CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-427

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

M E M O R A N D U M

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

DATE: August 7, 2009

FROM: Philip H. Sheridan, M.D.
Division of Neurology Products
Office of Drug Evaluation I

SUBJECT: **Financial Disclosure Statements for NDA 20-247 Study 4020**

TO: File **NDA 20-247**

DRUG: Sabril oral tablets

A safety study (Study 4020) was conducted in Europe by the previous sponsor (Aventis) of this NDA at the request of the European Medicine Agency (EMEA). The purpose of the study was to better characterize the visual field defect associated with vigabatrin use.

Prior to the submission of this NDA, the current sponsor, Ovation, made repeated efforts to obtain financial disclosure information for Study 4042 from Aventis. On December 7, 2005, Aventis responded to Ovation that Aventis could not locate the requested financial disclosure information.

Study 4020 was one of many studies regarding the visual field defect associated with vigabatrin use submitted with NDA 20247. The results of Study 4020 were not considered by the Agency to be critical in the safety review and approval of NDA 20247 or in the labeling of Sabril.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG

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
08/07/2009

Patent Information

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

Patent Information

Applicant:	Ovation Pharmaceuticals 4 Parkway North, Suite 200 Deerfield, IL 60615
Active Ingredient:	4-amino-5-hexenoic acid, (±)-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

[redacted]

b(4)

[redacted]

b(4)

Lundbeck Inc.
Four Parkway North
Deerfield, IL 60015
USA

Tel 847-282-1000
Fax 847-282-1081
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. 20-427 Sabril® (vigabatrin) Tablets
Amendment: Submission of Patent Information - FDA Form 3542a

Dear Dr. Katz:

Reference is made to pending NDA 20-427. 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 Swalec

Jenny Swalec
Sr. Director, Global Regulatory Affairs

Department of Health and Human Services
Food and Drug Administration

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

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

NDA NUMBER
20-427

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) Tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
vigabatrin	500 mg

DOSAGE FORM
Tablet

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.

☒ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ 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

EXCLUSIVITY SUMMARY

NDA # 20-427 SUPPL # HFD # 120

Trade Name Sabril Tablets

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?

5 (Hatch-Waxman)

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 ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

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: 8/24/09

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

13. / 14. Patent Information/Certification

U.S. Patent 3,960,927 covering the active ingredient vigabatrin expired June 1, 1993. Because vigabatrin is a new chemical entity, a five year period of exclusivity will prevail from the date of approval of the NDA. This is covered by one of the provisions of the Waxman-Hatch Patent Restoration Act of 1974.

Debarment Certification

Title:	Debarment Certification
Product Name:	Vigabatrin
Sponsor:	Ovation Pharmaceuticals 4 Parkway North, Suite 200 Deerfield, IL 60615
Date:	11 December 2005

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.

Jenny Swalec
Associate Director, Regulatory Affairs
Ovation Pharmaceuticals

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-427 Trade (generic) names Sabril® (vigabatrin)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

____ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ b. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

_____ _____

Signature of Preparer Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

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	DATE OF SUBMISSION
Lundbeck Inc.	07/14/2009
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
847/282-1066	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)* 20-427

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
vigabatrin	Sabril

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
4-amino-5-hexenoic acid or (+)-4-amino-hexenoic acid		MDL 71,754
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Tablet	500 mg	Orall

(PROPOSED) INDICATION(S) FOR USE:
Adjunctive therapy for the treatment of refractory complex partial seizures in adults

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 APENDING 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 22-006; [redacted]

b(4)

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	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	DATE:
Jenny Swalec	Jenny Swalec, Sr. Director Global Regulatory Affairs	07/14/2009

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
4 Parkway North, Suite 200, Deerfield, IL 60015	(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 Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-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.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]		
NDA # 20-427 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Sabril Established/Proper Name: vigabatrin Dosage Form: Tablets		Applicant: Ovation Pharmaceuticals Agent for Applicant (if applicable): Jenny Swalec
RPM: Tamy Kim		Division: DNP
NDAs: NDA Application Type: X 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (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.)		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)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **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.** ☐ No changes ☐ Updated Date of check: **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.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**
❖ User Fee Goal Date: June 30, 2008 Action Goal Date (if different): August 21, 2009		
❖ Actions		
• Proposed action		X AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*		☐ None Not approvable – 4/28/95 Approvable – 11/26/97 Not approvable – 10/27/98

[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.

❖ Promotional Materials *(accelerated approvals only)* 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 _____	☐ Received

❖ Application[2] Characteristics	
Review priority: X Standard ☐ Priority Chemical classification (new NDAs only): 1 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) X Restricted distribution, but not under Subpart H Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: _____	2/25/09
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes ☐ No
• Press Office notified of action (by OEP)	X Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None X HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ 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	
• Is approval of this application blocked by any type of exclusivity?	X No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	X No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	X No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	X Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Not approvable – 4/28/95 Approvable – 11/26/97 Not approvable – 10/27/98
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	See Approval Letter
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	See Approval Letter
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	X Medication Guide ☐ Patient Package Insert ☐ Instructions for Use

[3] Fill in blanks with dates of reviews, letters, etc.

	☐ None
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	See Approval Letter
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	See Approval Letter
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	See Approval Letter
• Most recent applicant-proposed labeling	See Approval Letter
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA 5/6/09; 12/18/06; 7/10/06 ☐ DRISK 6/7/09 ☐ DDMAC 6/10/09 ☐ CSS 8/4/08 ☐ Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	 5/1/09; 12/18/06; 7/10/06 5/1/09
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Multiple RPMs handled this NDA and a filing review cannot be located.
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant in on the AIP	☐ Yes X No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes X No ☐ Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	X Included
❖ 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 *(include certification)*	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☐ None. See PMR Templates & Approval Letter
• Outgoing communications *(if located elsewhere in package, state where located)*	Included, 8/18/09
• Incoming submissions/communications	Included, 8/18/09

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

❖ Postmarketing Commitment (PMC) Studies	☐ None. See PMR Templates & Approval Letter
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	Included, 8/19/09
• Incoming submission documenting commitment	Included, 8/19/09
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	☐ Not applicable 2/25/09
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☐ Not applicable 8/5/09
• Regulatory Briefing *(indicate date)*	X No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☐ No mtg NDA-resubmission 10/13/07
• EOP2 meeting *(indicate date)*	☐ No mtg Meeting to discuss development plan 2/18/05
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	1/7/09 and 1/8/09
• 48-hour alert or minutes, if available	Minutes available
Decisional and Summary Memos - Please see past action packages for previous cycles	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 8/21/09
Division Director Summary Review *(indicate date for each review)*	☐ None 7/27/09
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 7/21/09
Clinical Information[5] - Please see past action packages for previous cycles	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	7/21/09
• Clinical review(s) *(indicate date for each review)*	5/5/95 & 4/18/95
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	X None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	3/17/09; 7/9/08; 12/28/07
❖ 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	8/7/09
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☐ Not needed 8/4/08; 3/19/07
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)*	☐ None 7/16/09; 7/29/08 8/20/09 7/29/09

[5] Filing reviews should be filed with the discipline reviews.

• REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
Clinical Microbiology ☐ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Microbiology Review(s) *(indicate date for each review)*	X None
Biostatistics ☐ None. Please see past action packages for previous cycles	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 3/7/95
Clinical Pharmacology ☐ None. Please see past action packages for previous cycles	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	X None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 7/30/08; 9/15/05
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	X None
Nonclinical ☐ None. Please see past action packages for previous cycles	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None 7/21/09
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/22/08
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested
CMC/Quality ☐ None. Please see past action packages for previous cycles	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 8/5/08
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	X None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 6/5/09; 8/5/08
• BLAs only: Facility information review(s) *(indicate dates)*	X None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	X Not needed

❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	X None
❖ Environmental Assessment (check one) (original and supplemental applications)	
X Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	8/5/08
X Review & FONSI *(indicate date of review)*	8/23/02
X Review & Environmental Impact Statement *(indicate date of each review)*	8/5/08 8/23/02
❖ ☐ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested X Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 5/20/09 X Acceptable ☐ Withhold recommendation
• BLAs: o TBP-EER	Date completed: ☐ Acceptable ☐ Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Requested ☐ Accepted ☐ Hold

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 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG

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-in as Memo, because DARRTS will not allow me to check in as AP Checklist at this time. May be a flaw with new DARRTS 3.0 Roll out.

Kim, Tamy

From: Jenny Swalec [jswa@lundbeck.com]
Sent: Tuesday, August 18, 2009 8:11 PM
To: Kim, Tamy
Subject: RE: FDA Comments: CPS PMRs
Attachments: 081809 CPS PMRs.doc

Hi Tamy,

Rather than include in a formal amendment, I hope it is ok to email you our revised dates as per your below request. We accepted all your proposed text changes to the PMRs and the attached includes our revised dates (in track changes).

Thanks! Jenny

From: Kim, Tamy [mailto:Tamy.Kim@fda.hhs.gov]
Sent: Tuesday, August 18, 2009 11:57 AM
To: Jenny Swalec
Subject: FDA Comments: Sabril IFU, REMS and CPS PMRs

Hi Jenny,

We have the following comments on your REMS, IFU and CPS PMRs.

IFU

struction #19, in the second sentence, "syringes(s)" should be changed to "syringes." As currently stated, it may be confusing to readers with lower levels of literacy.

Please attach the IFU to the agreed upon Medication Guide.

REMS: Please note the following:

1. the re-insertion of the Communication Plan into the REMS;
2. the time parameters put into the Communication Plan; and
3. the removal of the reference to dispensing only a 30-day supply.

These changes should also be incorporated into the REMS Supporting Document. Please see attached REMS track-changes.

Please incorporate the above changes and submit the REMS (including the MedGuide and IFU) in its entirety to the NDAs as soon as possible.

<<Sabril REMS ToSponsor.8.18.09.doc>>

CPS PMRs:
Please see attached document. Please note, that we may have additional comments on your IS PMR/PMCs and will get in touch with you shortly about these.

<<CPS PMRs.8.18.09.doc>>

Thanks
y

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

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 20427	ORIG 1	OVATION PHARMACEUTICALS INC	SABRIL (VIGABATRIN) TABLET 500MG

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/s/

TAMY E KIM
08/27/2009

Kim, Tamy

Subject: RE: Exclusivity Summary Form Question

Hi Colleen and Dr. Temple,

Please see email below. The Exclusivities for NDA 20-427 and NDA 22-006 will depend on Mary Ann's answer below, so the Exclusivity summary is still in draft.

Thanks,
Tamy

From: Nighswander, Robbin M
Sent: Friday, August 07, 2009 11:28 AM
To: Holovac, Mary Ann
Cc: Kim, Tamy
Subject: Exclusivity Summary Form Question

Mary Ann

Writing to ask a question... that I should know the answer to but don't recall.

We are about ready to approve 2 NME applications on the same day for the same molecular entity (1 a tablet and 1 an oral solution).

At the instant of approval of the first, the 2nd now becomes a type 3 chemical entity rather than a type 1 which affects how we fill out the summary.

Do we fill out one as the NME and the other as the type 3? Does it matter which one we pick?

Also, does the fact that one of these also will enjoy Orphan exclusivity have any bearing on which one we pick?

Thanks

Robbin Nighswander, MS
Supervisory Regulatory Health Project Manager
Division of Neurology Products
(301) 796-1126
WO 22, Rm 4346

Sabril PMR/PMC Development Template: Effect of Taurine

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:	01/2010
	Study/Clinical trial Completion Date:	06/2011
	Final Report Submission Date:	11/2011
	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 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG

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/s/

SALLY U YASUDA
08/19/2009

Sabril NDA 20427 PMR/PMC Development Template

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

PMR Title: ***Using a Registry to Characterize Visual Loss in Adults***
PMR/PMC Schedule Milestones:

Final Protocol Submission:	by 8/2009
Study Completion Date:	by 7/2016
Final Report Submission:	by 9/2016

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 of the time required to collect long-term data, in the setting of a potentially useful drug for refractory CPS for which we have identified the risk and highlighted it in labeling and through the REMS that includes a registry. The registry will be used to collect this information.

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**

Sabril is known to cause irreversible damage to visual fields and may cause loss of visual acuity. Although studies have been performed questions still remain as to the dose-response relationship, the timing and risk of the visual changes, the rate of progression and potential for progression of the deficit following drug discontinuation.

   - **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

SABRIL causes irreversible bilateral concentric constriction of the visual field in 30 percent or more of patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation and can result in disability. In rare cases, SABRIL also can damage the central retina and may

decrease visual acuity.

Based on the data available, the onset of vision loss from SABRIL is unpredictable, and can occur within weeks of starting treatment or sooner, or at any time during treatment, even after months or years, although the risk of vision loss may increase with increasing duration of exposure. The risk of vision loss may increase with increasing dose and cumulative exposure, but there is no dose known to be free of risk of vision loss. It is possible that vision loss can worsen despite discontinuation of SABRIL.

- **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)?

A study analyzing data from the Registry provided for in the REMS to evaluate the development of visual lesions, timing and risk of the development of concentric field loss, the risk of visual acuity deficits, the potential for progression of the lesions if therapy is continued and the potential for progression once therapy has been discontinued.

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.

PMR Title: **In vitro induction potential of Sabril**

PMR/PMC Schedule Milestones:

Final Protocol Submission:	by 9/2009
Study Completion Date:	by 4/2010
Final Report Submission:	by 5/2010

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, although Sabril is associated with vision loss, there is an unmet need for Sabril for the treatment of refractory seizures. If there is a potential for drug interaction with other drugs that are metabolized with CYP1A2 and CYP3A4, then the benefit-risk ratio may change for the use of Sabril in these conditions.

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**

The characterization of potential drug interaction was incomplete in the NDA submission.

- **If the PMR is a FDAAA safety study/clinical trial, describe the risk**

The risk lies in the unknown potential for Sabril to induce CYP1A2 and CYP3A4, potentially resulting in loss of effect of other drugs

- **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**

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

An in vitro study to evaluate the ability of Sabril (vigabatrin) to induce CYP1A2 and CYP3A4 using methods described in the FDA Guidance for Industry: Drug interaction studies:-Study Design, Data Analysis and Implications for Dosing and Labeling.

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)

In vitro study to assess the drug interaction potential and conduct in vivo studies if necessary.

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 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG
NDA 20427	ORIG 1		SABRIL (VIGABATRIN) TABLET 500MG

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/s/

SALLY U YASUDA
08/19/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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

NDA 20-427

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 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sabril (vigabatrin) tablet 500 mg.

We also refer to your submissions dated December 23, 2005, October 10, 2006, and March 1, 2007.

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:

Drug Substance

1. Please provide a representative certificate of analysis (COA) for the [redacted] (translated into English), which includes the current specifications.

b(4)

Drug Product

[redacted]

NDA 20-427
CMC IR 1

b(4)

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 03:09:44 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

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) tablets.

We consider this a complete, class 2 response to our action letter. 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 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 note that you have not fulfilled the requirement. We are deferring submission of your pediatric studies until February 25, 2013. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of section 2 of the Pediatric Research Equity Act (PREA) within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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 any question, 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
2/26/2008 05:15:44 PM

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
[redacted]	[redacted] b(4)
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 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 readers 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 provide 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 raise questions. For all such 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
10/13/2007 09:56:09 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

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 2, 2007, of your March 1, 2007, submission to your new drug application (NDA) for Sabril (vigabatrin) tablets.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiency needs to be addressed:

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 Pharmacolgy

   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.

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
4/3/2007 08:16:56 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

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 October 11, 2006 of your October 10, 2006 submission to your new drug application (NDA) for Sabril (vigabatrin) tablets.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiency still needs to be addressed:

- 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.

Additionally, we have the following requests:

- Please submit the coding dictionary listing the adverse event verbatim terms and the MedDRA preferred terms for all adverse events included in the integrated safety data presentation.

- Please submit case report forms (CRFs) for all subjects experiencing a serious adverse event.

- Please submit a recommendation on scheduling under the Controlled Substances Act (CSA) and the basis for the recommendations.

- [redacted] b(4)

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 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. The sponsor needs to 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.

If you have any questions call me, Regulatory Project Manager, 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
11/9/2006 03:35:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

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) tablets.

We also refer to your January 12, 2006 response to our July 11, 2005 letter, in which you provided a list of your clinical trials, identifying those which you believe should be included in the "possibly suicide-related" adverse events analysis for your product.

We have reviewed your list and have the following specific comments:

- We agree with your selection of studies

We ask that you use this list to identify and further evaluate, as described in our previous letters, "possibly suicide-related" adverse events occurring in these trials, and respond to us within 6 months.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

Russell Katz
5/3/2006 07:42:50 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

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 December 27, 2005 of your December 23, 2005 submission to your new drug application (NDA) for Sabril (vigabatrin) tablets.

We do not consider this a complete response to our action letter. Therefore, the review clock will not start until we receive a complete response. The following deficiencies still need to be addressed:

1. Please submit the following death narratives:

0098/11920014 Cause of death: seizure
0098/12040015 Cause of death: pneumonia, respiratory arrest
0098/12110008 Cause of death: grand mal seizure, sudden death
0098/12300010 Cause of death: pneumonia, pulmonary carcinoma, multiple organ failure
0098/12340002 Cause of death: myocardial infarction
0098/12370012 Cause of death: carcinoma
0098/13030106 Cause of death: myocardial infarction
0098/13040002 Cause of death: myocardial infarction
0098/13040004 Cause of death: seizure

2. Please submit compete narratives for SAEs from the following studies:
0223
0101
4020
4103
R0003
4021

3. Please submit narratives for all withdrawals due to AEs from the safety update population studies.

4. In addition, the requested Integrated Analysis of Safety includes only updated overall AE risks and should include updates for deaths, SAEs, and withdrawals for AEs.

5. Please submit a complete analysis of vigabatrin's effect on the QT interval.

6. Please provide the raw data on individual tablets for the dissolution comparison data for the site change.

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

Sincerely,

{See appended electronic signature page}

Courtney Calder, Pharm.D.
Project Manager
Division of Neurology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Courtney Calder
2/15/2006 11:20:26 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

Ovation Pharmaceuticals, Inc.
Attention: Jeanine 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) Tablets.

We also refer to your September 27, 2005 response to our July 11, 2005 letter, in which you provided a list of your clinical trials, identifying those which you believe should be included in the possibly suicide-related adverse events analysis for your product.

We have reviewed your list and have the following specific comments:

1. Trials should only be included if they are placebo or "low dose-placebo" controlled. For the following studies, it is not clear from the brief description provided that this is the case:
    a. 097-335 (active control)
    b. 71754/3/W/007 (active control)
    c. 71754-3-W-012 (active control)

2. Please clarify the reasons the following trials were excluded (Please note the clarification that it was our intention to include studies with 30 or more total patients or normal volunteers, including both control and active treatment arms):
    a. 097-230, N=50 total, DBPC
    b. 097-246, N=42 total, DBPC
    c. 097-247, N=31 total, DBPC
    d. 097-253, N=42 total, DBPC
    e. 097-258, N=49 total, DBPC
    f. 097-263, N=56 total, DBPC
    g. 097-444, N=39 total, DBPC
    h. BRD S/4, N=48 total, DBPC

    Please submit a further explanation of why you think these studies do or do not meet the criteria outlined for selection.

3. Although not previously addressed in our requests, you can exclude studies that ***only*** enrolled pediatric patients 5 years of age or younger.

In your September 25, 2005 submission, you also ask the following question:

> "Will the NDA resubmission be considered incomplete if this analysis is not submitted with it?
>
> Response: The NDA resubmission will not be considered incomplete if this analysis is not submitted with it, but we expect that you will respond to this letter in a timely manner and ask that you submit this information within 6 months of agreement on the appropriate list of included studies. Ovation, having acquired the regulatory, distribution, and US marketing rights for vigabatrin, would ordinarily be responsible for providing this information even though studies occurred before the acquisition.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

{See appended electronic signature page}

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

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/s/

John Feeney
12/28/2005 10:55:18 AM
Signed for Dr.Katz

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

Ovation Pharmaceuticals, Inc.
Attention: Jeanine 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) Tablets.

We additionally refer to an Agency letter dated March 16, 2005, requesting you to evaluate "possibly suicide related" adverse events occurring in placebo-controlled trials for vigabatrin.

In response to our March 16, 2005 letter, we have received a number of questions about which studies were suitable for inclusion in the proposed analyses. Other questions have been about the data collection, classification, and presentation. Because many sponsors had similar questions, we are providing the following general clarifications of our requests. In some instances, we have modified our previous requests.

Trials

1. In our March 16, 2005 letter, we asked that only parallel-arm studies be included. We have reconsidered this request and now ask that crossover studies be included if they otherwise meet the stated requirements. Only the first period data from crossover studies (including within 1 day of stopping the first period of randomized treatment) should be included.

2. Also in our March 16, 2005 letter, we asked that short-term studies up to six months duration be included. We also have reconsidered this request and now ask that studies be included without an upper limit on duration.

3. Ongoing studies that are still blinded should not be included.

4. We reiterate that we want you to identify all trials that meet the described criteria (now modified) regardless of indication or approval status for any particular indication.

5. Our previous letter indicated that only trials with 30 "patients" should be included. We are now asking that volunteer studies be included as well, if they otherwise meet the criteria.

6. Studies using novel formulations, such as extended-release formulations, of approved anti-epileptic drugs (AEDs) [even if the novel formulation is not approved] should be included.

7. In order to comment on the list of studies included for purposes of these analyses, we ask that you submit a complete list of all clinical trials, indicating those that you believe should be included and excluded.

8. We request that, when you submit your completed dataset, you also submit two tables which will describe the features of the clinical trials. See the enclosed attachment for examples from other similar data requests. Note that for this request, the 4 variables, Extensive Diagnostic Screening, Exclude Treatment Resistant, Exclude Bipolar Disorder, and Exclude Family History of Bipolar are applicable to trials in psychiatric indications.

Miscellaneous

1. The policy of our electronic document room is that any electronic data files that are submitted to an NDA must be submitted as a SAS transport file. Therefore, please submit the data in this format.

1. Please do not submit narratives when you submit your completed SAS transport file. You should instead have the narratives ready to submit if specifically requested. We may ask to audit some subset of your narratives. Any narratives submitted should be in their blinded format.

2. We are revising the search strategy for "Possibly Suicide-Related" Adverse Events to simplify it. The following description replaces the strategy described in our original March 16, 2005 letter.

   Please search preferred terms, verbatim terms, and comment fields for the following text strings:

   - "suic", "overdos," "accident-", "injur-", "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "poison", "asphyxiation", "suffocation", "firearm", "burn", "drown", "gun", "immolate", "monoxide" should be included.

   Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string "cut" might identify the word "acute"). These terms might be characterized as "false positives" in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

Study #	Patient #	Treatment Assignment	Term in Which Text String Occurred

The patients in this table will have as many rows as they have potential events.

[Some sponsors have specifically asked if all adverse events coded as "accidental injury" should be included. The answer is yes.]

3. Narratives should be prepared for all events identified by the search described in Item 3 above, and for all deaths and serious adverse events (SAEs), even for those that do not otherwise meet the above search criteria for possibly suicide-related AEs.

   This latter requirement would apply, for example, to SAEs coded as seizures. For example, a patient might, as a suicide attempt, take an overdose of some drug that causes a seizure. The event might thus be classified as a seizure, when in fact it also represents a suicide attempt. Narratives should be prepared for ALL deaths and SAEs identified in a given trial.

4. Generally, events that are preexisting at baseline are not usually counted as treatment emergent if they recur during the course of a trial. However, in the requested analysis, suicidality-related events that occur during the course of the double-blind phase or within 1 day of beginning taper, switching or stopping treatment should be counted, even if they occur in a patient who had the condition at baseline.

5. In the March 16, 2005 letter, we stated that we would be available to review and comment on your specific plan for blinding and classifying the narratives. On further consideration, we believe there is adequate information available about the requested method. Therefore, we do not expect you to clear your plan through the Division; we expect that you will follow the standard outlines available. If, for any reason, you deviate from the established plan, the Division must review that proposal.

6. If previously prepared narratives do not include all of the identified elements from our request, the narratives should be rewritten to include this information. If some elements are not available, please note their absence in the narrative.

7. We have added a new code for the EVENT variable to denote completed suicides (the new "code 1") and would like to clarify that corresponding changes should be made to the code numbers presented under the section entitled Classification of "Possibly Suicide-Related" Adverse Events in our last letter. Note the new addition of subcategories 6a and 6b. The categories should now be numbered as follows:

   Completed suicide (code 1)
   Suicide attempt (code 2)
   Preparatory acts toward imminent suicidal behavior (code 3)
   Self-injurious behavior, intent unknown (code 4)
   Suicidal ideation (code 5)
   Not enough information (code 6)
   - Fatal (code 6a)
   - Non-fatal (code 6b)

Self-injurious behavior, no suicidal intent (code 7)
Other: accident; psychiatric; medical (code 8)

The description of the variable "EVENT" in the table should now read:

This variable contains the code for the first suicidality event. If a patient had more than one event in the desired "exposure window", then the most severe event should be listed. Severity is decided based on the following order of codes: 1>2>3>5>4>6. Every patient in every trial will be classified on this variable. For the majority of patients who are not identified as having a "possibly suicide-related adverse event", the classification will be 0 (no event). Similarly, those patients who have "possibly suicide-related adverse events" that are coded as 7 or 8 will also be classified for this variable as 0 (no event), because we will not be using codes 7 or 8 in our analyses. Patients with event codes 1 through 6 for suicide-related adverse events will be classified with their most severe event code.

8. In the proposed analysis, the final denominator is intended to be all patients studied. Therefore, the expectation is that the majority of patients will be coded as "no event." "No event" means that there was no suicide-related adverse event or, if there was, it was coded to 7 or 8.

9. The available materials on the classification system make it clear what training is necessary for individuals who will perform the classification. No further expertise is being required by the Division at this time. There is no expectation that external experts must be used as long as the individuals involved have undergone the appropriate training. A minimum of 4 "experts" in classification will be needed. Three will serve as primary raters and the fourth will function as a facilitator, if needed.

10. In the variable table for the SAS transport file, some sponsors have asked how to code the "LOCATION" variable when the trial was conducted in both North American and Non-North American sites. This variable should be coded to reflect the study site location where the individual patient was treated.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

For each trial included in the analysis, please provide a summary of important study characteristics in tabular form as shown in Tables 1 and 2 below. Many of the column headings are self-explanatory. However, the following headings merit clarification:

- **Number of Patients**: number of patients randomized to the drug and placebo treatment groups.
- **DB TX Duration**: the nominal duration of the analyzed double-blind treatment phase.
- **Protocol Dose**: the protocol-specified daily target dose expressed as a range for flexible dose studies and as individual doses for fixed dose trials.
- **Extensive DX Screening**: indicate yes if the study required confirmation of the diagnostic entry criteria by two or more independent raters. Otherwise, indicate no.
- **Exclude TX Resistant**: indicate yes if a study exclusion criterion was a history of treatment resistance or poor response of the index illness to previous treatment. Otherwise, indicate no.
- **Exclude Bipolar D/O**: indicate yes if a study exclusion criterion was a history or presence of bipolar disorder or mania in the patient. Otherwise, indicate no.
- **Exclude Family H/O Bipolar Disorder**: indicate yes if a study exclusion criterion was any family history of bipolar disorder or mania. Otherwise, indicate no.

TABLE 1: BASIC STUDY DESIGN

Drug	Study	Indication	Age Range (years)	Number of Patients		DB TX Duration (weeks)	Protocol Dose (mg/day)
				Drug	Placebo		
XYZ	123	Epilepsy	18 to 60	120	119	6	120 to 160
	456	Migraine	55 to 85	148	148	8	120, 140, 160
	789	Bipolar	18 to 65	119	110	12	120, 140
	1111	Epilepsy	18 to 70	71	69	13	120 to 160

TABLE 2: SCREENING AND KEY EXCLUSIONARY CRITERIA									
Drug	**Study**	**Indication**	**Extensive DXScreen**	**Placebo Lead-In**	**Exclude TX Resistant**	**Excl. Current Suicide Risk**	**Excl. H/O Suicide Attempt**	**Excl. Bipolar D/O**	**Excl. Family H/O Bipolar Disorder**
XYZ	123	Epilepsy	No	Yes	No	Yes	No	Yes	No
	456	Migraine	Yes	Yes	No	No	No	Yes	Yes
	789	Bipolar	Yes	Yes	Yes	Yes	No	Yes	Yes
	1111	Epilepsy	No	No	No	Yes	No	Yes	Yes

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/s/

John Feeney
7/11/05 12:30:23 PM
signed for Russell Katz, M.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-427

Ovation Pharmaceuticals, Inc.
Attention: Jeanine 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) Tablets.

There is evidence that patients with epilepsy are at an elevated risk for suicidality (suicidal thinking and behavior) and completed suicide. Despite this elevated population risk, the concern has been raised that some anti-epileptic drugs (AEDs) may be associated with an increased risk of suicidality. Given the recent observation of suicidality as a drug-induced adverse effect in pediatric patients exposed to various antidepressants in placebo-controlled trials, there is interest in examining data from placebo-controlled trials of AEDs to assess for a similar effect. Based on our experience with the pediatric antidepressant trials, the Division of Neuropharmacological Drug Products (DNDP) has developed a standard approach for evaluating drug-induced suicidality. Thus, we ask that you utilize the approach we have outlined in this letter for **evaluating "possibly suicide related" adverse events occurring in** placebo-controlled trials for vigabatrin.

We request that you identify the trials from your development program (regardless of whether the indication is approved or not) that meet the following criteria: placebo-controlled; parallel arm; short-term (up to six months); at least 30 patients total. Some trials in epilepsy may have utilized a subtherapeutic dose of a standard AED as a comparator arm. Those trials should be included (if they meet the other criteria described above) and the subtherapeutic comparator arm **should be coded as a "low dose-placebo" (see variable list below).**

Once we have agreed upon the list of trials upon which to focus this exploration, we ask that you utilize the following approach to identifying **and further evaluating "possibly suicide related"** adverse events occurring in these trials.

Search for "Possibly Suicide-Related" Adverse Events and Preparation of Narrative Summaries

Time Frame for "Possibly Suicide-Related" Adverse Events

This search should be strictly limited to adverse events that occurred during the double-blind phase of treatment, or within 1 day of stopping randomized treatment. Adverse events should not be included if they occurred prior to randomization or more than 1 day after discontinuing from randomized treatment. The end of trials with a tapering period should be set to be at the beginning of the tapering period. Events occurring more than 1 day after discontinuing from randomized treatment should be excluded even if discontinuation occurred before the nominal endpoint of the trial. For example, if a patient either discontinued of his own volition or was asked to discontinue by the investigator after 2 weeks of randomized treatment in a trial of 8 weeks duration, and the patient then experienced a "possibly suicide related" adverse event 2 days after stopping, that event should not be included.

Search Strategies for "Possibly Suicide-Related" Adverse Events

The following search strategies should be employed to identity adverse events of possible interest:

- Any events coded to preferred terms that include the text strings "suic" or "overdos," including all events coded as "accidental overdose" should be included.

- Regardless of the preferred term to which the verbatim term is mapped, all verbatim terms should be searched for the following text strings: "attempt", "cut", "gas", "hang", "hung", "jump", "mutilat-", "overdos-", "self damag-", "self harm", "self inflict", "self injur-", "shoot", "slash", "suic-", "poison", "asphyxiation", "suffocation", "firearm" should be included.

  Note: Any terms identified by this search because the text string was a substring of an unrelated word should be excluded (for example, the text string "cut" might identify the word "acute"). These terms might be characterized as "false positives" in the sense that the verbatim term was selected because one of the text strings occurred within that term but the term had no relevance to suicidality. Although we request that such terms be excluded, we ask that you prepare a table listing all such false positives, as follows:

Study #	Patient #	Treatment Assignment	Term in Which Text String Occurred

  The patients in this table will have as many rows as they have potential events.

- All deaths and other serious adverse events (SAEs) should be included.

- All adverse events coded as "accidental injury" should be included.

Preparation of Narrative Summaries for "Possibly Suicide-Related" Adverse Events

A complete set of narrative summaries should be prepared and collected for **all "possibly suicide-related" adverse events.** In some cases, narratives will have already been prepared, e.g., deaths and SAEs. In other cases, however, you will need to prepare narrative summaries by searching CRFs for any information that might be considered possibly relevant to suicidality. You should also utilize other relevant sources of information, e.g., hospital records, results of consults, questionnaire responses, etc, in preparing these narrative summaries. Depending on how much information is available, narrative summaries may be longer than 1 page, however, in no case, should more than 1 narrative summary be included on a single page. Following is the type of information that should be included in the original narrative summaries:

- Patient ID number
- Trial number
- Treatment group
- Dose at time of event (mg)
- **Recent dose change – elaborate on timing and amount of dose change**
- Sex
- Age
- Diagnosis
- History of suicidal thoughts
- History of suicide attempt
- History of self harm
- Adverse event Preferred term
- Adverse event Verbatim term
- Serious adverse event (y/n)
- Number of days on drug at time of event
- Treatment was discontinued following event (y/n)
- Patient had an emergency department visit and was discharged (y/n)
- Patient was hospitalized (y/n)
- **Patient died (y/n) – if yes,** elaborate on cause of death
- Associated treatment emergent adverse events
- Concurrent psychosocial stressors
- Psychiatric comorbidities
- Concomitant medications
    - Other pertinent information (e.g., family history of psychiatric disorders)-

Other relevant information for preparing narrative summaries:

-Patients may be identified as having events of interest in one or more of the above searches, and they may have more than one event of interest. In no case, however, should there be more than one narrative summary per patient. In cases where there is more than one event for a given patient, each different event should be clearly demarcated in the narrative.

-Only events occurring during the "exposure window" defined as during the double-blind phase (including the first day after abrupt discontinuation or the first day of taper, if tapering is utilized) should be included in the narrative summary, i.e., do not include any

prerandomization events or events occurring more than 1 day after stopping randomized treatment or during the tapering period.
-Do not exclude events of interest on the basis of your judgment that they might not represent "treatment-emergent" events; we feel this judgment is too difficult to make and we prefer to simply include all potentially relevant events, regardless of whether or not similar thoughts or behaviors may have occurred prior to treatment.

Classification of "Possibly Suicide-Related" Adverse Events

Once the narrative summaries for "possibly suicide-related" adverse events are prepared and collected, we ask that you accomplish a rational classification of these events using the approach that was well-characterized by the Columbia group for the pediatric suicidality narratives. This approach was described in detail by Dr. Kelly Posner at the September 13 and 14, 2004 advisory committee meeting. The details are provided in her slides for that meeting (available on FDA's website), in the transcript for that meeting, and in other reviews, etc. pertinent to pediatric suicidality and available on FDA's website at the following URLs:

- Slides
  http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4065S1_06_FDA-Posner.ppt
- Briefing Document, transcripts, etc.
  http://www.fda.gov/ohrms/dockets/ac/cder04.html#PsychopharmacologicDrugs

The categories of interest from FDA's standpoint are as follows:

Suicide attempt (code 1)
Preparatory acts toward imminent suicidal behavior (code 2)
Self-injurious behavior, intent unknown (code 3)
Suicidal ideation (code 4)
Not enough information (code 5)
Self-injurious behavior, no suicidal intent (code 6)
Other: accident; psychiatric; medical (code 7)

Those individuals who classify the narratives must have the appropriate expertise and training to accomplish this task.

Prior to their rational classification, the narratives must be blinded to details that might bias their assessments. The details of appropriate blinding of the narratives can also be obtained in the transcript from the advisory committee meeting referred to above, and the materials available on FDA's website pertinent to that meeting. We request that you block out the following information that could reveal treatment assignment:

- Identifying patient information, identity of study drug, and patient's randomized drug assignment
- All identifying information regarding the sponsor, the clinical trial number, and the location of the trial
- All years with the exception of years in remote history
- Study drug start and stop dates (month, day, and year)

- All medications, both prescription and non-prescription, whether taken before, during, or after the study; non-pharmaceutical substances (e.g., alcohol, tobacco) should not be blocked out
- Names of medications involved in overdoses; the number of pills consumed should not be blocked out
- Indications for medications started during or after the study
- Indications for study drug

Once you have decided on an approach to accomplishing the task of blinding and classifying the narratives, we would be happy to review and comment on your plan.

Data Submission to DNDP

In order to perform additional analyses investigating the relationship between exposure to AEDs and "suicide-related" adverse events in adults and the pediatric population, we would appreciate your submitting the following variables as outlined in the next table. Note that we are requesting information from placebo (and "low dose-placebo") controlled trials only. We would expect that you will provide us with a completed JMP dataset at the time of your NDA resubmission.

Variable name	Type	Description	Coding notes
SOURCE	Character	First few letters of your drug name	
INDICATION	Character	Disease being studied in trial	E.g., epilepsy- adjunctive, epilepsy- monotherapy, bipolar disorder, migraine, etc.
TRIAL	Character	Trial ID	
CTPID	Character	Patient ID within each trial	
UNIQUEID	Character	A unique ID for every patient	Composed of "TRIAL" and "CTPID" joined in that order with no intervening punctuation or dashes
AGE	Numeric	Patient age	In years
AGECAT	Numeric	Age category	1=5-11 2=12-17 3=18-24 y 4=25-64 y 5=65 y or more
GENDER	Numeric	Patient gender	1=female 2=male
RACE	Numeric	Patient race	1=White Caucasian 2=African-American 3=Hispanic 4=Asian 5=Other . = Missing

Variable name	Type	Description	Coding notes
SETTING	Numeric	Setting of trial	1=inpatient 2=outpatient 3=both
LOCATION	Numeric	Location of trial	1=North America 2=Non-North America
TXARM	Numeric	Randomized treatment	1=drug 2=placebo 3=active control 4=low dose-placebo No missing values are allowed in this variable.
TXLOW	Character	Name of drug used as low dose-placebo	Leave patients in other treatment arms blank
TXACTIVE	Character	Name of drug used as active control	Leave patients in other treatment arms blank
EVENT	Numeric	This variable contains the code for the first suicidality event. If a patient had more than one event in the desired **"exposure window", then the** most severe event should be listed. Severity is decided based on the following order of codes 1>2>4>3>5	0=no event 1=suicide attempt 2=preparatory acts toward imminent suicidal behavior 3=self-injurious behavior, intent unknown 4=suicidal ideation 5=not enough information No missing values are allowed in this variable.
EVENTDAY	Numeric	The number of days to the first suicidal event counting from the day of the first dose.	for patients without events, this variable should contain days until end of trial or until premature discontinuation for patients with more than one event, this variable should contain days until the most severe event that is listed under the variable **"EVENT"** No missing values are allowed in this variable.
DISCONT	Numeric	The patient discontinued before the end of the controlled portion of the trial	0=No 1=Yes No missing values are allowed in this variable

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Russell Katz
3/16/05 07:49:35 AM

MEMORANDUM OF MEETING MINUTES

Meeting Date: December 1, 2004
Application: NDA 20-427/Vigabatrin
Indication: Epilepsy (refractory complex seizures in adults; infantile spasms)
Type of Meeting: Clinical Development Plan
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Melina Griffis, R.Ph.

FDA Attendees:

Russell Katz, M.D., Division Director
Philip Sheridan, M.D., Medical Officer
Ed Fisher, Ph.D., Pharm/tox
Sally Yasuda, Ph.D., Biopharm
Kofi Kumi, Ph.D., Biopharm
Melina Griffis, R.Ph., Project Manager
John Feeney, M.D., Team Leader
Kun Jin, Ph.D., Biometrics
Lois Freed, Ph.D., Pharm/tox
Barry Rosloff, Ph.D., Pharm/tox
Martha Heimann, Ph.D., CMC

Ovation Attendees:

Dick Bittman, Ph.D.
Stephen Collins, M.D., Ph.D.
Tim Cunniff, Pharm.D.
Mike Rice, Ph.D.
Katherine Tracy, M.D., Ph.D.
Holli Carlson
Cyndy Collis
Ben Quintana, Ph.D.
Jeanine Swalec
Carol Westall, Ph.D.

Below is a summary of the meeting discussion:

CMC

Drug Substance

[redacted]

b(4)

. The firm was referred to *"Guidance for Industry: Drug Substance Chemistry, Manufacturing, and Controls Information"* for additional information. Submission of long term stability data for the commercial batches manufactured listed on page 13 of the briefing package is requested.

Drug Product (Tablets)

The firm was advised that the proposed product, which has a different film coat formulation and will be manufactured at a different site than submitted in the original NDA, should be linked to the formulation used for clinical studies.

The normal three batch stability requirement, with at least two batches manufactured at pilot scale, will apply to tablet batches manufactured at the Patheon, Toronto site. Stability data for the product manufactured at the Patheon site in France may be submitted as supporting stability

data. The Agency would not refuse to file an application if a minimum amount of stability data (3 to 6 months) is provided for the Toronto site.

Drug Product (Sachets)
The sachets will be reviewed as a new formulation under a separate NDA. The stability requirements are the same as for the tablets.

Biopharm

1) The plan for submission of Pharmacokinetic/Biopharmaceutics information for the new NDA is acceptable. It is requested that the sponsor submits in advance of submission of the NDA the list of Clinical Pharmacology and Biopharmaceutics studies in the original NDA they plan to cross reference for the new NDA.

2) The sponsor should include executive summaries of the pivotal pharmacokinetic/ biopharmaceutics studies in the new NDA. And, to expedite the review of the application, the sponsor should be prepared to submit expeditiously the pharmacokinetics and biopharmaceutics study reports they plan to cross reference from NDA 20-427.

3) Regarding the change of site in the manufacturing of the drug product, the sponsor was informed that at a minimum dissolution comparison data from the two sites would be needed. The sponsor was referred to the SUPAC IR for requirements if there are site changes in the manufacturing of the drug product.

4) The sponsor was advised to provide scientific justification why they do not need to formally evaluate the effect of vigabatrin on concomitant medications and vice versa.

PreClinical

1) Juvenile animal toxicity studies will be required for the approval of vigabatrin use in a pediatric population. In addition to possible effects on the retina and possible general systemic effects, the possible effect on myelination in the developing brain is of specific concern.

Clinical

1) For the indication of adjunctive therapy for complex partial seizures in adults, the Division would consider approvability with very restrictive labeling. If a study or studies showed that vigabatrin worked in truly "refractory" patients, less restrictive labeling might result. The resubmission should contain a comprehensive update of safety.
2) Although the Division feels that there is enough data for the infantile spasms indication to file an application, the quality of the efficacy and safety data must be examined. The primary data/study reports must be submitted for a complete review. These include the Elterman study (final study report pending), data from the United Kingdom (Appleton), from France (Dulac and Chiron), from Italy (Vigevano) and from Germany (Brandl).

3) Regarding the visual field defects risks associated with the use of vigabatrin, the following areas should be addressed in the resubmission:

   a- Is there a reliable and sensitive test to identify the defect early in adults and children? Specifically how sensitive is the H stimulus or the ERG in children who are very young and/or developmentally delayed?
   b- What is the degree of the visual field defects in those patients who develop it and are they reversible once the drug is stopped?

In order to address these issues the Division recommended that the sponsor do a thorough follow up on children previously treated with vigabatrin in addition to those currently being treated who have had ERGs or VFs. This would allow for the identification of any possible long term sequela. Specifically, the technique of multifocal ERG (that can map out the retina) could be used for children 6 years of age or older who had participated in the Elterman study.

4) Once submitted, this NDA would be presented at an Advisory Committee (AC); therefore, the Division recommended that the sponsor provide the data prior to the official NDA submission in order to assist preparation for the AC meeting. A rolling submission would allow review of some reports as they are finished prior to the start of the 6 month review clock. Also, Ovation should submit their briefing document for the AC at the same time the NDA is submitted.

Minutes Preparer: _____
Melina Griffis R.Ph.

Chair Concurrence: _____
Russell Katz, M.D.

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/s/

Russell Katz
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MEMORANDUM OF TELECON

DATE: September 24, 1998
APPLICATION NUMBER: NDA 20-427/Sabril (vigabatrin) Tablets; Anticonvulsant
BETWEEN:

M. Lorie Stewart; Director, US Regulatory Affairs
Hoechst Marion Roussel (816) 966-5170

AND

Name: Paul Leber, M.D., Russell Katz, M.D., Greg Burkhart, M.D., Gerard Boehm, M.D., Armando Oliva, M.D., Melina Malandrucco, R.Ph.
Division of Neuropharmacological Drug Products, HFD-120

BACKGROUND: Due to evolving data on visual field defects (VFD) associated with the use of Sabril, the Agency notified HMR on August 27, 1998 that, with the data available to date, an affirmative conclusion regarding the safety of Sabril for use under the conditions suggested in its proposed labeling cannot be reached. In response to the teleconference of August 27, 1998 HMR submitted a proposal (see attachment) for FDA consideration which is the basis for this (September 24, 1998) teleconference.

After a brief internal discussion of HMR's proposal the team telephoned Ms. Stewart to relay the following:

1) It is not possible within the time frame of the review cycle and the absence of advisory committee input for the Division to accept the conditions of the proposal at this time. Since HMR does not have plans for withdrawal of the NDA and the review cycle is nearing completion, the Division, with the information at hand, cannot recommend approving Sabril for marketing in the US.

2) Prior to determining whether the conditions of the proposal may be feasible the following critical issues need to be addressed:

   a) Evidence needs to be presented that Sabril provides a benefit or advantage to patients over other AEDs.
   b) Sufficient background data on the risk of VFDs associated with Sabril, as well as the risk of VFDs associated with other AEDs, needs to be collected.

Melina Malandrucco, R.Ph.

Paul Leber, M.D.
(or Chair Concurrence)

cc: Original NDA 20-427
HFD-100/Temple
HFD-120/Div. File
HFD-120/Leber/Katz/Burkhart/Boehm/Oliva/Malandrucco

MEMORANDUM OF TELECON

Appears This Way
On Original

DATE: January 8, 1998; 9:00 pm

APPLICATION NUMBER: [redacted] Sabril (vigabatrin) 500 mg Tablets

BETWEEN:

Name: Larry Dollar, PharmD., Michael Fiola, Charles Gorodetzky, M.D., Randy Hinkle, Sue Ruckh, Lorie Stewart
Phone: (816) 966-5170
Representing: Hoechst Marion Roussel

AND

Name: Russell Katz, M.D., Greg Burkhart, M.D., Gerry Boehm, M.D. Melina Malandrucco, R.Ph., Jackie Ware, Pharm.D.
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: To discuss 9 questions posed by HMR in response to the Agency's AE letter dated November 26, 1997. There were several areas the firm required further clarification and/or input in order to respond completely to the deficiencies within the AE letter.

Prior to responding to the questions it was conveyed to HMR that the Division's primary concerns were with the neuropathologic findings related to Sabril. Specifically, a more detailed description of the data was requested. Reports on autopsy and/ or brain biopsy, the number (including the regions) of brains examined, and which patients had tests performed (MRI & EP) should all be included.

The following are the specific questions with the appropriate responses by the Division :

1) Studies 024 and 025 have been used in your proposed labeling for efficacy presentations whereas, with the exception of the Treatment Emergent AE table (page 17 of proposed labeling), studies 024, 025 and, in some cases 021 have been used for the safety presentations. Do you want 024 and 025 consistently used throughout the labeling as the controlled clinical trials, or to have us add study 021 to the specific sections as you have proposed as we fill in the data you requested?

In writing labeling for safety it was requested that the firm use data from all three studies (021, 024, and 025); for efficacy only data from studies 024 and 025 would be required.

2) Regarding the request for a separate safety database for pediatric patients (page 5 of approvable letter), the 120-day safety update (submitted 8/29/94) contained presentations of safety data for approximately 200 pediatric patients who had participated in pediatric trials or who had been enrolled in adult trials. Pediatric discontinuations and serious events were presented with all other discontinuations and serious events in the 120-day safety update. The safety update under preparation

contains an additional 25 pediatric patients who were enrolled in adult trials. As of the cutoff date for the safety update under preparation, the US and Canadian pediatric trials are considered ongoing. However, since the cutoff date, the Canadian pediatric MRI, VEP and ophthalmologic databases were closed and these data are included in the safety update because these are areas of special safety interest. A section on the use of vigabatrin in Infantile Spasms is also included.

> Is FDA requesting that we present all pediatric AEs again, adding the 25 new patients, and/or is FDA asking us to present pediatric discontinuations and serious events separately?

Within the NDA there was no systematic, complete assessment of the pediatric data base separate from the overall data base. There appears to be enough pediatric data to write labeling; therefore we requested that HMR conduct a comprehensive synthesis of the pediatric safety information to be incorporated into a pediatric safety section within labeling.

3) Under the Anemia subsection of Precautions (page 12 of proposed labeling), please [redacted] b(4)

It was requested that all cases of [redacted] treatment be described in detail. HMR agreed to describe all cases that meet the definition of anemia and cases in which patients had an anemia adverse event.

4) Under Safety Issues in the approvable letter (page 5), you have requested comprehensive analyses of urinalysis (UA) and coagulation data. For coagulation data, is FDA requesting PT and PTT? For UA, analysis of specific gravity and pH was done for studies 024 and 025 (120-day safety update); if additional analyses are being requested, our proposal would be a standard UA protein, glucose, WBC, RBC and casts, if sufficient numbers to prepare a meaningful analysis are available. Please advise.

If there are lab values (ie; PTT, UA) available then the Division would like to see them. We are looking for the full panel of available findings from the North American controlled trials.

5) Under Safety issues in the approvable letter (page 5), you have requested "comprehensive clinical descriptions of dyspnea, dependent edema, dysmenorrhea and UTI." Is FDA requesting a written narrative for each of the approximately 200 patients or is there a tabular format that would meet your needs? You have also requested that peripheral edema (including dependent and leg) be combined with generalized edema (page 18 of proposed labeling); did you want all of these cases included in the reanalysis (which will increase the number of descriptions requested) or only those specifically described as "dependent edema"?

As stated in the response to question 3 we are interested in a detailed synthesis of the events in a format that is clear. This does not necessarily mean a narrative for each case.

6) Regarding FDA's request for a case definition for peripheral neuropathy [redacted] many different case definitions can be proposed. Does the DA have a case definition that has worked well? b(4)

The Division does not at this point have a good case definition for peripheral neuropathy but we recommended that HMR create definitions by a clinical description and to subset these descriptions further into categories which only included those patients who had actual nerve conduction studies and/or biopsy. To follow an ordered hierarchy approach like this would be a reasonable approach.

7) Regarding the FDA's request for new analyses of cognitive/neuropsychiatric AEs [redacted], we are unclear as to what is being requested. Please clarify. b(4)

There are several terms used to describe cognitive/neuropsychiatric Aes which don't always convey clinically meaningful information to the prescriber. Therefore, we have proposed three broad categories in which to group these terms. In addition, we have requested that each cognitive/neuropsychiatric Ae be examined and described in clinically meaningful terms. HMR will need to retrieve data possibly from primary reports to get an insight as to what happened in each individual case.

8) Regarding the FDA's request for a statement about the risk of absence seizures and absence status and vigabatrin [redacted] we are unclear as to what is being requested. Please clarify. b(4)

There is evidence described in various literature sources that drugs which increase GABA may cause absence status, therefore, we are requesting that HMR describe these cases of confusion or cognitive impairment that were evaluated for absence status.

9) Regarding Phase IV investigations (page 7 of approvable letter), what types of studies/designs does the FDA have in mind?

It was recommended that all potential neurotoxic issues are examined and followed prospectively in a longitudinal study. A relatively substantial cohort could be followed forward in time and assessed periodically. Retrieval of information may be necessary.

Recorder: [signature] Melina Malandrucco, R.Ph

Chair Concurrence: [signature] 1/26/98 Russell Katz, M.D.

cc: Original NDA's 20-427
HFD-120/Div. File
HFD-120/Leber/Katz/Sherry/Burkhart/Boehm
/Malandrucco/Ware

TELECON

Div

facsimile
TRANSMITTAL

To: Lori Stewart
Sponsor: Hoechst Marion Roussel, Inc
Fax #:
Re: Pharm/Tox Comments to September 26, 1997 submission
Date:
Pages: 1 (including cover letter)

Dear Ms. Stewart,

The pharm/tox reviewer has the following comment in regards to the September 26, 1997 submission:

- The proposed study comparing adult and immature rats should address the question of whether GVG is capable of interfering with myelination in the developing brain (as opposed to decreasing myelin already deposited) and, if either of these effects occur, are they reversible.

Feel free to call me if you should have any questions.

Center for Drug Evaluation and Research
FDA

20-427
- ORIG NDA
HFD-120 Division files
GJ 10/21/97
10/21/97
10/21/97

From the desk of...
Melina Malandrucco, R.Ph.
Project Manager
Division of Neuropharmacological Drug Products /
HFD-120
Food and Drug Administration
Rockville, Maryland 20857

301-594-5526
Fax: 301-594-2859

NDA 20-427

Hoechst Marion Roussel, Inc.
Attention: Gregory A. Hileman, Ph.D.
Mail Station H4-M2110
P.O. Box 9627
Kansas City, Missouri 63134-0627

OCT 16 1996

Dear Dr. Hileman:

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

Reference is also made to your letter of September 12, 1996, requesting a waiver of the requirements for the submission of paper case report forms and/or case report tabulations in conjunction with the forthcoming Sabril® (vigabatrin) amendment containing a reconstructed safety database as requested in our not approvable letter dated April 29, 1995.

You have represented in your letter that the electronic case report forms and case report tabulations will be prepared in a manner that is substantially consistent with the FDA's proposed rules regarding electronic signatures and electronic records, proposed 21 CFR Part 11, 59 FR 45160 (August 31, 1994).

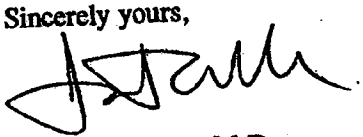
We have concluded that under 21 CFR 314.90(b)(2), your alternative electronic submission justifies a waiver of the "hard copy" requirements of 21 CFR 314.50(f). Consequently, your waiver request is granted.

Should future retrieval be deemed necessary, and as a condition of granting this waiver, you are required to maintain paper copies of the case report forms and tabulations as required under 21 CFR 312.57(b).

Finally, we ask that you contact the Center's Division of Information Systems Design (DISD) to ensure that the electronic CRF and CRT submissions are also consistent with the Center's electronic archiving policy.

If you have any further questions, please contact Jacqueline H.Ware, Pharm.D., Regulatory Management Officer at (301) 594-2777.

Sincerely yours,



Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc: Original NDA
HFD-120 Div. File
HFD-120/Leber/
HFD-120/Katz/McCormick/Ware
HFD-101/Temple
HFD-1/Woodcock/Axelrad
HFD-70

file: a:\sabril\sabcrfl1.wpc
draft: 9/19/96 (JW)
final: 10/3/96

WAIVER
(letter)

M E M O R A N D U M

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

DATE: 10 Apr 95

FROM: R. Young, HFD-344

SUBJECT: Information Alert: April 95 inspection of Marion Merrell Dow per January 31, 1995 Consultation Request for NDA 20-427 (vigabatrin)

TO: Cynthia McCormick, M.D., HFD-120

An EIR will follow, but I would like to give you a quick, informal report on the inspection.

We conducted an unannounced visit of Marion Merrell Dow on [redacted]. The field inspector was [redacted] of our [redacted] from HFD-344 also participated. b(4)

A. Company organization as it relates to the clinical development of the drug. This drug was discovered and brought into clinical trial by Merrell Richardson (Cincinnati). Merrell Richardson had overseas development centers in England and France. The overseas centers operated somewhat independently of Cincinnati. Merrell Richardson was later bought by Dow and became Merrell Dow.

Marion Laboratories (Kansas City) was a company without research facilities outside the U.S. It was acquired by Merrell Dow and became Marion Merrell Dow (MMD). After the acquisition, the Merrell Richardson research facilities in Cincinnati were moved to Kansas City, but it seems that not many Merrell Dow employees survived the move. Meanwhile the Merrell Richardson overseas development centers stayed in place.
MMD is now being acquired from Dow by Hoechst.

The NDA was prepared by MMD which consists largely of Marion Laboratory employees who have little first hand knowledge of the US clinical trials run out of Cincinnati or overseas trials run out of England or France.

B. Overseas clinical trials. The trials run out of the French development site tend to be the earlier trials (more than ten years old) and the trials run out of England tend to be the later trials. Essentially the MMD employees do not have any personal knowledge of the organization or conduct of these trials. For example, for the trials run out of France they do

not know if case report forms were or were not used for a particular trial and they do not know if the case report forms if used are still available. They do not have them in Kansas City.

MMD suspects that some case report forms are in existence because they obtained some for subjects who dropped out of trials or had serious adverse reactions.

C. Reporting of overseas trial adverse drug experience. Merrell Dow realized that it needed to salvage as much information as it could about adverse drug reactions. Where there were case report forms, it attempted to abstract these on a standardized form. For the studies out of the France center it went to the study reports of trials and abstracted all of the adverse reactions reported in the clinical trial study report as single line items. There were over a thousand subjects in this category. The exact numbers are disclosed in the NDA.

D. Specific reporting instances in the US trials. The US trials were handled from the case report forms. To code the reactions MMD had a dictionary with terms, etc. We attempted to trace several instances of the use of concomitant medications, opthalmalogic adverse drug reactions, and seizure activity from case report forms to the submitted report or data base. For the most part we were successful.

E. Impression. The inspection team pretty much agrees that MMD was straight forward in its explanations. MMD appeared to have thought about how it was going to retrieve and organize its data and then went ahead and did it. MMD staff referred several times to meetings with HFD-120 over the years and seemed to think that it had explained how it was going to approach the extraction and reporting of adverse events and had HFD-120s concurrence. For the most part, somewhere in the NDA MMD attempted to explain as clearly as it felt necessary what it was doing and how it was doing it. MMD was definitely handicapped by not having employees who had first hand knowledge of the development program of this drug until a very late stage its development - almost NDA preparation.

MARION MERRELL DOW INC.

ORIG AMEND

Marion Park Drive
MAIL: P.O. Box 9627
Kansas City, Missouri 64134-0627
Telephone: 816/966-5000

IV(BC)

March 24, 1995

Dr. Paul Leber
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
4th Floor, Woodmont II Bldg.
1451 Rockville Pike
Rockville, MD 20852

Subject: NDA 20-427
Sabril® Oral
(vigabatrin, MDL 71,754)

AMENDMENT
Chemistry, Manufacturing and Controls
Response to FDA Request

Dear Dr. Leber:

Reference is made to a telephone conversation between Dr. M. Guzewska, Reviewing Chemist, and the undersigned on February 22, 1995.

Dr. M. Guzewska's requests and our responses are as follows:

1. **Supply a list of samples with required details that will be available for the FDA laboratories.**

   Response:

   We have provided the requested information in each of the two enclosed Analytical Methods Validation volumes.

2. **Provide the location at which the samples could be collected.**

   Response:

   The samples will be available at:

   Marion Merrell Dow Inc.
   2110 E. Galbraith Road
   Cincinnati, OH 45215-6300

   Attention: Mr. Carl Rodenkirchen
   (513)-948-7726

3. **Provide the Analytical Method Validation Package in triplicate. Also, indicate the locations for all the methods in the above document.**

Response:

We are enclosing herewith the Analytical Methods Validation Package in triplicate, as requested. We are providing an introductory page in each of the two volumes of the Analytical Methods Validation Package (which was submitted to the Agency on February 9, 1995) which provides the general format of this submission. A comprehensive list of analytical methods and their location in the document is also provided immediately following the Table of Contents. Additional details can be found in the Table of Contents which is provided in both volumes.

We trust that we have fully responded to the Agency's requests. Should you have any questions, please contact the undersigned at (816) 966-7104.

Sincerely,

pp James Boyd

Dhiren N. Shah, Ph.D.
Technical Manager
Global Regulatory CMC

DNS/cgb

Enclosures (2 volumes)
Desk Copy: Dr. M. Guzewska

M E M O R A N D U M

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

DATE: March 17, 1995

FROM: Regulatory Management Officer
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Div. Scientific Investigations:
NDA 20-427/ Sabril (vigabatrin) tablets

TO: Dr. Robert Temple

At this time the investigations done by DSI at the clinical sites have not been completed. I have spoken with Ms. Carol Currier as to the status of the investigations on three separate occassions. During the last telecon on 3/13/95, Ms. Currier felt that the investigations could be completed by April 15, 1994.

Once the investigations have been completed, I will send them up to be included in the package.

Robin M. Pitts, R. Ph.

cc:
ORIG NDA
HFD-120
HFD-120/PLeber/RKatz
HFD-120/RPitts
DOC: m:\wpfiles\sabirl\Dsi.mem

MEMO OF TELEPHONE CALL

Date:	March 13, 1995
NDA:	20-427
Subject:	DSI
Drug:	Sabril® (vigabatrin)
Indication:	Antiepileptic
Sponsor:	Marion Merrell Dow Inc.
contact:	Carol Currier, HFD-344
Phone #:	594-1204

I contacted Ms. Currier at HFD-344 for the status of the clinical investigations. I informed Ms. Currier that I had looked in Comis and found that Sabril clinical investigation sites are currently still pending. I also informed her that on January 9, 1995 and on February 10, 1995 I had contacted her with the same information.

Ms. Currier informed me that indeed that they are aware that the investigations are not completed. She informed me that one of the investigations is currently taking place, and that the other investigations will be completed by April 15, 1995.

I thanked Ms. Currier for looking into my request.

Robin Pitts, R.Ph.
Regulatory Management Officer

NDA:ORIG 20-427
NDA:DIV FILE
HFD-120/Leber/Katz/McCormick
HFD-120/Pitts
Doc # m:\dos\wpfiles\sabril\tel.20

12.1

13.1

ORIGINAL

MARION MERRELL DOW INC.

Marion Park Drive
MAIL: P.O. Box 9627
Kansas City, Missouri 64134-0627
Telephone: 816/966-5000

ORIG AMENDMENT
NDA

March 8, 1995

Dr. Paul Leber
Division of Neuropharmacological Drug Products (HFD-120)
Center for Drug Evaluation and Research
Food and Drug Administration
4th Floor, Woodmont II Bldg.
1451 Rockville Pike
Rockville, MD 20852

Subject: NDA 20-427
Sabril® Tablets
(vigabatrin, MDL 71,745)

AMENDMENT
Chemistry, Manufacturing and Controls
Response to FDA Request

Dear Dr. Leber:

The purpose of this communication is to respond to a telephone request made by your Dr. M. Guzewska to the undersigned on March 6, 1995.

The information requested by Dr. Guzewska and our response is given below:

To revise the stability protocol for the drug substance produced at MMD's Garessio and Midland facilities to include a statement to indicate that the relative humidity of the stability storage room will be monitored.

Response:

We hereby provide revised protocols in Attachments 1 and 2 which include the above comment.

Should you have any questions, please contact the undersigned at (816) 966-7104.

Sincerely,

Dhiren N. Shah

Dhiren N. Shah, Ph.D.
Technical Manager
Global Regulatory CMC

Attachments

MEMO OF TELEPHONE CALL

Date:	February 10, 1995
NDA:	20-427
Subject:	DSI
Drug:	Sabril® (vigabatrin)
Indication:	Antiepileptic
Sponsor:	Marion Merrell Dow Inc.
contact:	Carol Currier, HFD-344
Phone #:	594-1204

I contacted Ms. Currier at HFD-344 for the status of the clinical investigations. I informed Ms. Currier that I had looked in Comis and found that Sabril clinical investigation sites are currently still pending. I also informed her that on January 9, 1995 I had contacted her with the same information.

Ms. Currier informed me that indeed that was correct, and that she would look into the situation and asked that I call back mid-March to the status. She said that she would put the word out to the field that these investigations need to be completed.

I thanked Ms. Currier for looking into my request.

Robin Pitts, R.Ph.
Regulatory Management Officer

NDA:ORIG 20-427
NDA:DIV FILE
HFD-120/Leber/Katz/McCormick
HFD-120/Pitts
Doc # m:\dos\wpfiles\sabril\tel.19

E L E C T R O N I C M A I L M E S S A G E

Date: 31-Jan-1995 02:26pm EST
From: Christina Good
GOODC
Dept: HFD-100 WOC2 6019
Tel No: 301-594-6758 FAX 301-594-5298

TO: Robin Pitts (PITTSR)
TO: Phillip Vincent (VINCENTP)
TO: Michael Jones (JONESM)

Subject: NDA 20-427 Sabril EA--TELECON

I received a telephone conference call from Vicki Selzer and Dhien Shah of M. M. Dow company who submitted the application for NDA 20 20=427 Sabril **Tablets.** They called at 2 pm on Tuesday, January 31, 1995. **They had questions** regarding our comments on the EA deficiencies.

Below are my comments, etc. by each EA item and comment number (please refer to my deficiency memo to Robin Pitts Dated 1/23/95.

Item 4
I stated that the general street address for each manufacturing complex .d be sufficient for the FOI and confidential EA. An reference to a building number could be made only in the confidential material.

Item 6
(3) They asked what was meant by disposal from site of drug substance manufacture. I said are there every any disposed off lots which would be disposed. If so, please discuss the disposal. They said okay.

(6) I stated that we only needed the MSDS's for the drug substance, and if had, the drug product. The did not need to submit the MSDS's for other manufacturing components, etc. The MSDS's submitted for the substance needed to be in the FOI copy.

[general comment regarding (4)--the Italian site of manufacture is currently making [redacted] for non US use. They will increase their production by [redacted] for the US market. This information will be explained in the amended EA.] b(4)

Item 13
They stated that the archival copies were signed. I said we would need copies of the signed pages for the review and FOI EAs. They stated that there is a new responsible person--I suggested they change the signature page and have the new person sign. I suggested they submit some note explaining why the s and signatures (where ever present) have changed.

Item 15
The data summary table needs to be in the FOI and confidential EA. The data

upport the summary table DOES NOT have to be in the FOI version. I made a ı. ake in my memo to Robin Pitts asking for it in confidential version. This was not my intent nor is it our policy to place this information on data to support the test results in the non-confidential section.

They expect to submit a totally amended EA next week through the division. A desk copy for the EA reviewer will be submitted with this package. They will be completing redoing the EA package rather than submit just certain amended pages. We agreed this was the best approach given the number of changes/additions that were requested in the deficiency memo.

Chris Good

MEMO OF TELEPHONE CALL

Date:	January 26, 1995
NDA:	20-427
Subject:	Environmental Assessment Deficiencies
Drug:	Sabril® (vigabatrin)
Indication:	Antiepileptic
Sponsor:	Marion Merrell Dow Inc.
Phone #:	(816) 966-5352

At the request of Dr. Katz and Dr. Blum, I contacted Dr. Ken White (covering for Dr. Gregory Hileman) to officially convey the Environmental Assessment deficiencies. Due to time constraints the memorandum from Dr. Good was sent via facsimile to the sponsor. The sponsor was told that this is the official communication of the EA deficiencies. A letter concerning these deficiencies will not be issued.

Robin Pitts, R.Ph.
Regulatory Management Officer

(attachment)

NDA:ORIG 20-427
NDA:DIV FILE
HFD-120/Leber/Katz/McCormick/JFeeney
HFD-120/Pitts
HFD-102/ Vincent/Good
Doc # m:\dos\wpfiles\sabril\tel.8

MEMO OF TELEPHONE CALL

Date:	January 9, 1995
NDA:	20-427
Subject:	DSI
Drug:	Sabril® (vigabatrin)
Indication:	Antiepileptic
Sponsor:	Marion Merrell Dow Inc.
contact:	Carol Currier, HFD-344
Phone #:	594-1204

I contacted Ms. Currier at HFD-344 for the status of the clinical investigations. I informed Ms. Currier that I had looked in Comis and found that Sabril clinical investigation sites are currently still pending.

Ms. Currier informed me that indeed that was correct, and that she would look into the situation and asked that I call back mid-February as to the status.

I thanked Ms. Currier for looking into my request.

Robin Pitts, R.Ph.
Regulatory Management Officer

NDA:ORIG 20-427
NDA:DIV FILE
HFD-120/Leber/Katz/McCormick
HFD-120/Pitts
Doc # m:\dos\wpfiles\sabril\tel.18