CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-006

CHEMISTRY REVIEW(S)

Sabril™
(vigabatrin) for Oral Solution
NDA 22-006

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Ovation Pharmaceuticals, Inc.
4 Parkway North, Suite 200
Deerfield, IL 60015

Indication: Monotherapy for the treatment of Infantile Spasms and for the treatment of partial epilepsy in subjects who have not responded adequately to other anti-epilepsy drugs.

Presentation: Powder enclosed in 50 x 60 mm child-resistant aluminum foil packet (sachet). The 500 mg dose packet contains (b) (4) of white to off-white granular powder. 50 packets are packaged per box.

EER Status: Acceptable, 15-Jun-09 – E. Johnson

Consults: EA – Categorical exclusion granted under 21 CFR 25.31(b)
Methods Validation – Revalidation by Agency not requested

Original Submission: 17-Oct-2006

Post-Approval Agreements: None

Drug Substance:

Vigabatrin is a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T) which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter gamma aminobutyric acid (GABA). The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS.

The drug substance, vigabatrin, is a small, synthetic molecule with an empirical formula of $C_6H_{11}NO_2$ and a molecular weight of 129.16. Vigabatrin is also the drug substance of NDA 20-427 which has not been approved by the FDA as of this review; consequently it is considered a New Molecular Entity (NME). Vigabatrin has one chiral center and is a racemic mixture of the R- and S-enantiomers. Vigabatrin is an amino acid with two ionizable groups, a carboxylic acid (pKa = 4.0) and an amine (pKa = 9.7); the pH of an aqueous solution of vigabatrin ranges from 6.342 to 6.972. Known chemically as (±)-4-amino-5-hexenoic acid, it is a white to off-white, non-hygroscopic, (b) (4) powder with

a melting range of 171-176°C. Vigabatrin is freely soluble in water and in aqueous solvents; slightly soluble in methanol; very slightly in ethanol and chloroform; and practically insoluble in toluene and n-hexane. (b) (4) polymorphs and one metastable form have been identified, with form I being the thermodynamically stable form and that form manufactured by the applicant.

Reference is made to NDA 20-427 (Sabril tablets) for complete drug substance information. The stability data for a dozen commercial batches support a (b) (4) retest period for the bulk drug substance stored inside (b) (4) controlled room temperature, 25º C (77º F); excursions permitted to 15-30º C (59- 86º F).

Conclusion: Drug substance is acceptable.

Drug Product:

The drug product is a powder for oral solution enclosed in an aluminum foil packet (sachet). A unit-dose packet contains 500 mg of vigabatrin in **(b) (4)** of white to off-white granular powder. The granular powder is intended to be dissolved in water for oral administration to neonates from birth to 2 years of age. The maximum daily dose is 150 mg/kg, which would calculate to not more than 750 mg per day for a 5 kg neonate.

Povidone (b) (4) only excipients; both are compendial. Povidone (b) (4) The release specification for drug product includes: appearance, identification by RP-HPLC and IR, related substances by RP-HPLC, assay by RP-HPLC, content uniformity, weight, and microbial limits. A commitment was made to add a specification to establish a specification for reconstitution time after 10 commercial batches had been manufactured and tested.

The applicant proposed a 36-month shelf-life for the U.S. product. In a stability update (**Amendment dated 30-Jan-2009**), 36 months of long-term stability data were provided for the primary batches manufactured at the Patheon YMO facility and packaged in the proposed U.S. commercial foil packets. These batches demonstrated good stability for the drug product. In the **Amendment dated 24-Apr-2009**, the applicant provided 3 months of site-specific stability data for 3 registration/validation batches manufactured at Patheon CRO, the new proposed commercial manufacturing facility. These data were comparable to the Patheon YMO data. Thus, a **36-month expiration date** is appropriate for the drug product, when stored at controlled room temperature [25º C (77º F); excursions permitted to 15-30º C (59- 86º F)].

Conclusion: Drug product is acceptable.

Additional Items:

- During the review of the NDA, the applicant notified FDA by e-mail that the drug product manufacturing site of York Mills Operations (YMO) facility in Toronto, Ontario) would close and cease manufacturing at the end of 2008. The manufacturing site of Sabril (vigabatrin) powder for oral solution has subsequently been transferred to Patheon's Cincinnati Regional Operations (CRO) facility in Ohio. In addition, the packaging of Sabril was transferred from Patheon YMO to (b) (4). These new sites were considered in the Office of Compliance review; potential differences in the manufacturing processes were considered in ONDQA's CMC review.
- The applicant developed a suitable test for Reconstitution Time and committed to establish an acceptance criterion after 10 commercial batches have been manufactured and tested.
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used for testing (release, stability, and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.
- The applicant agreed to place the first 3 commercial batches and one batch of drug substance per year on stability under long term conditions at 25°C/60% RH, following the approved stability protocol.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval.**

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/s/

Christine Moore
7/20/2009 03:12:53 PM
CHEMIST
Division I Director (acting)
ONDQA/CDER/FDA

NDA 22-006

Sabril (vigabatrin)
for Oral Solution

Ovation Pharmaceuticals, Inc.

Monica D. Cooper, Ph.D.
ONDQA Pre-Marketing Assessment
Division I/Branch I

Reviewed for the Division of Neurology Products (DNP)
HFD-120

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-006

2. REVIEW #: 1

3. REVIEW DATE: 02-Jul-2009

4. REVIEWER: Monica D. Cooper, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA 22-006 (N000)	17-Oct-2006

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Resubmission (N000 RS)	28-Dec-2007
Amendment (N000 BC) (Response to IR Letter)	26-Jun-2008
Amendment (N000 BC) (Stability Update)	14-Jul-2008
Amendment (N000 BZ) (Stability Update)	30-Jan-2009
Amendment (N000 BC) (Updated Facility Information)	05-Feb-2009
Amendment (N000 BC) (Information on Product Launch Batches)	25-Mar-2009
Amendment (N000 BC) (Syringe Durability Study)	02-Apr-2009
Amendment (N000 BC) (New DP Facilities and Supporting Data)	24-Apr-2009
Amendment (N000 XA) (Updated Patient Instructions and Container Label)	22-Jun-2009

7. NAME & ADDRESS OF APPLICANT:

Name	Ovation Pharmaceuticals, Inc.
Address	4 Parkway North, Suite 200 Deerfield, IL 60015
Representative	Jenny Swalec Director, Global Regulatory Affairs
Telephone	847-282-1066
FAX Number	847-317-9112

8. DRUG PRODUCT NAME/CODE/TYPE:

Proprietary Name	Sabril
Non-Proprietary Name (USAN)	vigabatrin
Code Names	MDL 71,754 and RMI 71,754
Chemistry Type	1
Submission Priority	P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Anticonvulsant for Infantile Spasms (Pediatric Indication)

11. DOSAGE FORM: Powder for Oral Solution

12. STRENGTH/POTENCY: 500 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: __**X**__Rx _____OTC

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

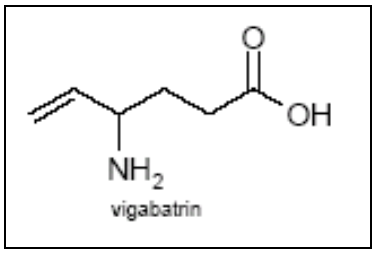
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Names: (1) 4-amin-5-hexenoic acid,
(2) (±)-4-amino-hexenoic acid,
(3) dl-4-amino-5-hexanoic acid,
(4) vinyl γ-aminobutyric acid, and
(5) vinyl GABA

US Adopted Name (USAN): vigabatrin
International Nonproprietary Name (INN): vigabatrin
Laboratory Codes: MDL 71,754 and RMI 71,754



Chemical Formula: $C_6H_{11}NO_2$
Molecular Weight: 129.16
CAS Number: 60643-86-9

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
(b) (4)	III	(b) (4) (b) (4)	(b) (4)	1	Adequate	05-Jun-2008 (M. Cooper)

[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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS & CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	15-Jun-2009	E. Johnson
LNC	N/A	----	----
Methods Validation	*Not Necessary*	----	----
DMEPA	Tradename: Sabril Acceptable	01-May-2009	T. Jones-Smith
EA	Categorical Exclusion: Acceptable	See Review Date Above	M. Cooper
Microbiology	N/A		

The Chemistry Review for NDA 22-006

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This new drug application (22-006) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. A letter was sent to the applicant on 10-Jun-2008 outlining the information needed to complete this application. The applicant responded in an amendment dated 26-Jun-2008. In addition, the applicant provided two stability updates in the amendments dated 14-Jul-2008 and 30-Jan-2009. All CMC deficiencies were adequately resolved.

Due to the postponement of the Sabril Advisory Committee meeting until January 2009, the NDA review cycle was extended beyond the closure of the drug product manufacturing facility at the end of 2008. The applicant submitted new drug product facilities and supporting data in the amendment dated 24-Apr-2009.

The Office of Compliance has given an overall acceptable recommendation for the manufacturing and testing facilities (see Establishment Evaluation Summary at the end of this review).

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

There are no Phase 4 commitments.

II. Summary of Chemistry Assessments

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

Vigabatrin is an oral anti-epilepsy drug, which was first approved in the United Kingdom in 1989 and is currently approved in over 50 countries. Approved indications include monotherapy for the treatment of Infantile Spasms and for the treatment of partial epilepsy in subjects who have not responded adequately to other anti-epilepsy drugs. Vigabatrin is a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of action is dose-dependent inhibition of GABA-T and consequent increased levels of GABA in the CNS.

Drug Substance

The drug substance, vigabatrin, is a small, chemically-synthesized, organic molecule with the chemical name (±)-4-amino-5-hexenoic acid. Vigabatrin has one chiral center and is a racemic mixture of the R and S enantiomers. It is a white to off-white (b) (4) powder with a melting point of 171 – 176°C. Vigabatrin is not hygroscopic; however, it is highly soluble in aqueous media. Since vigabatrin is an amino acid, it has two ionizable groups – a carboxylic acid (pKa = 4.0) and an amine (pKa = 9.7). (b) (4) polymorphs (Form I (b) (4) have been identified – (b) (4) is metastable, has been rarely observed (not in any production lots), and converts to Form I under ambient storage conditions over a period of months. Form I is the thermodynamically stable form and is the form developed by the applicant. Forms I (b) (4) are readily distinguished by IR.

The drug substance manufacturing process involves (b) (4) A retest date of (b) (4) granted for the bulk drug substance when stored at controlled room temperature (see NDA 20-427 CMC Review #9, H. Sarker, 05-Aug-2008). The drug substance is stored in (b) (4)

Reference was made to NDA 20-427 (Sabril Tablets) for complete drug substance information (see NDA 20-427 CMC Review #9, H. Sarker, 05-Aug-2008).

Drug Product

The drug product is a powder for oral solution enclosed in an aluminum foil pouch/packet (sachet). A unit-dose is 500 mg of vigabatrin in (b) (4) of white to off-white granular powder. Povidone (b) (4) are the only excipients; both are compendial. Povidone (b) (4)

The drug product has a 48-month shelf-life in Europe and Canada, packaged in slightly different foil pouches. The applicant proposed a 36-month shelf-life for the U.S. product. In a stability update (**Amendment dated 30-Jan-2009**), 36 months of long-term stability data were provided for the primary batches manufactured at the Patheon YMO facility and packaged in the proposed U.S. commercial foil packets. These batches demonstrated good stability for the drug product. In the **Amendment dated 24-Apr-2009**, the applicant provided 3 months of site-specific stability data for 3 registration/validation batches manufactured at Patheon CRO, the new proposed commercial manufacturing facility. These data were comparable to the Patheon YMO data. Thus, a **36-month expiration date** is appropriate for the drug product, when stored at controlled room temperature.

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

The drug product, Sabril (vigabatrin) for Oral Solution (500 mg), is a granular powder enclosed in an aluminum foil pouch. The granular powder is intended to be dissolved in water for oral administration to neonates from birth to 2 years of age. The maximum daily dose is 150 mg/kg, which would calculate to not more than 750 mg per day for a 5 kg neonate.

C. Basis for Approvability or Not-Approval Recommendation

This new drug application (22-006) is recommended for **APPROVAL** from the perspective of chemistry, manufacturing, and controls. Information requests outlining the information needed to complete this application were communicated by mail, teleconference, and e-mail throughout the review cycle. All CMC deficiencies were adequately resolved.

III. Administrative

A. Reviewer's Signature

/s/ M.D. Cooper, Ph.D.

B. Endorsement Block

Chemistry Reviewer:	Monica D. Cooper, Ph.D.
Pharmaceutical Assessment Lead:	Martha Heimann, Ph.D.
Branch Chief:	Ramesh Sood, Ph.D.
Project Manager:	Tamy Kim

C. CC Block

Orig. NDA 22-006
HFD-120/Division File

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

/s/

Monica Cooper
7/2/2009 06:21:41 PM
CHEMIST

Ramesh Sood
7/6/2009 03:37:30 PM
CHEMIST