	28-AUG-2007 (assigned 11-SEP-2007)
Amendment	21-SEP-2007 (biopharmaceutics amendment)

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.[1]
Address:	4125 Premier Drive High Point, NC 27265
Representative:	Dale A. Kruep, Ph.D., Director, Regulatory Affairs
Telephone:	(336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE (620)

12. STRENGTH/POTENCY: 125, 250, and 500 mg per capsule

13. ROUTE OF ADMINISTRATION: ORAL (001)

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

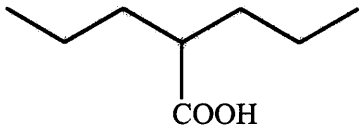
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

[1] Banner Pharmacaps Inc. has JDS Pharmaceuticals LLC (JDS) as a marketing partner for this drug product.

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: (reproduced from 3.2.S.1.2)

Valproic acid is 2-propylpentanoic acid and has the following structure:



Molecular formula: $C_8H_{16}O_2$
Molecular weight: 144.22

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]					Adequate	07-JUL-2006	
14194	4	Banner Pharmacaps, Inc.	Gelatin Masses (Soflet and Softgel Formulations)	1	Adequate	30-APR-2007 02-AUG-2007	Information on new 250mg strength added in 17-JUL-2007, amendment
[redacted]					Adequate	[redacted] 02-AUG-2007 (black ink)	[redacted]
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1

b(4)

b(4)

b(4)

[1] Action codes for DMF Table:

1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review
[4] The applicant has been requested to withdraw th——— ottle that had been proposed for use in packaging the 500 mg strength with a ——— from the application. See deficiency comment on p. 20 of chemistry review #2. b(4)

b(4)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
ANDA	73484	Banner Pharmacaps	Application referenced for drug substance information. Valproic Acid Capsules AP 29-JUN-1993

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not needed at this time, for details see P.8 evaluation in CR#1 and p. 18 of CR#3.
EES	PAI Inspection	01-FEB-2007	Pending	
Pharm/Tox				Not needed
Biopharm				Informal consultation on dissolution method for coordination of reviews
Methods Validation				Decision to forward to labs postponed until specification/method updates are made.
DMETS/DDMAC	Trade name consult	08-JAN-2007	Pending	A new proprietary name and backup is proposed. The consult for these and the other labeling was sent to DDMAC by the PM L. Chen.
EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, the application is considered to be approvable (AE).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Valproic Acid Delayed Release Capsules and it is manufactured in three strengths, 125, 250, and 500 mg/capsule. The capsules are orange soft gelatin capsules and the gelatin formulation is modified so that the drug product has enteric or delayed release properties.[2] The fill of the capsules is neat valproic acid. The capsule imprinting for the 125, 250, and 500 mg strengths is "JDS", "JDS1", and JDS2", respectively. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with [redacted] caps as well as in [redacted] corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. There are immediate release forms of the drug approved that have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

The manufacturing is typical for the production of soft gelatin capsules, but with the [redacted] during the b(4)
production of the soft gelatin mass, the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. The release of the drug from the gelatin is dependent on the rupturing of the shell [redacted] b(4)

[2] For a more detailed discussion of [redacted] and proposed changes see p. 9. b(4)

[redacted] during manufacturing. [redacted] The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2). b(4)

B. Description of How the Drug Product is Intended to be Used

The 125 mg, 250 mg, and 500 mg strengths of the product are to be packaged in 100 ct HDPE bottles (50/60, 100, and 150 cc, respectively). The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

In the 21-SEP-2007, amendment, the applicant changed the dissolution method from one containing [redacted] sodium dodecyl sulfate (SDS) in the media to [redacted] SDS. For details of what information are required as a result, see the draft letter attached. Approvability is also dependent on a satisfactory recommendation from the Office of Compliance regarding the inspection of the various sites. A recommendation is currently pending. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/10/04/07
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

LChen/DNP/Regulatory PM
MHeimann/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I

7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Craig Bertha
10/4/2007 08:40:27 AM
CHEMIST

Hardcopy in your office with amendments.

Ramesh Sood
10/4/2007 02:17:52 PM
CHEMIST

DATE: 18-OCT-2007

TO: N22-152 Division File

FROM: Craig Bertha, Ph.D.

SUBJECT: Establish Evaluation Request Status

See the attached summary reproduced from the Establishment Evaluation System regarding the overall recommendation of ACCEPTABLE from the Office of Compliance for the N22-152 application.

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22152/000
Org Code : 120
Priority : 3S

Sponsor: BANNER PHARMACAPS
4125 PREMIER DR
HIGH POINT, NC 272658144

Stamp Date : 22-DEC-2006
PDUFA Date : 22-OCT-2007
Action Goal :
District Goal: 23-AUG-2007

Brand Name : VALPROIC ACID DELAYED RELEASE CAPSULES
Estab. Name:
Generic Name: VALPROIC ACID DELAYED RELEASE CAPSULES
Dosage Form: (DELAYED RELEASE CAPSULE)
Strength : 125 MG, 250 MG, 500 MG

FDA Contacts:	S. GOLDIE	Project Manager	301-796-2055
	C. BERTHA	Review Chemist	301-796-2410
	M. HEIMANN	Team Leader	301-796-1678

Overall Recommendation: ACCEPTABLE on 18-OCT-2007by C. CRUZ (HFD-323) 301-827-9013

Establishment : CFN : FEI : 3004436627
BANNER PHARMACAPS
4344 FEDERAL DR
GREENSBORO, NC 274108128

DMF No: 14194 AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : CSG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-MAR-07
Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1063522 FEI : 3001451366

BANNER PHARMACAPS INC

4125 PREMIER DR

HIGH POINT, NC 272658144

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile : CSG OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-OCT-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted]

b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

DMF No: 6428 AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 01-FEB-07
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI :

[redacted] b(4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : CSG OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 31-JAN-07
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

---

cc:
DNP/LChen
DNP/EBastings
ONDQA/DIV 1/CBertha
ONDQA/DIV 1/MHeimann
ONDQA/DIV 1/RSood
ONDQA/DIV 1/SGoldie

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/s/

Craig Bertha
10/18/2007 02:03:15 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-152

Stavzor™ (valproic acid) Delayed Release Capsules, 125, 250, and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 3

3. REVIEW DATE: 06-AUG-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)
Amendment	01-JUN-2007 (assigned 21-JUN-2007)
Amendment	02-JUL-2007 (assigned 10-JUL-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	19-JUL-2007 (assigned 30-JUL-2007)

7. NAME & ADDRESS OF APPLICANT:

Name: Banner Pharmacaps, Inc.[1]

Address: 4125 Premier Drive
High Point, NC 27265

[1] Banner Pharmacaps Inc. has JDS Pharmaceuticals LLC (JDS) as a marketing partner for this drug product.

Representative: Dale A. Kruep, Ph.D., Director, Regulatory Affairs

Telephone: (336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE (620)

12. STRENGTH/POTENCY: 125, 250, and 500 mg per capsule

13. ROUTE OF ADMINISTRATION: ORAL (001)

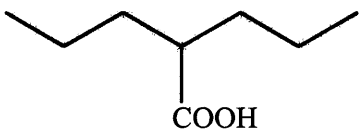
14. Rx/OTC DISPENSED: _X_ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: (reproduced from 3.2.S.1.2)

Valproic acid is 2-propylpentanoic acid and has the following structure:



Molecular formula: $C_8H_{16}O_2$
Molecular weight: 144.22

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
[redacted]					Adequate	07-JUL-2006	b(4)
14194	4	Banner Pharmacaps, Inc.	Gelatin Masses (Soflet and Softgel Formulations)	1	Adequate	30-APR-2007 02-AUG-2007	Information on new 250mg strength added in 17-JUL-2007, amendment
[redacted]					Adequate	[redacted] 02-AUG-2007 (black ink)	b(4)
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1 b(4)
							Review not needed per bottle review policy for solid oral dosage forms. See P.7 of CR#1
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[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted

6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review
[4] The applicant has been requested to withdraw the [redacted] bottle that had been proposed for use in packaging the 500 mg strength with a [redacted], from the application. See deficiency comment on p. 20 of chemistry review #2. b(4)
[5] [redacted] b(4)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
ANDA	73484	Banner Pharmacaps	Application referenced for drug substance information. Valproic Acid Capsules AP 29-JUN-1993

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not needed at this time, for details see P.8 evaluation in CR#1 and p. 18 below.
EES	PAI Inspection	01-FEB-2007	Pending	
Pharm/Tox				Not needed
Biopharm				Informal consultation on dissolution method for coordination of reviews
Methods Validation				Decision to forward to labs postponed until specification/method updates are made.
DMETS/DDMAC	Trade name consult	08-JAN-2007	Pending	A new proprietary name and backup is proposed. The consult for these and the other labeling was sent to DDMAC by the PM L. Chen.
EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable (AE) pending the resolution of the issues outlined in the information request letter of 31-JUL-2007, for the 125 mg and 500 mg strengths. The approval of the newly added 250 mg strength can be recommended once the applicant adequately addresses the issues outlined in the attached letter at the end of this review, assuming an appropriate response to the 31-JUL-2007, letter is given. **It is requested that the ONDQA project manager forward the comments in the attached draft letter to the applicant as an information request.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Valproic Acid Delayed Release Capsules and it is manufactured in three strengths, 125, 250, and 500 mg/capsule. The capsules are orange soft gelatin capsules and the gelatin formulation is modified so that the drug product has enteric or delayed release properties.[2] The fill of the capsules is neat valproic acid. The capsule imprinting for the 125, 250, and 500 mg strengths is _____, and_____ respectively. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. All strengths of the drug are proposed to be packaged in HDPE bottles (100 ct each) with _____caps as well as in _____ corrugated cardboard boxes for bulk storage and shipping for repackaging purposes only, not for marketing. b(4) b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. There are immediate release forms of the drug approved that have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

[2] For a more detailed discussion of the _____ and proposed changes see p. 11. b(4)

The manufacturing is typical for the production of soft gelatin capsules, but with the [redacted] during the production of the soft gelatin mass, the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach [redacted] The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2). b(4) b(4)

B. Description of How the Drug Product is Intended to be Used

The 125 mg, 250 mg, and 500 mg strengths of the product are to be packaged in 100 ct HDPE bottles (50/60, 100, and 150 cc, respectively). The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily.

C. Basis for Approvability or Not-Approval Recommendation

After chemistry review #2, which covered the 125 mg and 500 mg strengths alone, there were several issues affecting approvability. The drug product specifications had an [redacted] After discussion with the medical officer, it was concluded that there were no clinical data provided that could support [redacted] for these delayed release dosage forms. The applicant has observed [redacted] in the stability samples of the drug product that have been stored at the intermediate and the accelerated stability conditions, however, the occurrences are also package/strength dependent [redacted] package for 500 mg strength). The applicant is being asked to withdraw [redacted] packaging presentation for the 500 mg strength (they state they will not market until supporting data are obtained). In the 100 ct presentations, for storage of the 125 mg and 500 mg strengths under the intermediate and long term conditions, there were no reports of failure to meet the physical evaluation testing which examines for [redacted] capsules. Thus, the [redacted] should be removed from the acceptance criteria for this delayed release soft gelatin capsule drug product. The expiry period requested for the 125 mg strength of [redacted] can not be supported considering the stability failures for the physical evaluation. The data support a [redacted] month expiry for the 125 mg strength at this time. These issues were included in the information request letter of 31-JUL-2007. No response has been received as of yet for this request. b(4) b(4) b(4) b(4)

Chemistry review #3 includes the evaluation of the 19-JUL-2007, amendment adding the 250 mg strength of the product. As for the 125 mg strength, there is only 12 months of

long term stability data provided for the 250 mg strength and considering the principles of ICH Q1E and Q1D, no more than a [redacted] expiry period can be granted for this strength. And in the 100 ct presentation, for storage of the 250 mg strength under the intermediate and long term conditions, there were also no reports of failure to meet the physical evaluation testing which examines for [redacted] capsules. There are some labeling comments that should be addressed by the applicant as well. See the draft letter at the end of this review. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/08/06/07
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

LChen/DNP/Regulatory PM
MHeimann/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I

19 Page(s) Withheld

✔ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Craig Bertha
8/7/2007 08:52:34 AM
CHEMIST

Martha Heimann
8/7/2007 09:11:07 AM
CHEMIST
Signed for Dr. Ramesh Sood.

Appears This Way
On Original

CHEMISTRY REVIEW

NDA 22-152

Valproic Acid Delayed Release Capsules, 125 and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 2

3. REVIEW DATE: 30-JUL-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment	01-JUN-2007 (assigned 21-JUN-2007)
Amendment	02-JUL-2007 (assigned 10-JUL-2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.
Address:	4125 Premier Drive High Point, NC 27265
Representative:	Dale A. Kruep, Ph.D., Director, Regulatory Affairs

Telephone: (336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

11. DOSAGE FORM: CAPSULE, DELAYED RELEASE (620)

12. STRENGTH/POTENCY: 125 or 500 mg per capsule

13. ROUTE OF ADMINISTRATION: ORAL (001)

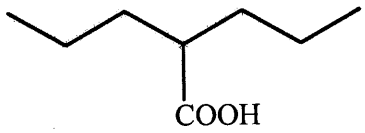
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____**SPOTS product – Form Completed**

__X__ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: (reproduced from 3.2.S.1.2)

Valproic acid is 2-propylpentanoic acid and has the following structure:



Molecular formula: $C_8H_{16}O_2$
Molecular weight: 144.22

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
					Adequate	07-JUL-2006	
14194	4	Banner Pharmacaps, Inc.	Gelatin Masses (Soflet and Softgel Formulations)	1	Adequate	30-APR-2007	
					Adequate	25-JUL-2005	
							Review not needed per bottle review policy for solid oral dosage forms. See P.7
							Review not needed per bottle review policy for solid oral dosage forms. See P.7
							Review not needed per bottle review policy for solid oral dosage forms. See P.7
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b(4)

b(4)

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application

5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review
[4] The applicant has been requested to withdraw the [redacted] bottle that had been proposed for use in packaging the 500 mg strength with a [redacted], from the application. See deficiency comment on p. 20. b(4)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
ANDA	73484	Banner Pharmacaps	Application referenced for drug substance information. Valproic Acid Capsules AP 29-JUN-1993

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				Not needed at this time, for details see P.8 evaluation
EES	PAI Inspection	01-FEB-2007	Pending	
Pharm/Tox				Not needed
Biopharm				Informal consultation on dissolution method for coordination of reviews
Methods Validation				Decision to forward to labs postponed until specification/method updates are made.
DMETS	Trade name consult	08-JAN-2007	Pending	No proprietary name is proposed. Consult forwarded by C. Calder (previous PM).
EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable (AE) pending the resolution of the issues outlined in the attached letter. It is requested that the ONDQA project manager forward the comments to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Valproic Acid Delayed Release Capsules and it is manufactured in two strengths, 125 and 500 mg/capsule. The capsule is a soft gelatin capsule and the gelatin formulation is modified so that the drug product has enteric or delayed release properties. The fill of the capsules is neat valproic acid. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. Both strengths of the drug are proposed to be packaged in HDPE bottles with ——— caps as well as ——— corrugated cardboard boxes for bulk storage and shipping. b(4)

The drug substance is valproic acid (chemical name 2-propylpentanoic acid) and it is a high boiling liquid at room temperature. It has a characteristic odor. There are immediate release forms of the drug approved that have the same maximum daily dose proposed for this drug product, but these are associated with gastric side effects such as nausea and vomiting. The delayed release property is purported to help alleviate these side effects.

The manufacturing is typical for the production of soft gelatin capsules, but with the ——— during the production of the soft gelatin mass, the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the b(4)

proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2).

B. Description of How the Drug Product is Intended to be Used

The 125 mg and 500 mg strengths of the product are to be packaged in 100 ct HDPE bottles. Note that there will be bulk packages used for shipping for repackaging [redacted] packagers proposed). The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The applicant currently [redacted] After discussion with the medical officer, it was concluded that there was no clinical data that could support this [redacted] The applicant has observed [redacted] in the stability samples of the drug product that have been stored at the intermediate and the accelerated stability conditions, however, the occurrences are also package/strength dependent. The [redacted] should be removed from the acceptance criteria for this delayed release soft gelatin capsule drug product. The expiry period requested for the 125 mg strength of [redacted] can not be supported considering the stability failures for the physical evaluation. The data support a [redacted] month expiry for the 125 mg strength at this time. b(4) b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/07/30/07
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

LChen/DNP/Regulatory PM
MHeimann/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I

17 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Craig Bertha
7/31/2007 09:19:07 AM
CHEMIST

Martha Heimann
7/31/2007 09:28:19 AM
CHEMIST
Signed for Dr. Ramesh Sood.

Appears This Way
On Original

CHEMISTRY REVIEW

NDA 22-152

Valproic Acid Delayed Release Capsules, 125 and 500 mg

Banner Pharmacaps, Inc.

Craig M. Bertha, Ph.D.
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-152

2. REVIEW #: 1

3. REVIEW DATE: 21-FEB-2007 to BC, revised 07-MAR-2007

4. REVIEWER: Craig M. Bertha, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	20-DEC-2006 (assigned 26-JAN-2007)
Amendment	25-JAN-2007 (assigned 02-FEB-2007)
Amendment	31-JAN-2007 (assigned 06-FEB-2007)
Amendment	07-FEB-2007 (assigned 16-FEB-2007)
Amendment	15-FEB-2007 (assigned 22-FEB-2007)

7. NAME & ADDRESS OF APPLICANT:

Name:	Banner Pharmacaps, Inc.
Address:	4125 Premier Drive High Point, NC 27265
Representative:	Dale A. Kruep, Ph.D., Director, Regulatory Affairs

Chemistry Review Data Sheet

Telephone: (336) 812-8700 ext. 3303

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): valproic acid
c) Code Name/# (OGD only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(2); Reference listed drug is Depakote® Tablets, Abbott Laboratories, NDA 18-723

10. PHARMACOL. CATEGORY: treatment of manic episodes associated with bipolar disorder, as monotherapy and adjunctive therapy for multiple seizure type and prophylaxis of migraine headaches

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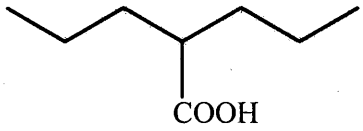
Chemistry Review Data Sheet



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[redacted]					Adequate	25-JUL-2005	
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7
[redacted]							Review not needed per bottle review policy for solid oral dosage forms. See P.7

b(4)

b(4)

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Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

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EES	PAI Inspection	01-FEB-2007	Pending	
Pharm/Tox				Not needed
Biopharm				Informal consultation on dissolution method for coordination of reviews
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EA	N/A			As per 21 CFR 25.31(a)
Microbiology				Not needed

The Chemistry Review for NDA 22-152

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is considered to be approvable (AE) from a CMC perspective. The comments in the draft letter should be forwarded by the PM to the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None at this time.

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A. Description of the Drug Product(s) and Drug Substance(s)

The drug product is Valproic Acid Delayed Release Capsules and it is manufactured in two strengths, 125 and 500 mg/capsule. The capsule is a soft gelatin capsule and the gelatin formulation is modified so that the drug product has enteric or delayed release properties. The fill of the capsules is neat valproic acid. The drug product is proposed to have the following indications: seizure disorders, manic episodes, migraine prophylaxis. Both strengths of the drug are proposed to be packaged in HDPE bottles with _____ caps as well as _____ corrugated cardboard boxes for bulk storage and shipping. b(4)

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The manufacturing is typical for the production of soft gelatin capsules, but with the _____ during the production of the soft gelatin mass, the durability of the dosage form is enhanced such that it can withstand acid conditions similar to what would be encountered in the stomach. The final formulation and manufacturing process to prepare the gelatin mass was determined empirically by a series of studies in coordination with increases in scale. The final moisture content and hardness of the capsules is said to be important for the proper delayed release performance. There is no pre-clinical section to the application, as it is submitted under 505(b)(2). b(4)

B. Description of How the Drug Product is Intended to be Used

The 125 mg strength of the product is packaged in 100 ct HDPE bottles and in pharmacy bulk packages. The 500 mg strength of the product is packaged in 100 [redacted]ct HDPE bottles and pharmacy bulk packages. The drug product is a solid oral delayed release dosage form. The maximum daily dose is 60 mg/kg/day. For mania the recommended initial dose is 750 mg daily in divided doses. For epilepsy for adults and children 10 years and older the initiation of therapy should be with 10-15 mg/kg/day. For migraine, the recommended starting dose is 250 mg twice daily. b(4)

C. Basis for Approvability or Not-Approval Recommendation

The application is not recommended for approval at this time. The major deficiencies are outlined below. Additional issues are captured in the deficiency comments included in the draft letter at the end of this review. No risk management steps are proposed at this time.

The drug product has displayed physical instability under accelerated, intermediate, and in some cases, even under the long term stability storage conditions. This will necessitate the [redacted]in the expiry period[redacted]proposed by the applicant. [redacted] b(4)

[redacted]It is not evident what is causing the instability (temperature, humidity, or both) as the applicant has not reported the water content or the hardness of the capsules during the stability studies. The [redacted] of the 500 mg strength appear to be the least stable combinations. There is also no mention in the application of product stability during use. Presently it is not clear if there is a packaging change that may help increase the product stability. Faced with a severely shortened expiry period, the applicant need to consider such changes. However, the possibility of achieving a timely approval would diminish. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

CBertha/ONDQA/Reviewer/3/07/07
RSood/ONDQA/DIV I/Branch Chief_____

C. CC Block

CCalder/DNP/Regulatory PM
MHeiman/ONDQA/DIV I/Branch I/PAL
SGoldie/ONDQA/DIV I

56 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Craig Bertha
3/7/2007 12:08:18 PM
CHEMIST

Ramesh Sood
3/7/2007 12:34:11 PM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-152
Applicant:	Banner Pharmacaps, Inc.
Stamp Date:	22-Dec-2006
PDUFA Date:	22-Oct-2007
Trademark:	N/A (no trademark proposed)
Established Name:	valproic acid
Dosage Form:	Delayed-release capsule
Route of Administration:	Oral
Indication:	Anticonvulsant, treatment of acute manic episodes associated with bipolar disorder, and migraine prophylaxis
PAL:	Martha R. Heimann, Ph.D.
	Yes No
ONDQA Fileability:	To be determined based on applicant's response to information request.
Comments for 74-Day Letter	☒ ☐

Summary and Critical Issues:

Summary

Valproic acid (chemical name: 2-propylpentanoic acid) was originally marketed, as Depakene® Capsules and Syrup by Abbott Laboratories in 1978. Currently, there are a number of approved products containing the valproate moiety as the free acid (Depakene), sodium salt (Depacon® Injection), and valproic acid/valproate sodium coordinate complex, divalproex sodium, which is marketed as Depakote® Delayed Release Tablets, Depakote Sprinkle Capsules and Depakote ER Extended Release Tablets). Both the delayed-release and extended-release Depakote tablet formulations are approved for treatment of seizure disorders, manic episodes and migraine prophylaxis. Banner Pharmacaps, Inc. (BPI) proposes marketing of delayed-release capsules containing 125 mg or 500 mg valproic acid. The NDA is submitted under Section 505(b)(2) and relies on the Agency's findings of safety and effectiveness for Depakote (divalproex sodium) Delayed Release Tablets, 125 mg, 250 mg and 500 mg (as valproic acid) and bioequivalence of the 500 mg strength to the referenced drug.

Drug Substance

The active ingredient, valproic acid, is a colorless to pale yellow, slightly viscous, clear liquid with a slight characteristic odor. It is a well characterized small molecule with molecular formula $C_8H_{16}O_2$ and molecular weight 144.2. It is slightly soluble (~1.1-3 mg-mL) in 0.1 M HCl and water, freely soluble (> 10%) in 0.1 N NaOH, and has a pK_a of 4.6. The bulk drug

substance is manufactured by ——— in ——— and DMF ——— is cross-referenced for CMC information. The applicant notes that valproic acid supplied by ——— ——— is used in the manufacture of immediate-release valproic acid capsules under BPI's ANDA 73-484 (approved 29-Jun-2003). b(4)

Drug Product

The proposed product is a clear, brown, oval, soft gelatin delayed-release capsule that will contain 125 mg or 500 mg valproic acid. There are no excipients in the capsule fill. The capsule shell formulation is based on BPI's proprietary "Enteri-Care" technology. This technology is based on ——— b(4)

The components of the enteric shell are identified in the application and a gelatin formula, which is shown below, is included in the *Pharmaceutical Development Section.* In the *Description and Composition Section,* however, the sponsor states that some information is proprietary and cross-references their DMF 14194. *No information regarding location of the information within the DMF is provided for the theoretical composition of the capsule shell or manufacturing processes. The DMF was examined briefly and this information was not located.*

Ingredients	%
Gelatin	
Methacrylic acid copolymer	
Ammonium Hydroxide	
Glycerin	
TEC	
Water	
FD&C Yellow #6	

b(4)

Development of the gelatin process is described in a draft technical report which is appended to the *Pharmaceutical Development Section.* The gelatin process development was not performed using valproic acid.

The encapsulation process is provided in the NDA in the form of flow diagrams and blank master batch record. All information on manufacture of the gelatin mass is cross-referenced to the sponsor's DMF 14194. *This information could not be located within the DMF.*

The proposed regulatory specifications for valproic acid delayed release capsules, 125 mg and 500 mg, are typical for an enteric release product. Analytical procedures for assay and related substances are modified from the test methods in the USP monographs for Valproic Acid and Valproic Acid Capsules. These analyses are performed by GC rather than HPLC. The dissolution test is modified from the USP method for divalproex sodium delayed release tablets by ——— SLS ——— b(4)

The firm has submitted 6 and 18 months long term stability data, and 6 and 12 months intermediate stability data, respectively, for 125 mg and 500 mg tablets. Accelerated data through 6 months are provided for both strengths.

Critical issues for review

Controls for the drug substance are incorporated by cross-reference to DMF———, which has been reviewed recently and found acceptable. [L. Hussain review dated 07-Jul-2006.] The applicant's acceptance specification is provided in the NDA and analytical procedures are modified from the methods described in the USP monograph for Valproic Acid. No critical review issues have been identified. b(4)

With regard to the drug product, there are several critical issues related to the dosage form, manufacturing process controls, specifications, commercial container closure system and packaging sites, and stability:

- *Enteric gelatin matrix.* BPI developed the enteric gelatin technology relatively recently; this appears to be the first NDA submission. The ruggedness of the capsule shell in the gastric environment is unclear. Although the stability batches nominally comply with USP requirements, at least one batch, 125 mg capsule lot # P060203B1, failed the acid phase of dissolution testing at Stage 2 (N = 12). This is a safety concern as gastric administration of valproic acid (e.g., valproic acid immediate release capsules) is associated with side effects such as nausea and vomiting.
- *Process controls.* Section 3.2.P.3.4 *Control of Critical Steps and Intermediates* consists of a single page table entitled "Tentative Recommendations on Critical Parameters for Manufacturing." This information is presented in the Quality Overall Summary (QOS) with a note that the tentative processing parameters are based on ——— however, the ——— process does not appear to have been reviewed by the Agency. b(4)
- *Specifications.* The proposed dissolution procedure uses pH 7.5 buffer——— SLS ———; initial stability data for the 500 mg strength was generated ——— The appropriateness of ——— SLS to the dissolution medium is questionable given that the same pH buffer, without SLS, is used for testing of divalproex sodium delayed release tablets. Although the sponsor was advised (by OCP) during the pre-NDA meeting to investigate alternate media and provide justification, no justification is provided.
- *Container closure systems.* CMC documentation is provided for the packaging materials that were used in primary stability studies. As the firm intends to ship bulk product to repackagers (see below), it is not clear that the commercial packaging will be equivalent.
- *Packaging sites.* The applicant indicates that for stability purposes 125 mg capsules were packaged at the BPI facility in Greensboro, NC and 500 mg capsules were packaged ——— No commercial packagers are identified in the application and the firm states in the QOS that final packaging and labeling for marketed container sizes will be performed under CGMPs, FDA Repackaging Guidelines and in conformance with the stability packaging performed by BPI. In the absence of facility information for commercial packaging sites it is not possible to ensure that the product is packaged by FDA approved and inspected facilities. b(4)

Additional issues

Administrative: Based on no net increase in use of the active moiety valproic acid, a claim for categorical exclusion under 21 CFR 25.31(a) is submitted.

Establishment Evaluation: Facilities identified in the NDA as intended commercial manufacturing sites, except excipient and packaging component test sites, are listed in Attachment 1. This information has been forwarded to the ONDQA PM for EES entry. The sponsor has been asked to identify all commercial packaging sites. [Information request forwarded through the clinical project manager on 16-Jan-2007.]

Fileability/Reviewability: The sponsor has cross-referenced their DMF 14194 for composition and manufacturing information for the enteric gelatin formulation. The information could not be located within the DMF. Since drug release is controlled by the gelatin capsule shell, this information is considered critical to the CMC review. A request that the sponsor location information (i.e., date of submission, page numbers, etc.) for all information relevant to the enteric gelatin formulation was forwarded through the clinical project manager on 16-Jan-2007.

Labeling/Established Name: The active ingredient is the free acid; therefore, there is no issue of consistency between the USAN name and the labeled potency.

Comments for 74-Day Letter

The following comments should be conveyed in the 74-Day Letter:

Limited stability data (6 months long-term, intermediate and accelerated) are provided for the 125 mg strength. In accordance with our policy, the assigned expiration dating period will be based on the extent and quality of the stability data provided.

As communicated during the November 30, 2005 pre-NDA meeting, justification for the choice of dissolution medium and test parameters should be provided. This should include information **on alternate media evaluated (e.g., different pH's, SLS concentrations, etc.) and the resulting** dissolution profiles. **b(4)**

Review, Comments and Recommendation:

A recommendation regarding fileability can not be made at this time. Provided the firm addresses the deficiency related to DMF 14194, i.e., absence of cross-referenced information, the application would be fileable. Although the physicochemical properties of the enteric gelatin matrix are critical to product performance, the actual manufacturing processes do not appear complex and the submission does not appear to require a separate manufacturing sciences review. Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D. _____
Pharmaceutical Assessment Lead

_____
Date

Ramesh Sood, Ph.D. _____
Branch Chief

_____
Date

ATTACHMENT 1

Manufacturing Establishments for Valproic Acid Delayed Release Capsules

Facility Information	Function
[redacted] Registration No. FEI [redacted] Site Contact: Not provided; to be requested by PM Tel. No. Not provided; to be requested by PM	Drug substance manufacturer
Banner Pharmacaps Inc. 4125 Premier Drive High Point, NC 27265 Registration No. FEI 3001451366 Site Contact: Rosanne-Sylvia-Heeter Tel. No. (336) 812-8700 ext 3885	Drug product manufacturer, finished product testing, stability testing, bulk packaging Drug substance acceptance testing
Banner Pharmacaps Inc. 4344 Federal Drive Greensboro, NC 27410 Registration No. FEI 3004436627 Site Contact: Rosanne-Sylvia-Heeter Tel. No. (336) 812-8700 ext 3885	Packaging of drug product for post-approval and annual stability studies

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/

Martha Heimann
1/24/2007 02:48:24 PM
CHEMIST

Have revised to include DMF and fileability issue, 74-day letter comment requesting justification for dissolution method, and facilities information.

Ramesh Sood
1/24/2007 03:19:19 PM
CHEMIST