

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-006

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

Patent Information

Title:	Patent Information
Product Name:	Vigabatrin
Sponsor:	Ovation Pharmaceuticals 4 Parkway North, Suite 200 Deerfield, IL 60615
Date:	28 December 2007

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Ovation Pharmaceuticals, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Ovation is expressly prohibited

Patent Information

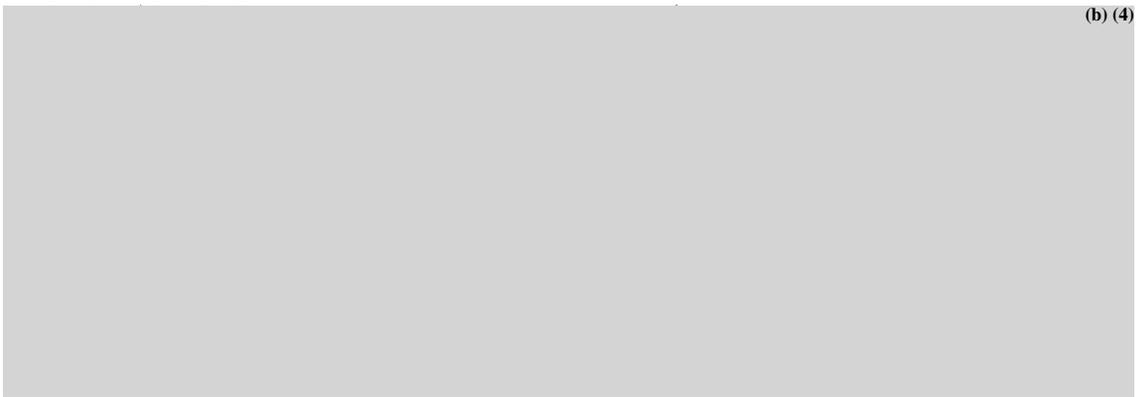
Applicant:	Ovation Pharmaceuticals 4 Parkway North, Suite 200 Deerfield, IL 60615
Active Ingredient:	4-amino-5-hexenoic acid, (\pm)-4-amino-5-hexenoic acid, dl-4-amino-5-hexanoic acid, vinyl γ -aminobutyric acid, vinyl GABA
Medical Uses:	Adjunctive therapy for the treatment of refractory complex partial seizures in adult patients. (NDA 20-427) Monotherapy for the treatment of Infantile Spasms. (NDA 22-006)
Strength:	500 mg
Dosage Form:	Tablet; Sachet
Proposed Trade Name:	Sabril
Generic Name:	vigabatrin
Patent Statement:	US Patent Number: 3,960,927 Expiration Date June 1, 1993

The undersigned declares that US Patent Number 3,960,927 covers the active ingredient vigabatrin which is the subject of this application for which approval is sought.



Timothy M. Cunniff, Pharm.D.
Vice President, Global Regulatory Affairs
Ovation Pharmaceuticals

Request for Market Exclusivity



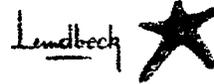
(b) (4)



(b) (4)

Lundbeck Inc.
Four Parkway North
Deerfield, IL 60015
USA

Tel 847-282-1000
Fax 847-282-1001
www.lundbeckinc.com



July 14, 2009

Dr. Russell Katz, Director
Food and Drug Administration
Division of Neurology Products
Center for Drug Evaluation and Research
5901B Ammendale Road
Beltsville, MD 20705

**Re: NDA No. 22-006 Sabril® (vigabatrin) for Oral Solution
Amendment: Submission of Patent Information - FDA Form 3542a**

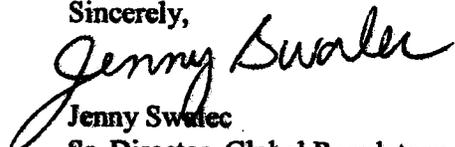
Dear Dr. Katz:

Reference is made to pending NDA 22-006. Included in this submission is the required patent information (FDA Form 3542a).

Please note that Lundbeck Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

If you have any questions concerning this submission, please contact me at 847-282-1066, fax 847-317-9112, or email jswa@lundbeck.com.

Sincerely,


Jenny Swatec
Sr. Director, Global Regulatory Affairs

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

22-006

NAME OF APPLICANT/NDA HOLDER

Lundbeck Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

SABRIL (vigabatrin) for Oral Solution

ACTIVE INGREDIENT(S)

vigabatrin

STRENGTH(S)

500 mg

DOSAGE FORM

Powder for Oral Solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit Indication or method of use information as identified specifically in the proposed labeling.)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed

Jenny Swalec

7/14/09

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Jenny Swalec	
Address Four Parkway North, Suite 200	City/State Deerfield, IL
ZIP Code 60015	Telephone Number 847-282-1066
FAX Number (if available) 847-317-9112	E-Mail Address (if available) JSWA@lundbeck.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-006

SUPPL #

HFD # 120

Trade Name Sabril Oral Solution

Generic Name vigabatrin

Applicant Name Lundbeck, Inc.

Approval Date, If Known 8/21/09

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, **EXPLAIN** why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 (Orphan Drug Designation)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Tamy Kim, PharmD

Title: Senior Regulatory Project Manager

Date: 8/24/09

Name of Office/Division Director signing form: Division of Neurology Products/Russell Katz, MD

Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

TAMY E KIM
08/24/2009

RUSSELL G KATZ
08/25/2009

EXCLUSIVITY SUMMARY

NDA # 22-006

SUPPL #

HFD # 120

Trade Name Sabril Oral Solution

Generic Name vigabatrin

Applicant Name Lundbeck, Inc.

Approval Date, If Known

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YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7 (Orphan Drug Designation)

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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YES NO

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(Answer either #1 or #2 as appropriate)

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YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Tamy Kim, PharmD
Title: Senior Regulatory Project Manager
Date: 8/6/09

Name of Office/Division Director signing form: Division of Neurology Products/Russell Katz, MD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

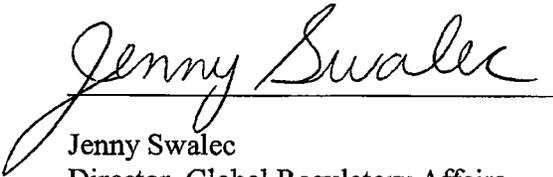
Debarment Certification

Title:	Debarment Certification
Product Name:	Vigabatrin
Sponsor:	Ovation Pharmaceuticals 4 Parkway North, Suite 200 Deerfield, IL 60615
Date:	01 December 2007

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Ovation Pharmaceuticals, Inc. and any unauthorized use or disclosure of such information without the prior written authorization of Ovation is expressly prohibited

Ovation hereby certifies that it is not debarred, and did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

A handwritten signature in cursive script that reads "Jenny Swalec". The signature is written in black ink and is positioned above a horizontal line.

Jenny Swalec
Director, Global Regulatory Affairs
Ovation Pharmaceuticals

MEMORANDUM

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

Division of Neurology Drug Products (HFD-120)
Center for Drug Evaluation and Research

Date: August 18, 2009

From: Philip H. Sheridan, M.D.
Division of Neurology Drug Products, HFD-120
Office of Drug Evaluation I

Subject: Financial Disclosure Statements for NDA 22006, Study W019

To: File NDA 22-006

Drug: Sabril (vigabatrin) for Treatment of Infantile Spasms

Protocol W019 was a multicenter safety and efficacy study of vigabatrin as therapy for newly diagnosed infantile spasms. The principal investigator was Dr. R. E. Appleton at the Alder Hey Children's Hospital in Liverpool, England. Forty patients were enrolled in the study.

The study was sponsored by Hoechst Marion Roussel Ltd. (now Sanofi-Aventis) which provided vigabatrin and some funding for the study. The study was not intended to be a pivotal study to support an NDA submission. The Clinical Study Report was completed on March 3, 1997. The results of the study were published in a peer-reviewed scientific journal (*Epilepsia* 40 [11] 1627-1633, 1999).

NDA 20-427 was submitted by Hoechst Marion Roussel Ltd. (now Sanofi-Aventis) to the Agency in 1994 for Sabril for the adjunctive treatment of intractable complex partial seizures in adults. A non-Approvable letter was issued in 1998 by the Agency.

In March 2004, Ovation (now Lundbeck) acquired the North American regulatory, distribution, and marketing rights for vigabatrin from Sanofi-Aventis. Ovation made two requests in writing in 2005 to Aventis requesting the financial disclosure information for a list of vigabatrin studies which included Study W019. Aventis sent a letter dated December 7, 2005 to Ovation stating that the requested information was not available. This correspondence was submitted to the Agency by Ovation as part of its financial disclosure for its resubmission of NDA 40-427 (for the adjunctive treatment of intractable complex partial seizures) in December 2007.

A new NDA (NDA 22006) for Sabril for the treatment of infantile spasms was also submitted to the Agency by Ovation in December 2007. This submission used Study W019 as a pivotal study. In response to an Agency request for further financial disclosure documentation for Study W019, Ovation (Lundbeck) requested the principal

investigator Dr. Appleton to certify that neither he nor his coinvestigators received any outcome-based payments for Study W019 and that none of them have any proprietary interest in Sabril (e.g. patents, trademarks, or licensing agreements). This certification is appended below and satisfies the requirement for financial disclosure for Study W019.

Lundbeck Inc.
Four Parkway North
Deerfield, IL 60015
USA

Tel 847-282-1000
Fax 847-282-1001
www.lundbeckinc.com



August 17, 2009

Dr. Russell Katz, Director
Food and Drug Administration
Division of Neurology Products
Center for Drug Evaluation and Research
5901B Ammendale Road
Beltsville, MD 20705

**Re: NDA No. 22-006 Sabril® (vigabatrin) for Oral Solution
Amendment: Response to August 11, 2009 Request for Financial Disclosure
Information for Study W019**

Dear Dr. Katz:

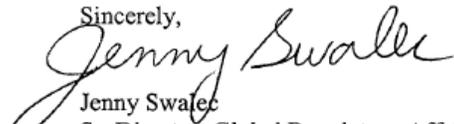
Reference is made to a request received from Dr. Tamy Kim of your Division via email on August 11, 2009 to provide an official statement in response to the following questions for Study W019:

1. Were there outcome payments to the investigators (payments based upon the outcome of the study)?
2. Did any of the investigators have any proprietary interest in Sabril (e.g., patents, trademarks, or licensing agreements)?

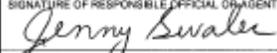
Reference is also made to an August 13, 2009 teleconference with Dr. Kim and Dr. Norman Hershkowitz during which it was communicated to Lundbeck Inc. that a statement from the principle investigator addressing the above questions would satisfy the Agency's above requirement. Included in this submission is a Financial Disclosure form signed by Dr. RE Appleton, the principle investigator for Study W019 and co-author of the clinical study report for the study.

Please note that Lundbeck Inc. considers this application and all correspondence related thereto as confidential proprietary information and hereby claims protection from disclosure under the applicable sections of Title 18 of the United States Code and Title 21 of the Code of Federal Regulations.

If you have any questions concerning this submission, please contact me at 847-282-1066, fax 847-317-9112, or email jswa@lundbeck.com.

Sincerely,

Jenny Swalec
Sr. Director, Global Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE <i>(Title 21, Code of Federal Regulations, Parts 314 & 601)</i>		Form Approved: OMB No. 0910-0439 Expiration Date: April 30, 2009 See OMB Statement on page 2.
		FOR FDA USE ONLY
		APPLICATION NUMBER
APPLICANT INFORMATION		
NAME OF APPLICANT Lundbeck Inc.		DATE OF SUBMISSION 08/17/2009
TELEPHONE NO. (Include Area Code) 847/282-1066		FACSIMILE (FAX) Number (Include Area Code) 847/317-9112
APPLICANT ADDRESS (Number, Street, City, State, County, ZIP Code or Mail Code, and U.S. License number if previously issued): Lundbeck Inc. 4 Parkway North, Suite 200 Deerfield, IL 60015		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, Telephone & FAX number) IF APPLICABLE NA
PRODUCT DESCRIPTION		
NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 22-006		
ESTABLISHED NAME (e.g., Proprietary name, USFDA name) vigabatrin		PROPRIETARY NAME (trade name) IF ANY Sabril
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) 4-amin-5-hexenoic acid or (+)-4-amine-hexenoic acid		CODE NAME (if any) MDL 71,754
DOSAGE FORM: Powder for Oral Solution	STRENGTHS: 500 mg	ROUTE OF ADMINISTRATION: Oral
(PROPOSED) INDICATION(S) FOR USE Infantile Spasms		
APPLICATION DESCRIPTION		
APPLICATION TYPE (check one) <input checked="" type="checkbox"/> NEW DRUG APPLICATION (CDA, 21 CFR 314.50) <input type="checkbox"/> ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) <input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)		
IF AN ANDA, IDENTIFY THE APPROPRIATE TYPE <input checked="" type="checkbox"/> 505 (b)(1) <input type="checkbox"/> 505 (b)(2)		
IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____		
TYPE OF SUBMISSION (check one) <input type="checkbox"/> PRE-SUBMISSION <input type="checkbox"/> ORIGINAL APPLICATION <input checked="" type="checkbox"/> AMENDMENT TO PENDING APPLICATION <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> ANNUAL REPORT <input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT <input type="checkbox"/> OTHER		
IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____		
IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY <input type="checkbox"/> CRE <input type="checkbox"/> CBE-00 <input type="checkbox"/> Prior Approval (PA)		
REASON FOR SUBMISSION Submission of Study W019 Financial Disclosure Information		
PROPOSED MARKETING STATUS (check one) <input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (PR) <input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)		
NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC		
ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.) Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFR), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.		
See attached.		
Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) IND 17,213; NDA 20-427; DMF 16443		

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one) <input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling	
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(v)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (i)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input checked="" type="checkbox"/>	19. Financial information (21 CFR Part 54)	
<input type="checkbox"/>	20. OTHER (Specify)	
<p>CERTIFICATION</p> <p>I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:</p> <ol style="list-style-type: none"> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820. 2. Biological establishment standards in 21 CFR Part 600. 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809. 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202. 5. Regulations on making changes in application in FD&C Act section 505A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12. 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81. 7. Local, state and Federal environmental impact laws. <p>If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.</p> <p>The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.</p> <p>Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.</p>		
SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT		DATE:
		08/17/2009
TYPED NAME AND TITLE		
Jenny Swalec, Sr. Director Global Regulatory Affairs		
ADDRESS (Street, City, State, and ZIP Code)		Telephone Number
4 Parkway North, Suite 200, Deerfield, IL 60015		(847) 282-1066
<p>Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p>		
Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research Central Document Room 5901-B Ammerdale Road Beltsville, MD 20705-1266	Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research (HFM-88) 1401 Rockville Pike Rockville, MD 20852-1448	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SABRIL® (vigabatrin) for Oral Solution
NDA 22-006
Establishment Information

Location for Manufacturing, Packaging, Release Testing, Stability Testing for the Drug Substance:

Sanofi-Aventis Bulk S.p.A
Via Roberto Lepetit 142
12075 Gressio (cuneo), Italy
Registration Number: 3003677897

Location for Raw Material Testing, Manufacturing, and Testing for the Drug Product:

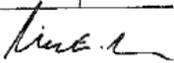
Patheon Pharmaceuticals, Inc.
Cincinnati Regional Operations (CRO)
2110 East Galbraith Road
Cincinnati, OH 45237-1625
Registration Number: 1510437

Location for Packaging, Cartoning, Component Testing for the Drug Product:

(b) (4)



INVESTIGATOR FINANCIAL DISCLOSURE FORM

1. Product Name: Sabril (vigabatrin)	
2. Protocol Number/Name: 71754/3/W/019	
3. Principle Investigator [<input checked="" type="checkbox"/>] Subinvestigator [<input type="checkbox"/>]	
4. Investigator/Subinvestigator Name: Dr. RE Appleton Institution Name (if applicable): Alder Hey Children's Hospital	
5. Address: Eaton Road Liverpool L12 2AP United Kingdom	
6. Telephone: 0151 252 5851 / 5375	7. Fax: 0151 252 5152
8. Indicate by marking YES or NO if any of the financial interests or arrangements of concern to the U.S. FDA (described below) apply.	
YES NO [<input type="checkbox"/>] [<input checked="" type="checkbox"/>]	Did you (or any of the other investigators to the best of your knowledge) receive any "outcome" payments from the study (payments based upon the outcome of the study- i.e., more money paid for a positive study, less money for a negative study). If yes, please attach details: _____
YES NO [<input type="checkbox"/>] [<input checked="" type="checkbox"/>]	Do you or did you (or any of the other investigators to the best of your knowledge) have any proprietary interest in Sabril (e.g., patents, trademarks, or licensing agreements such as a royalty from Sanofi-Aventis on sales) in any country around the world? If yes, please attach details: _____
9. Signature: 	10. Date: 15th August 2009

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22006	----- ORIG 1	-----	----- SABRIL (VIGABATRIN)

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

/s/

PHILIP H SHERIDAN
08/18/2009

NORMAN HERSHKOWITZ
08/18/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC,
OR AN ANTIBIOTIC DRUG FOR HUMAN USE
(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT

Lundbeck Inc.

DATE OF SUBMISSION

07/14/2009

TELEPHONE NO. (Include Area Code)

847/282-1066

FACSIMILE (FAX) Number (Include Area Code)

847/317-9112

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):

Lundbeck Inc.
4 Parkway North, Suite 200
Deerfield, IL 60015

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

NA

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 22-006

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)

vigabatrin

PROPRIETARY NAME (trade name) IF ANY

Sabril

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

4-amin-5-hexenoic acid or (+)-4-amino-hexenoic acid

CODE NAME (if any)

MDL 71,754

DOSAGE FORM:

Powder for Oral Solution

STRENGTHS:

500 mg

ROUTE OF ADMINISTRATION:

Oral

(PROPOSED) INDICATION(S) FOR USE:

Infantile Spasms

APPLICATION DESCRIPTION

APPLICATION TYPE

(check one)

- NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
 BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

- 505 (b)(1) 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____

Holder of Approved Application _____

TYPE OF SUBMISSION (check one)

- ORIGINAL APPLICATION AMENDMENT TO PENDING APPLICATION RESUBMISSION
 PRESUBMISSION ANNUAL REPORT ESTABLISHMENT DESCRIPTION SUPPLEMENT EFFICACY SUPPLEMENT
 LABELING SUPPLEMENT CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY

- CBE CBE-30 Prior Approval (PA)

REASON FOR SUBMISSION

Patent Information

PROPOSED MARKETING STATUS (check one)

- PRESCRIPTION PRODUCT (Rx) OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____

THIS APPLICATION IS

- PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 17,213; NDA 20-427; DMF (b) (4)

This application contains the following items: (Check all that apply)		
<input type="checkbox"/>	1. Index	
<input type="checkbox"/>	2. Labeling (check one)	<input type="checkbox"/> Draft Labeling <input type="checkbox"/> Final Printed Labeling
<input type="checkbox"/>	3. Summary (21 CFR 314.50 (c))	
<input type="checkbox"/>	4. Chemistry section	
<input type="checkbox"/>	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
<input type="checkbox"/>	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
<input type="checkbox"/>	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
<input type="checkbox"/>	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
<input type="checkbox"/>	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
<input type="checkbox"/>	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
<input type="checkbox"/>	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
<input type="checkbox"/>	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
<input type="checkbox"/>	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
<input type="checkbox"/>	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
<input type="checkbox"/>	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)	
<input checked="" type="checkbox"/>	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
<input type="checkbox"/>	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))	
<input type="checkbox"/>	15. Establishment description (21 CFR Part 600, if applicable)	
<input type="checkbox"/>	16. Debarment certification (FD&C Act 306 (k)(1))	
<input type="checkbox"/>	17. Field copy certification (21 CFR 314.50 (l)(3))	
<input type="checkbox"/>	18. User Fee Cover Sheet (Form FDA 3397)	
<input type="checkbox"/>	19. Financial Information (21 CFR Part 54)	
<input type="checkbox"/>	20. OTHER (Specify)	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Jenny Swalec, Sr. Director Global Regulatory Affairs	DATE: 07/14/2009
---	---	---------------------

ADDRESS (Street, City, State, and ZIP Code) Parkway North, Suite 200, Deerfield, IL 60015	Telephone Number (847) 282-1066
--	--------------------------------------

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Annapolis Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HF-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Kim, Tamy

From: Jenny Swalec [jswa@lundbeck.com]
Sent: Wednesday, August 19, 2009 4:23 PM
To: Kim, Tamy
Subject: RE: Sabril IS PMRs/PMCs
Attachments: 081909 Sabril IS PMRs_PMC.doc; 081909 Sabril IS PMC.pdf

Hi Tamy,

We accept all your proposed text changes to the IS PMRs/PMC. Attached is a word document with all your proposed changes accepted. Also attached is a formal NDA amendment containing a written commitment to conduct study number 5. Please let me know if the language isn't sufficient in the amendment cover letter and I will change it and re-submit.

Thanks, Jenny

From: Kim, Tamy [mailto:Tamy.Kim@fda.hhs.gov]
Sent: Wednesday, August 19, 2009 12:45 PM
To: Jenny Swalec
Subject: Sabril IS PMRs/PMCs

Hi Jenny,

Attached in track changes are revised Sabril IS PMRs and a PMC. Please note that we changed the controlled trial in infants (b) (4), so we will need a written commitment for this trial.

Sabril IS PMRs.8.19.09.doc>>
Thanks,
Tamy

Tamy Kim, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Food and Drug Administration
Phone: 301-796-1125
Email: tamy.kim@fda.hhs.gov

This electronic mail message and any attached files contain information intended for the exclusive use of the individual or entity to which it is addressed and may contain information that is proprietary, privileged, confidential and/or exempt from disclosure under applicable law. If you are not the intended recipient, you are hereby notified that any viewing, copying, disclosure or distribution of this information may be subject to legal restriction or sanction. Please notify the sender, by electronic mail or telephone, of any unintended recipients and delete the original message without making any copies. E-mail attachments may contain viruses which could damage your computer. While we have taken precautions to minimize this risk, we cannot accept liability for any such damage. Therefore, you should perform your own virus checks before opening an e-mail attachment.

2 Page(s) have been Withheld in Full after this page as B4 (CCI/TS)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22006	ORIG 1	OVATION PHARMACEUTICA LS INC	SABRIL (VIGABATRIN)

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

/s/

TAMY E KIM
08/27/2009

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-006 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Sabril Established/Proper Name: vigabatrin Dosage Form: Oral Solution		Applicant: Ovation Pharmaceuticals, Currently Lundbeck Agent for Applicant (if applicable): Jenny Swalec
RPM: Tamy Kim		Division: DNP
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
<p>❖ User Fee Goal Date: June 30, 2008 Action Goal Date (if different): August 21, 2009</p>		
<p>❖ Actions</p> <ul style="list-style-type: none"> • Proposed action • Previous actions (<i>specify type and date for each action taken</i>) 		<p>X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR</p> <p>X None</p>
<p>❖ Promotional Materials (<i>accelerated approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____</p>		<p><input type="checkbox"/> Received</p>

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input checked="" type="checkbox"/> Restricted distribution (21 CFR 314.520), but not under Subpart H (under FDAAA) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	Orphan Drug Designation
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

Officer/Employee List	
❖ Copy of this Action Package Checklist ³	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s): Approval Action on 8/21/09
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	See Approval Letter
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	See Approval Letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	Included
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	X Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	See Approval Letter
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	See Approval Letter
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	See Approval Letter
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	See Approval Letter
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input type="checkbox"/> RPM <input type="checkbox"/> DMEPA 5/6/09 <input type="checkbox"/> DRISK 6/7/09 <input type="checkbox"/> DDMAC 6/10/09 <input type="checkbox"/> CSS 8/4/09 <input type="checkbox"/> Other reviews
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	5/1/09; 12/18/06
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	Multiple RPMs handled this NDA and a filing review cannot be located.
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	X Included
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html 	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes X No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>) 	Orphan Designation, therefore, exempt.
<ul style="list-style-type: none"> ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>) 	X Verified, statement is acceptable
<ul style="list-style-type: none"> ❖ Postmarketing Requirement (PMR) Studies 	<input type="checkbox"/> None See PMR/PMC Templates
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	Included 8/19/09
<ul style="list-style-type: none"> • Incoming submissions/communications 	Included 8/19/09
<ul style="list-style-type: none"> ❖ Postmarketing Commitment (PMC) Studies 	<input type="checkbox"/> None See PMR/PMC Templates

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	Included 8/19/09
<ul style="list-style-type: none"> Incoming submission documenting commitment 	Included 8/19/09
<ul style="list-style-type: none"> ❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>) 	<ul style="list-style-type: none"> - CMC information request letter – 3/18/09 - CMC information request letter - 6/10/08 - 74-day letter – Filing issues indentified – 2/26/08 - Refuse to file – 4/5/07 - Unacceptable for filing – 2/11/06 - Refuse to file – 11/9/06
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> PeRC (<i>indicate date; approvals only</i>) 	X Not applicable
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	<input type="checkbox"/> Not applicable 8/5/09
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date</i>) 	X No mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg NDA 20-427-resubmission combined with NDA 22-006 mtg 10/13/07
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	X No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	1/7/09 and 1/8/09
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	Minutes available
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/21/09
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/27/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/21/09
Clinical Information⁵	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	7/21/09
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	7/22/09; 7/18/09
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	X None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	3/17/09; 7/8/08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	8/18/09, 8/7/09 7/22/09

⁵ Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None tQT 1/28/09
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed 8/4/08; 3/19/07
❖ Risk Management <ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input type="checkbox"/> None 7/16/09; 7/29/08 8/20/09 7/29/09
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested Included
Clinical Microbiology <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	X None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	X None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	X None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	X None
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/10/08
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	X None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	X None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/30/08
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	None 6/26/08
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8/7/09
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/21/09
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/22/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	X No carc
❖ ECAC/CAC report/memo of meeting	X None
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	X None requested
CMC/Quality <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/20/09
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	X None
• CMC/product quality review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 7/6/09
• BLAs only: Facility information review(s) (<i>indicate dates</i>)	X None

<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	<p>X Not needed</p>
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	<p>X None</p>
❖ Environmental Assessment (check one) (original and supplemental applications)	
<p>X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i></p>	<p>7/6/09</p>
<p>X Review & FONSI <i>(indicate date of review)</i></p>	<p>See CMC Reviews</p>
<p>X Review & Environmental Impact Statement <i>(indicate date of each review)</i></p>	<p>See CMC Reviews</p>
<ul style="list-style-type: none"> ❖ <input type="checkbox"/> NDAs: Methods Validation 	<p> <input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed </p>
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	<p> Date completed: 7/6/09 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation </p>
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	<p> Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold </p>

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22006	ORIG 1	OVATION PHARMACEUTICA LS INC	SABRIL (VIGABATRIN)

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

/s/

TAMY E KIM

08/27/2009

Checked this in as a Memo, since DARRTS 3.0 will not let me check this in as a checklist.

Sabril NDA 22006 PMR/PMC Development Template
PMR #1

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: A toxicology study in the juvenile rat examining the potential for vigabatrin exposure during development to produce neuronal damage.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 07/2010
Study/Clinical trial Completion Date: 09/2011
Final Report Submission Date: 03/2012
Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We have identified a significant potential risk based on a nonclinical finding in rats (neuropil vacuolation) that is highlighted in labeling. Additional studies are needed to examine sequelae or effects on endpoints that were not adequately evaluated in the original NDA studies, particularly the potential for neuronal damage. This issue is appropriate for PMR instead of pre-approval because it involves a further characterization of an already identified potential risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The neurotoxicity of vigabatrin (VGB) in young animals needs to be further characterized. The brain lesions resulting from VGB exposure in the juvenile rat appear to be of a qualitatively different nature from those seen in the adult. In addition to demonstrating increased sensitivity to the neurotoxic effects of VGB seen in adults, the juvenile rat exhibits a different pattern of pathology. The lesions seen in the juvenile rat appears to primarily involve the neuropil, whereas in the adult rat lesions appeared primarily in white matter areas. The neuropil are gray matter regions composed primarily of axons and dendrites of adjacent neurons and not myelinated fibers. Most of the anatomical regions reported to contain vacuolization in the initial juvenile rat study (#OV-1007) were consistent with regions primarily containing clusters (nuclei) of neurons, including the substantia nigra pars compacta, thalamus, hippocampus, subiculum and deep cerebellar nuclei. Failure to demonstrate involvement of neurons in this vacuolization may have resulted from inappropriate histological stains, inappropriate survival intervals, or sampling bias. In neither juvenile study (#OV-1007 or #OVNC-9004) were neuropathological examinations conducted at sufficiently early time points to definitively rule out the possibility of neuronal degeneration. At the time points evaluated (survival intervals of 1-2 months), one would expect any degenerating neurons to be completely absorbed and thus be undetectable. Although a count of total surviving neurons might have detected increased neuronal degeneration, such counts were not made.

The potential of vigabatrin to induce neuronal apoptosis when administered during the critical period in rats should be examined. It is known that from a few days prior to birth to about 2 weeks postnatally the developing rat brain undergoes a natural burst of neuronal apoptosis. It is also known that during this critical period the administration of anesthetics, sedatives and other anticonvulsants result in significantly increased neuronal apoptosis. Therefore, rats exposed during this period should be examined shortly after this critical window for evidence of increased neuronal cell death as detected by special histochemical stains (e.g. the Fluoro-Jade dyes, Capsase 3 immunocytochemistry or suppressed silver methods) for localizing neuronal degeneration.

In order to resolve whether VGB during development can result in neuronal degeneration and to more fully characterize the unique neurotoxic effects of VGB, a toxicology study in the juvenile rat is needed.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A toxicology study in the juvenile rat examining the potential for vigabatrin exposure during development to produce neuronal damage. The study protocol should be submitted to the Division for comment prior to study initiation.

Required

Observational pharmacoepidemiologic study

Registry studies

Continuation of Question 4

Primary safety study or clinical trial

Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Sabril NDA 22006 PMR/PMC Development Template
Nonclinical PMR #2

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: A juvenile animal toxicity study of vigabatrin in a non-rodent species.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 09/2012
Study/Clinical trial Completion Date: 03/2014
Final Report Submission Date: 09/2014
Other: MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

We have identified a significant potential risk based on a nonclinical finding in rats (neuropil vacuolation) that is highlighted in labeling. A juvenile animal toxicity study of VGB in a second, non-rodent species (e.g., dog) is needed in order to more fully understand the relevance of the neurotoxicity findings in rats to humans. This issue is appropriate for PMR instead of pre-approval because it involves a further characterization of an already identified potential risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The neurotoxicity of vigabatrin (VGB) in young animals needs to be further characterized. The brain lesions resulting from VGB exposure in the juvenile rat appear to be of a qualitatively different nature from those seen in the adult. In addition to demonstrating increased sensitivity to the neurotoxic effects of VGB seen in adults, the juvenile rat exhibits a different pattern of pathology involving grey matter regions of the brain. In order to more fully characterize the unique neurotoxic effects of VGB in young animal and their relevance to humans, a juvenile animal study in a second, non-rodent species (e.g., dog) is needed.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A juvenile animal toxicity study of vigabatrin in a non-rodent species. The study protocol should be submitted to the Division for comment prior to study initiation.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Sabril NDA 22006 PMR/PMC Development Template
Nonclinical PMR #3

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodent.

PMR/PMC Schedule Milestones:

Final protocol Submission Date:	<u>01/2010</u>
Study/Clinical trial Completion Date:	<u>06/2011</u>
Final Report Submission Date:	<u>11/2011</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The results of a recently published study indicate that taurine supplementation prevents or ameliorates retinal toxicity induced by vigabatrin in albino rodents. An additional study is needed to determine if these findings can be replicated in animals and, if so, how relevant they are to vigabatrin-induced visual field defects in humans. This issue is appropriate for PMR instead of pre-approval because it involves a further characterization of an already identified risk.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

A recently published study (Jammoul F et al. Ann Neurol 65:98-107, 2009) reports that oral administration of taurine prevented or ameliorated vigabatrin--induced retinal toxicity in albino rats and mice. The relevance of these findings to humans is unclear since, in the sponsor's studies, vigabatrin did not induce retinal toxicity in animals with pigmented retinas (Long-Evans rat, dog, monkey). Vigabatrin is thought to exacerbate light-induced retinal toxicity in albino rodents, whereas the mechanism(s) underlying vigabatrin-induced visual field defects in humans is unknown. However, considering the seriousness of the human retinal findings, it is important that the sponsor attempt to replicate the results of Jammoul et al. (2009). In the sponsor's study, vigabatrin should be administered by the oral route (not intraperitoneal, as used by Jammoul et al. 2009) in albino rat or mouse. The sponsor should also attempt to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP Vision Res 20:1127-1131, 1980). If this is successful, the sponsor should test the effects of taurine in both albino and pigmented animals.

3. If the study/clinical trial is a PMR, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
 Animal Efficacy Rule
 Pediatric Research Equity Act
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
 Assess signals of serious risk related to the use of the drug?
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial:** any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A study examining the protective effect of taurine on vigabatrin-induced retinal damage in rodent, as reported by Jammoul et al. (Jammoul A F et al. Ann Neurol 65:98-107, 2009), but administering vigabatrin by the oral route. An attempt should be made to induce retinal toxicity in pigmented animals by, for example, exposing them to high intensity light for an appropriate duration following induction of mydriasis (cf. Rapp LM, Williams TP Vision Res 20:1127-1131, 1980). If this is successful, the study should be conducted in both albino and pigmented animals. The final study protocol should be submitted to the Agency for comment prior to study initiation.

Required

- Observational pharmacoepidemiologic study
 Registry studies

Continuation of Question 4

- Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 Pharmacokinetic studies or clinical trials
 Drug interaction or bioavailability studies or clinical trials
 Dosing trials
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 Immunogenicity as a marker of safety
 Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 Dose-response study or clinical trial performed for effectiveness
 Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22006	ORIG 1		SABRIL (VIGABATRIN)

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/s/

SALLY U YASUDA
08/19/2009

Sabril Infantile Spasms PMR/PMC Development Template

This template should be completed by review management and included for each PMR/PMC in the Action Package.

PMC Title: *Timing for Withdrawal/Discontinuation of Sabril in Infantile Spasms*

PMR/PMC Schedule Milestones:

Protocol Submission: by 7/2010
Study Start: by 7/2013
Final Report Submission: by 3/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This issue is appropriate for PMC instead of pre-approval because Infantile Spasms is a life-threatening condition for which there is no other approved treatment. We have identified a significant risk (visual loss) that is highlighted in labeling and through the REMS that includes a registry (elements to assure safe use). The risk may be linked to duration of therapy, and the purpose of this PMC is to determine if a shorter duration of therapy than that used in the clinical trials is sufficient to elicit remission of spasms.

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3.*
 - **Which regulation?**
 - Accelerated approval
 - Animal efficacy confirmatory studies
 - Pediatric requirement
 - FDAAA required safety study/clinical trial
 - **Describe the particular review issue leading to the PMR**
 - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**
 - **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?

Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this PMC

Sabril is known to cause irreversible damage to visual fields and may cause loss of visual acuity. Current evidence suggests that this risk may increase with increased duration of therapy. Identifying the minimal duration of therapy required to achieve efficacy would reduce the risk of visual loss.

5. What type of study or clinical trial is required or agreed upon (describe)?
An adequately controlled trial in infants treated with Sabril (vigabatrin) for infantile spasms to further characterize the minimum duration of therapy required for sustained suppression of

spasms. It is possible that a shorter duration of therapy will mitigate the risk of vision damage. The protocol for the trial should be discussed with the Agency prior to being submitted as a special protocol assessment (SPA).

Required

- Pharmacoepidemiologic study (list risk to be evaluated)
- Registry studies
- Primary safety study or clinical trial (list risk to be evaluated)
- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

19 - NDA 22006

PMR Title: To characterize the pharmacokinetics of Sabril in infants with infantile spasms who are 1 month to 5 months of age

PMR/PMC Schedule Milestones:

Protocol Submission: by 01/2010
Study Start: by 07/2013
Final Report Submission: by 03/2014

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement (e.g., unmet need, life-threatening condition, long-term data needed, only feasible to conduct post-approval, prior clinical experience indicates safety, small subpopulation affected, theoretical concern).

This issue is appropriate for PMR instead of pre-approval because there is an unmet need for Sabril for the treatment of refractory seizures and efficacy studies have been conducted in infants including 1-5 months of age. No pharmacokinetic data is available in this age group. It is important to know how the PK differs in this age group compared to older infants. These populations are at potential risk for high drug exposure that could lead to toxicity, if the PK differs in this age group compared to older infants.

2. If required, characterize the PMR. Check all that apply and add text where indicated. *If not a PMR, skip to 3.*
 - **Which regulation?**
 - Accelerated approval
 - Animal efficacy confirmatory studies
 - Pediatric requirement
 - FDAAA required safety study/clinical trial
 - **Describe the particular review issue leading to the PMR**
 - *No PK data available in the ages 1-5 months*
 - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**
 - **If the PMR is a FDAAA safety study/clinical trial, does it:**
 - Assess a known serious risk related to the use of the drug?
 - Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

3. For a post-approval FDAAA study/clinical trial, describe the new safety information

Not applicable.

4. If not required by regulation, characterize the review issue leading to this PMC

Not applicable.

5. What type of study or clinical trial is required or agreed upon (describe)?

An open label clinical trial to assess the single and multiple dose (at steady state) pharmacokinetics of Sabril (vigabatrin) at a clinically relevant dose in infants with infantile spasms who are 1-5 months of age.

Required

Pharmacoepidemiologic study (list risk to be evaluated)

Registry studies

Primary safety study or clinical trial (list risk to be evaluated)

- Subpopulation (list type)
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing studies
- Additional data or analysis required for a previously submitted or expected study (provide explanation)
- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup)
- Dose-response study performed for effectiveness
- Nonclinical study, not safety-related (specify)
- Other

6. Is the PMR/PMC clear and feasible?

- Are the schedule milestones and objectives clear?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, and determine feasibility?

CDTL or PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22006	ORIG 1		SABRIL (VIGABATRIN)

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/s/

SALLY U YASUDA
08/19/2009

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: June 19, 2008

TO: Tamy Kim, Regulatory Project Manager
Dr. Norman Hershkowitz, Medical Officer

FROM: Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-006

APPLICANT: Ovation Pharmaceuticals, Inc.

DRUG: Sabril® (vigabatrin) Powder for Oral Solution

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: treatment of infantile spasms

CONSULTATION REQUEST DATES: February 28, 2008

DIVISION ACTION GOAL DATE: June 30, 2008 (An Advisory Committee meeting is planned for early August; an action will be delayed until after this date.)

PDUFA DATE: June 30, 2008

I. BACKGROUND:

NDA 22-006 is a new drug marketing application for Sabril® (vigabatrin) Powder for Oral Solution. Vigabatrin is a new chemical entity being developed for the treatment of infantile spasms (IS). It also is proposed for the treatment of partial epilepsy in subjects who have not responded adequately to other antiepilepsy drugs. Currently the product is approved in the UK and various European countries for both of these indications. Drs. Elterman, Shields, and Bebin's sites were selected for inspection due to enrollment of large numbers of study subjects. The goals of the inspections were to assess adherence to FDA regulatory requirements; specifically, investigator oversight, protocol compliance, accuracy of primary efficacy endpoint data, and protection of subjects' rights, safety, and welfare.

The following protocol was inspected:

- **Protocol:** #1-A, entitled "Clinical Experience and Use of Vigabatrin (Sabril®) in Subjects with Infantile Spasms"

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor City, State or Country	Protocol #	Inspection Date	Final Classification
Roy D. Elterman, MD Dallas Pediatric Neurology Associates 12801 N. Central Expressway Suite 580, Plaza 3 Dallas, TX 75243-1708	Protocol #1-A	April 28 - May 5, 2008	VAI
W. Donald Shields, MD Mattel Children's Hospital at UCLA Division of Pediatric Neurology 10833 LeConte Avenue Room 22-474 MDCC, Box 951752 Los Angeles, CA 90095-1752 Phone: 310-206-8808	Protocol #1-A	April 29 - May 12, 2008	Pending
Martina Bebin, MD UAB Department of Neurology Epilepsy Center CIRC 312 1719 6th Avenue South Birmingham, AL 35292-3280 Phone: 205-996-6893 or 205-934-0683	Protocol #1-A	April 28 - 30, 2008	NAI
Ovation Pharmaceuticals, Inc. 4 Parkway North, Suite 200 Deerfield, IL 60015 Phone: 847-282-1066 Fax: 847-317-9112 Email: jswalec@ovationpharma.com	Protocol #1-A	May 29 - June 18, 2008	Pending

Key to Classifications

NAI = No deviation from regulations.

VAI-No Response Requested= Deviations(s) from regulations.

VAI-R = Response Requested = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Roy D. Elterman, MD, Site #1
Dallas Pediatric Neurology Associates
12801 N. Central Expressway
Suite 580, Plaza 3
Dallas, TX 75243-1708
 - a. **What was inspected:** Forty-seven (47) subjects were enrolled at Dr. Elterman's site. Only three subjects completed the study. A complete review of 16 subjects' records was conducted. Informed consent documents for all subjects were reviewed.
 - b. **General observations/commentary:** The inspection revealed minor protocol deviations related to obtaining laboratory values as specified in the protocol, as well as instances of recordkeeping violations. Additionally, two subjects were allowed to participate in the study in violation of exclusion criteria. Specifically, Subject #183 was removed from the study, started on adrenocorticotrophic hormone (ACTH), and subsequently re-entered into the study. The subject was concurrently taking the study drug and ACTH for a period of time, in violation of the protocol. Subject #187 had a history of Miller Dieker Type #1 disease and participated in the study in violation of protocol exclusion criteria.
 - c. **Assessment of data integrity:** The review division should evaluate the significance and impact, if any, of the participation of Subjects #183 and 187 in the study given the violation of protocol exclusion criteria as stated above. Otherwise, data for this site appear acceptable in support of the pending application.
2. W. Donald Shields, MD, Site #2
Mattel Children's Hospital at UCLA
Division of Pediatric Neurology
10833 LeConte Avenue
Room 22-474 MDCC, Box 951752
Los Angeles, CA 90095-1752
 - a. **What was inspected:** At Dr. Shields' site, 49 subjects were screened, 48 subjects were enrolled and randomized, and 8 subjects completed the study. A complete review of 16 subjects' records was performed. Informed consent documents for all subjects were reviewed.
 - b. **General observations/commentary:** The inspection revealed protocol deviations related to dosing for two subjects. Specifically, Subject #0203 was randomized to a high-dose regimen, but received the protocol-specified doses at delayed intervals. Subject #0256 was overdosed during the initial treatment

phase due to an incorrectly obtained weight. Additionally, there were several instances of laboratory examinations that were not performed as specified in the protocol, as well as several deviations in performing global evaluations per protocol.

Observations noted for Dr. Shields' site are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

- c. **Assessment of data integrity:** Other than the deficiencies pertaining to dosing deviations for Subjects #0203 and 0256 mentioned above, data for Dr. Shields' site appear acceptable in support of the pending application.

- 3. Martina Bebin, MD, Site #4
UAB Department of Neurology
Epilepsy Center
CIRC 312
1719 6th Avenue South
Birmingham, AL 35292-3280

- a. **What was inspected:** At Dr. Bebin's site, 81 subjects were screened, and 61 subjects were enrolled. Ten subjects completed the study. Informed consent documents for all subjects were reviewed. An audit of all 61 enrolled subjects' records was conducted.
- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data for this site appear acceptable in support of the pending application.

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

- a. **What was inspected:** The inspection included review of standard operating procedures and monitoring reports. Monitoring reports for protocol #1-A at Drs. Elterman, Shields, and Bebin's sites were reviewed.
- b. **General observations/commentary:** No significant regulatory violations were noted.
- c. **Assessment of data integrity:** Data monitored by this sponsor appear acceptable in support of the pending application.

Observations noted for Ovation Pharmaceuticals, Inc. are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

As mentioned above, the inspection of Dr. Elterman revealed protocol exclusion criteria violations with respect to the study participation of Subjects #183 and 187. For Dr. Shields' site, the inspection revealed protocol dosing violations for Subjects #0203 and 0256. The review division should evaluate the significance and impact, if any, of these observations. The inspection of Dr. Bebin's site found no significant regulatory violations. Data generated from Dr. Bebin's site appear acceptable for use in support of the pending application. The inspection of Ovation Pharmaceuticals, Inc. found no significant regulatory violations, and thus data monitored by the sponsor appear acceptable for use in support of the pending application.

As previously mentioned, observations noted above for Dr. Shield's site, as well as the inspection of Ovation Pharmaceuticals, Inc., are based on the Form FDA 483 and communications with the field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Sheryl Gunther, Pharm.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief, Good Clinical Practice Branch I
Division of Scientific Investigations
Office of Compliance

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/s/

Sheryl Gunther
6/26/2008 08:18:08 AM
PHARMACOLOGIST

Sherbert Samuels
6/26/2008 09:46:43 AM
CSO
Signed on behalf of Dr. Constance Lewin



NDA 22-006

INFORMATION REQUEST LETTER

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec
Director, Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your December 28, 2007, new drug application (NDA) resubmitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) Powder for Oral Solution 500 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

Finished Product Specification

1. Please include a test and an acceptance criterion for Reconstitution Time to be monitored at release and throughout stability.
2. In your specification table in Section 3.2.P.5.1 you noted that microbial limits tests would be performed at release only. However, in the post-approval stability section (Section 3.2.P.8.2), you indicated that microbial limits tests would be performed at release and on a yearly basis on stability. Please correct your drug product regulatory specification table in Section 3.2.P.5.1 to indicate that microbial limits tests will be conducted at release and on stability.

Labeling

3. On your Carton and Container Labels, the Directions for Use should state, "Dissolve entire contents in 10 mL (2 teaspoons) of milk, infant formula, or water using a calibrated 10 mL syringe."
4. On your Carton and Container Labels and in the Package Insert, you should state more prominently that the unused portion of the reconstituted oral solution must be discarded after use.

NDA 22-006
CMC IR 1

If you have any questions, please call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

6/10/2008 12:37:27 PM



NDA 20-427 & 22-006

INFORMATION REQUEST LETTER

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin).

We are reviewing your product launch proposal for the drug product manufactured at Patheon Inc, in Toronto, Canada. We have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide a list of batches, quantity per batch, proposed expiration dates for all lots that remain within the expiration and produced at the Patheon facility prior to ceasing production.
2. Provide the contact information of the responsible individual(s) or department who will assume the QC responsibilities of the batches produced and related records (batch records, stability studies, rejected lots, complaints, release testing records, etc.)
3. Identify the location where these records will be maintained for FDA review throughout shelf-life to expiration, and one year thereafter.
4. Provide the location of the final distribution site where the product will be stored.
5. Indicate whether any of the batches were involved in an OOS or manufacturing deviation that required reprocessing or rework.

If you have any questions, call Don Henry, Regulatory Project Manager, at 301-796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

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/s/

Ramesh Sood
3/18/2009 03:29:11 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-006

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec, Associate Director, Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) Powder for Oral Solution.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Priority. Therefore, the user fee goal date is June 30, 2008.

As previously conveyed during the February 25, 2008 teleconference, the Division will be unable to take an action by the PDFUA date due to the timing of the Advisory Committee to be held to discuss this product. An action will occur after the Advisory Committee Meeting has occurred.

During our filing review of your application, we identified the following potential review issues:

1. Although the proposed label mentions animal abuse potential studies, these studies were not found in the NDA. Given that a human abuse potential study was not conducted due to safety concerns, the animal abuse studies are critical to the CSS review of whether vigabatrin has abuse potential (in addition to assessment of clinical adverse events).
2. The proposed label has no mention of CSA scheduling and the Drug Abuse and Dependence section implies that vigabatrin does not have abuse potential. However, no statement was found in the NDA regarding the proposed scheduling of vigabatrin (or proposal to not schedule) or the rationale supporting that conclusion.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We also request that you submit the following information:

The Division of Risk Management requests the Vigabatrin Medication Guide. While there is a space in the RiskMAP for a Medguide to be inserted (Appendices 3 and 4), there is no MedGuide there.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are granting a waiver of the pediatric study requirement for this drug product.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. Please note that satisfaction of the requirements in section 2 of PREA alone may not qualify you for pediatric exclusivity.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(I)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Melina Griffis, R. Ph., Regulatory Project Manager, at (301) 796-1078.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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**MINUTES OF MEETING
NDA 20-427 & NDA 22-006**

Drug: Sabril (vigabatrin) Tablets and Powder for Solution
Sponsor: Ovation Pharmaceuticals, Inc.
Date: June 6, 2007
Where: White Oak Bldg. 22, Conf. Room 1417; 11 am - 12 noon
Attendees: Agency:

Russell Katz, MD	Division Director
John Feeney, MD	Medical Team Leader & Deputy Director (acting)
Gerry Boehm, MD	Safety Reviewer
Alice Hughes, MD	Safety Team Leader
Ron Farkas, MD	Medical Reviewer
Phil Sheridan, MD	Medical Reviewer
Ed Fisher, PhD	Pharmacology Reviewer
Wiley Chamber, MD	Deputy Director, Division of Anti-Infectives & Ophthalmology
Robbin Nighswander, MS	Supervisory Regulatory Project Manager

Firm:

Robert Anders, PharmD	VP, Clinical Operations
Sandy Bialek-Smith, BS, MT (ASCP)	Associate Director, Clinical Operations
Stephen Collins, MD, PhD	CSO & VP, Clinical Operations
Tim Cunniff, PharmD	VP, Regulatory Affairs
Mahlaqa Patel, BA	Senior Manager, Regulatory Affairs
Roger Porter, MD	Consultant
Jenny Swalec, BS	Director, Regulatory Affairs
Katherine Tracey, MD, PhD	VP, Clinical Research
Steve Wanaski, PhD	Director, Preclinical Research

Purpose: Type A meeting to discuss the firm's proposal for NDA resubmission.

Background: Briefing package: May 22, 2007

Question 1: *Does FDA agree with the general approach Ovation has taken to further evaluate abnormal MRI findings reported in a small number of IS patients treated with VGB?*

Preliminary Response: The overall approach seems logical.

This includes review of Dr. Pearl's data, the summary MRI data for 213 children from 5 sites (in U.S., Canada, and France), the data from over 200 children from pediatric CPS studies, case reports from the global post-marketing database, and literature reports.

Furthermore, a retrospective epidemiologic study is proposed to characterize the incidence and prevalence of MRI abnormalities in patients with IS both with and without vigabatrin therapy.

Meeting Discussion: See below.

Question 2: Given the existing MRI data in adults and older children treated with VGB for refractory CPS versus the existing MRI data in infants treated with VGB, does FDA agree that the level of potential risk differs between the two patient populations?

Preliminary Response: This is a complicated issue that will require further discussion at the meeting.

Some sections of the meeting package seem to draw a clear distinction between the IME seen predominantly in the white matter of the adult animal models and the subcortical grey matter lesions seen in the juvenile rat model (that may correspond to the type of lesion reported by Dr. Pearl and others in the IS patients). Other sections of the meeting report seem to equate the two lesions. This requires clarification.

It appears that the lesions reported by Dr. Pearl and seen in about 23 of the 213 additional cases from the 5 centers are a different lesion from the IME previously reported in the adult animal model. [Most of the 213 apparently did not have baseline MRI's, so an incidence of 11% is uncertain.] The vacuolar changes in the juvenile rat were in the neuropil, predominantly within the gray matter. This presumably correlates with the predominantly subcortical gray matter lesions seen reported by Dr. Pearl. The IME in adult mice, rats, and dogs is microvacuolation predominantly in the white matter.

Previous submissions to the CPS NDA summarized data from over 500 adult patients with serial MRI's, serial evoked potentials, autopsies or biopsies that demonstrated a lack of findings suggestive of IME. It is not easily discernible from your submission which of the 500 had which type(s) of evaluations. You should clarify this. In any event, it is only the MRI summary reports rather than the scans themselves that are available from the previous sponsor as discussed on page 76 of 81. This raises the possibility that the original studies 15 years ago were primarily looking for IME-like white matter lesions and may not have reported any subcortical gray matter lesions. In short, how reliable and complete is the data on the 500 patients? Did they all have the appropriate MRI studies? How many of these patients had both baseline *and* on-treatment MRIs? Overall, how many patients had baseline MRIs, on-treatment MRIs and evoked potential examinations (and/or other data such as autopsies, biopsies), and follow-up MRIs and evoked potential examinations and/or other examinations? Was the quality of the MRIs sufficient to capture the types of lesions that are of concern? In order to assess the quality of the available data for the CPS population, we need more information regarding what data in the MRI report were assessed, and what the findings were at baseline, on-treatment, and at follow-up (similar to the data that you have provided for the IS MRI data [see pages 29-40 of your briefing document]).

Similar questions also apply to the pediatric population with CPS.

In order to fully evaluate whether there appears to be a differential risk in the CPS and infantile spasm populations, it is critical for us to more fully understand the basis for your assertion that none of the types of lesions observed in some patients treated for infantile spasms were observed in adults or children treated for CPS. If the nature of the data available for the CPS population is inadequate, further study of this population may be necessary.

It would be helpful to present the pediatric MRI data in the CPS studies by age.

Meeting Discussion: In response to the preMeeting comments, the sponsor provided arguments that the characteristics of IME are consistent across studies, but the location differs (summary slides attached). Extensive discussion about the nature of the lesion was held. The sponsor believes that the lesion seen in the juvenile toxicity study represents IME in deep grey matter structures. By extension, the sponsor believes that the newly described deep grey matter lesions seen on MRI in patients treated for infantile spasms represents IME.

In response to Agency questions, the sponsor explained that the lesions appeared to be reversible; however, the Agency was not convinced and asked that additional support be provided to address this.

The firm noted that the original pediatric MRIs for refractory CPS patients have recently been found by the original sponsor and will be completely re-read, looking specifically at deep grey matter areas.

Question 3: Does FDA concur with the design of our epidemiological protocol to assess MRI abnormalities?

Preliminary Response: The results of your proposed study may be difficult to interpret for a number of reasons. First, because many patients will only have one MRI (you estimate 50% on p.69 of your briefing document) and MRIs are not being done systematically and regularly over time, the relationship between drug exposure and lesion development will be difficult to assess. We will be in a position of assessing prevalent rather than incident lesions for many patients, which may not permit adequate causality assessment. Second, because this is not a randomized trial, there will be underlying differences in patients in the untreated and treated groups (and the high and low dose groups). If any of these differences are related to the outcome measure, this may lead to confounding. Third, it will be difficult to classify and interpret exposure, given that patients switch medications, change dosages, and stop treatments over time (and MRIs will not be available for each of these treatment changes). A randomized, controlled trial with systematic MRI assessments over time would provide more readily interpretable data and would also permit a rigorous assessment of clinical correlates and long-term sequelae, and we strongly encourage you to consider this design.

We have a number of additional specific comments regarding the study design of the epidemiological study that you have proposed:

- The proposed study does not assess the functional impact or long-term sequelae of the observed abnormalities, regarding which we currently have a paucity of information. It would be useful to assess this.
- Please explain in greater detail by which MRI (images and reports) will be reviewed by Ovation. Who would be reviewing the report for Ovation. The flow diagram on page 14 of your study protocol does not provide sufficient detail regarding this process.
- We request that you provide summary information (including demographic and treatment data) regarding the subjects who were excluded from the study, and report the reasons for exclusion.

Meeting Discussion: In response to the preMeeting comments, the firm proposed to conduct a prospective clinical study in IS as a post-marketing commitment (PMC). The retrospective epidemiology study would be conducted prior to NDA submission and would include a 100% independent masked review of MRI scans. The firm also proposed to include MRI and EP monitoring in the proposed labeling. The Agency noted that EP monitoring in children (with sedation) may be an issue given the additional risk of sedation.

With regard to the epidemiology study, the Agency noted concerns about the timing of MRIs as related to initiation of therapy, dosing changes. It is not clear how this data could be interpreted.

The sponsor confirmed that ACTH therapy would be used as the first line of therapy at some of the study sites but not all.

Question 4: Does FDA agree with our proposal to have independent “masked” neuroradiologists assess 20% of collected MRI scans and that a full masked review of all (100%) MRI scans collected for this study is not required unless significant discrepancies (>5%) are determined in the subset?

Preliminary Response: Given the relatively low number of MRI’s (approximately 150), a full masked review is practical and will give more credible results. This is particularly important given that the MRI data you provided us with thus far for patients from CPS and IS trials is based on your review of MRI reports rather than the MRIs themselves. Moreover, we believe that a 20% masked review would provide a sensitivity that was unacceptably low based on your estimates of the sensitivity and specificity (and positive and negative predictive value).

Meeting Discussion: As discussed in Q3 above, the sponsor has agreed to a 100% review of the MRI scans.

Question 5: Does FDA concur with the resubmission strategy for the CPS and IS NDAs?

Preliminary Response: The answer to this question depends on how confident we can be that your conclusions are supported by the data. It is disconcerting to learn from your current submission that the MRI data from children with refractory CPS are being reported (p59) “for the first time.” Likewise, you state (p19) that, “Of the 27 clinical studies with evidence of MRI or VEP testing, clinical study reports were located for 23 of them.” And in the table of pediatric CPS studies on pages 21-25, it appears that original MRI reports were not included in the patient CRFs for a significant number of patients. (In completed study 192, you state that the original MRI report is available for only 1 patient.)

For the pediatric CPS studies, we note that all the MRIs for the 200 patients were read by a single reader at a single center. This is not reassuring.

For the adult MRI data, you state (p20), “Contrary to the findings in animals, no MRI change from baseline *which was consistent with IME* [DNP emphasis] was observed in humans.” Based on your current submission, it appears that the view of what is consistent with IME may have changed from 10 years ago. On p26, you state, “Brain MRI imaging was used to assess for IME as observed *in pre-clinical studies* [again DNP emphasis].” Now that the juvenile toxicity data have shown a

somewhat different pattern of IME, do the MRIs need to be re-read with a broader perspective?

There were some “patients of concern” identified by the panel of experts who reviewed the adult CPS data; we have identified some pediatric CPS patients from your submission whose MRI reports raised (b) (4) patients, will MRIs or MRI reports be available for our review?

As discussed in question 2, before it can be concluded that the CPS NDA can be submitted prior to the new studies of the subcortical grey lesions, it should be established that the newly described lesions are distinct and that the data from the original CPS studies are sufficiently reliable and complete.

DNP understand that CSS has already addressed your question about the need for primary data in support of the abuse liability assessment.

Meeting Discussion: Following discussion at the meeting, Dr Katz advised the firm that their current proposal was not unreasonable. Furthermore, the submission of NDA 22-006 for IS could be submitted at the same time as the resubmission of NDA 20-427 for CPS.

Dr Katz also confirmed with the sponsor that we would have sufficient data at the time of NDA submission to schedule an Advisory Committee.

In response to an Agency question regarding the feasibility of conducting and completing the PMC study in IS in a timely manner, the firm replied that they were convinced that the study could be completed and would include follow-up of subjects for up to a year.

Russell Katz, M.D.
Division Director

Robbin Nighswander, M.S.
Supervisory Regulatory Project Manager

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/s/

Russell Katz
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-006

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec, Associate Director, Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

We acknowledge receipt on March 9, 2007, of your March 8, 2007, submission to your new drug application (NDA) for Sabril (vigabatrin) sachet.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

Like you, we are aware of the recent public presentation by Dr. Phillip Pearl from Children's National Medical Center in Washington, D.C., in which he described reversible MRI changes in 3 children during treatment with Sabril. These 3 cases represented 20% of the children treated by Dr. Pearl for whom serial MRIs (including pre-treatment studies) were available. Because of the longstanding issue of intramyelinic edema (IME) with vigabatrin, these reports raise important new concerns. We know from your infantile spasms application (Section 8.1.8 Recent Literature Publication-MRI Findings) that you have begun to address these reports, convening an expert panel of neurologists on February 25, 2007. You state that additional data are needed and you allude to a planned masked review by neurologists and neuroradiologists. You state that you will "summarize all data gathered to date in both the Advisory Committee Briefing document and the 120 day Safety Update."

Presumably, you did not discuss these new findings in the adult partial seizure application because the 3 cases were pediatric patients. We believe that the new MRI findings may be relevant for both applications. The carefully collected MRI data from adults enrolled in your controlled trials in the early 1990's showed no evidence of treatment-emergent MRI changes. We are not aware of cases of MRI changes of this nature occurring in pediatric patients either. In order to fully evaluate the safety of vigabatrin and provide directions for use (including any recommendations about monitoring), DNP requires that you review the new data in light of previous knowledge and provide your conclusions.

Additionally, we have the following request:

1. Please submit primary data for any studies that you wish for us to consider in the review of the abuse liability of vigabatrin. In particular, we will need primary data from the following nonclinical studies:
 - receptor binding studies for all CNS sites, not just "abuse-related targets"

- self-administration study in monkeys
- drug discrimination studies in rats
- studies on tolerance
- studies on physical dependence

2. Clinical Pharmacology

- Please clarify the relationship between studies AUS911 and AUS03 by providing a summary of the basis for concluding that they are the same and explain the inconsistencies between the two reports (we note that some of the results are different between the two studies although you assert that these two studies are the same). Please submit an amendment to the clinical pharmacology section of the NDA submission accordingly.
- Please provide specific information for the studies that support labeling statements including study number, study date, NDA/IND submission #, series #, submission date, and section/volume #; or otherwise provide full study reports.

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Courtney Calder, Project Manager, at 301-796-1050.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): HFD-520/DAIOP Frances LeSane, CPMS (Wiley Chambers has been involved with this NDA)		FROM: HFD-120/ Division of Neurology Products		
DATE March 19, 2007	IND NO.	NDA NO 22-006	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT March 8, 2007
NAME OF DRUG Sabril (vigabatrin) tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE Pdufa goal date in six months
NAME OF FIRM: OVATION				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This submission is located in the EDR: \\CDSESUB1\N22006\N_000\2007-03-08 It is a new NDA for Sabril. Please let me know who the reviewer is. Thank you! Courtney				
SIGNATURE OF REQUESTER Courtney Calder, Pharm.D. Regulatory Project Manager 301-796-1050 calderc@cder.fda.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Courtney Calder
3/19/2007 06:11:15 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-006

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec, Associate Director, Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (the Act) for Sabril (vigabatrin) sachet. Reference is also made to the Agency's letter dated November 9, 2006, which notified you that we are refusing to file this NDA under 21 CFR 314.101(d). This letter is to notify you that, for the reasons described below, rather than refusing to file the application, we have determined that the NDA is incomplete and cannot be accepted for filing.¹

According to section 736(a)(1)(E) of the Act a human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 526 [of the Act] shall not be subject to a fee under [section 736(a)(1)(A)], *unless the human drug application includes an indication for other than a rare disease or condition*. The NDA included an indication which is not an orphan indication.² Because NDA 22-006 includes an indication for other than a rare disease or condition it does not qualify for the orphan exception to user fees. You did not submit any user fees with your supplement. Because an application is considered incomplete and cannot be accepted for filing until all fees owed have been paid, this application is not accepted for filing. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15251-6909

Checks sent by a courier should be addressed to:

Food and Drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

¹ Please note that you still need to address the issues identified in the Agency's November 9, 2006, letter when you respond.

² NDA 22-006 included two indications 1) infantile spasms, which is orphan designated and 2) refractory complex partial seizures, which is not orphan designated.

NDA #-###/S-###

Page 2

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (301) 796-1050.

Sincerely,

{See appended electronic signature page}

Courtney Calder, PharmD
Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Courtney Calder
12/11/2006 10:39:39 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-006

Ovation Pharmaceuticals, Inc.
Attention: Jenny Swalec, Associate Director, Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your October 17, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (Vigabatrin) sachet.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

- You submitted narratives for only a subset of patients with serious adverse events (SAEs). Please submit narratives for all of the SAEs, regardless of the attribution of cause.
- The adult patient narratives previously requested for NDA 20-427 (for all of the SAEs, regardless of the attribution of cause) must be submitted to NDA 20-427 to allow a full review of NDA 22-006.

We also have the following additional comments:

- Although a matter of review, we are concerned that the data you submitted on long-term follow-up of ophthalmic function in patients treated with vigabatrin for infantile spasms (IS) may not provide adequate safety experience to support NDA approval. As communicated to you most recently at the pre-NDA meeting, we believe it is critical to address the long-term ophthalmic function of patients now in late childhood or early adulthood who were treated with vigabatrin for IS in the United States or in Europe. As a start, we request that you submit such data on ophthalmic function for as many of the patients in the pertinent vigabatrin efficacy trials as possible. Obtaining follow-up data from as many of these patients as possible is important in order for the data to be considered representative of the IS population as a whole. We believe similar long-term follow-up data representative of other patient cohorts (for example, experience at a referral center) should also be submitted. We recognize that it may not be possible to obtain complete, recent ophthalmic data for all patients in a given cohort, but we request that you document reasonable efforts to determine for all patients if severe visual disability is present, and if so, the attributed cause.

- Please submit a full study report for study 4102.
- Please submit case report forms (CRFs) for all subjects experiencing a serious adverse event.
- Please submit the published literature reports of studies for which you cannot obtain the full study reports or raw study data (for example the Vigevano study in Italy and the Brandl study in Germany).
- Please submit SASCODES for analyzing the primary and secondary efficacy measures of the 3 controlled studies (Studies 1A, W019, and FR03). Please do not use any MACRO statement in the SASCODES.
- Although NDA 20-427 is cross-referenced for information on the manufacture and control of vigabatrin drug substance, a substantial amount of information on the drug substance was submitted in the current application. Please confirm that all drug substance documentation submitted in NDA 22-006 is the same as that submitted to NDA 20-427.
- With regard to the proposed product labeling we note the following:
 1. You refer to the drug product as a “vigabatrin sachet” in the submission and in proposed labeling. As the Agency does not recognize the term sachet as a dosage form, please revise the established name for the drug product to “(vigabatrin) Powder for Oral Solution”.
 2. The Directions for Use instruct the caregiver to dissolve the contents of the sachet in 10 mL of milk, infant formula or other liquid, administer directed amount and discard unused portion. A caregiver may use a household spoon rather than a standard measure. This may not be considered a problem if the entire contents of the sachet are to be administered; however, for younger patients, especially neonates, it is unlikely that the entire contents of the sachet will be administered. It would therefore be necessary to measure both the volume of liquid added and the dose withdrawn with a reasonable degree of accuracy. Inclusion of a more accurate dosing device (e.g., calibrated oral syringe or dropper) with the drug product is recommended.
- Please submit a recommendation on scheduling under the Controlled Substances Act (CSA) and the basis for the recommendations.
- The proposed product labeling for Sabril, which states “The abuse and dependence potential of Sabril has not been evaluated in human studies,” is misleading and inaccurate. It probably would not have been possible (or ethical) to conduct a human abuse liability study with the drug, but the abuse potential evaluation needs to include the following from available data:
 1. ***Discussion of abuse-related safety results from efficacy trials.*** Large clinical trials (Levinson & Devinsky, 1999, for example) compared vigabatrin to placebo and assessed its neurobehavioral effects. The authors concluded that the drug had a higher incidence of

events coded as depression (12.1% vs. 3.5%, $p < 0.001$) and psychosis including behavioral disturbances, irritability, agitation and anxiety) and symptoms of psychosis (including delusions, auditory and visual hallucinations, extreme aggression and paranoia) (2.5% vs. 0.3%, $p = 0.028$).

2. **Discussion of dependence & withdrawal.** The ISS of NDA 20-427 includes a section on withdrawal effects and states that seizures have occasionally been noted in adults during discontinuation of vigabatrin therapy. Status epilepticus has occurred in "rare instances" following withdrawal of the drug. A slow tapering of the drug rather than abrupt discontinuation has been recommended.
 3. **Discussion of epidemiological data related to abuse, misuse, diversion, overdose and suicide.** The drug has been marketed in many countries worldwide for at least 2 decades. Please provide complete actual usage data including a history of abuse and complete summaries and reports of abuse and dependence-related reports to be included in the product labeling. In addition, all adverse events data from the WHO Uppsala Centre, as well as individual country sources, along with all of the foreign language approved product labelings, translated into English, should be provided.
- The Clinical Pharmacology section of the submission needs the following items:

1. Please submit the analytical method report for the study report for AUS03.

In addition, the following items have already been requested and should be available by the time the application is resubmitted:

1. In the Submission of 8/15/05 you stated that the study report of Prt 097-332.5 "Pharmacokinetics of the Enantiomers of VGB in Infants and Children" would be included as "Reports of Human Pharmacokinetic (PK) Studies". There appears to be an executive summary that can be found by going through "summary of clinical pharmacology/effects of age". Please send the full study report as soon as possible. This should include the analytical study report. You should also send the PK data (raw data and calculated parameters) in SAS transport files. The PK files should include columns for subject ID, age, gender, weight, height, treatment, period, sequence, time after dose, and plasma concentrations for each analyte at the specified time point.
2. You should submit SAS transport files for the PK data for the other clinical pharmacology studies for which study reports have been provided in the submission (the two PK studies evaluating BE of the sachet and tablet as well as the Phenytoin drug interaction study) .

Within 30 days of the date of this letter, you may request in writing a meeting about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the

NDA 22-006

Page 4

date you requested the informal conference. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee.

If you have any questions, call Courtney Calder, Project Manager, at 301-796-1050.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

(b) (4)

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/s/

Russell Katz
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