Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
January 7, 2009

Topic: The committee discussed new drug application (NDA) 20-427, vigabatrin, Ovation Pharmaceuticals, Inc., for the proposed indication of adjunctive therapy for the treatment of refractory complex partial seizures in adults.

These summary minutes for the January 7, 2009 Peripheral and Central Nervous System Drugs Advisory Committee meeting were approved on January 23, 2009.

I certify that I attended the January 7, 2009 Peripheral and Central Nervous System Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.

_____*-Signed*_____
Diem-Kieu H. Ngo, Pharm.D., BCPS
(Designated Federal Official)

_____*-Signed-*_____
Larry B. Goldstein, M.D.
(Acting Chair)

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
January 7, 2009

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on January 7, 2009. A verbatim transcript will be available in approximately six weeks, sent to the Division and posted on the FDA website at http://www.fda.gov/ohrms/dockets/ac/cder09.html#PeripheralCentralNervousSystem.

All external requests for the meeting transcripts should be submitted to the CDER Freedom of Information Office.

The Peripheral and Central Nervous System Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research, met on January 7, 2009 at the Hilton Washington DC/Rockville, The Ballrooms, 1750 Rockville Pike, Rockville, Maryland. Prior to the meeting, the members and temporary voting and non-voting members were provided the background materials from the FDA and the sponsor. The meeting was called to order by Larry B. Goldstein, M.D. (Acting Chair); the conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Designated Federal Official). There were approximately 175 people in attendance. There were nine Open Public Hearing (OPH) speakers.

Issue: On January 7, 2009, the committee discussed new drug application (NDA) 20-427, vigabatrin, Ovation Pharmaceuticals, Inc., for the proposed indication of adjunctive therapy for the treatment of refractory complex partial seizures in adults.

Attendance:
Peripheral and Central Nervous System Drugs Advisory Committee Members present (voting): Larry B. Goldstein, M.D. (Acting Chair); Lily K.F. Jung, M.D., M.M.M.; Ying Lu, Ph.D.; Matthew Rizzo, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee Members absent (voting): Britt Anderson, M.D., Ph.D.; Mark W. Green, M.D., Ph.D.; Gregory L. Holmes, M.D., Ph.D.; Sandra F. Olson, M.D.; Stacy A. Rudnicki, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee Temporary Voting Members: Marshall S. Balish, M.D.; Harry T. Chugani, M.D.; Stephanie Y. Crawford, Ph.D., M.P.H.; Richard L. Gorman, M.D.; Richard R. Heckert, M.D.; Deborah G. Hirtz, M.D.; Jacqueline S. Gardner, Ph.D.; Frances E. Jensen, M.D.; Eli Mizrahi, M.D.; Lewis S. Nelson, M.D.; Michael A. Rogawski, M.D., Ph.D.; Wayne R. Snodgrass, M.D., Ph.D.; Gerald van Belle, Ph.D.; Marielos L. Vega, B.S.N., R.N.; Steven L. Weinstein, M.D.; Constance E. West, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee Temporary Non-Voting Member: Michael Bartenhagen (Patient Representative)

Industry Representative present (non-voting): Roy E. Twyman, M.D.

Drug Safety and Risk Management Advisory Committee Members (voting): Judith M. Kramer, M.D., M.S.; Timothy S. Lesar, Pharm.D.

Pediatric Advisory Committee Member (voting): Leon Dure, M.D.

Risk Communication Advisory Committee Member (voting): Betsy L. Sleath, Ph.D.

FDA Participants (non-voting): Robert Temple, M.D.; Russell G. Katz, M.D.; Wiley Chambers, M.D.; Ronald Farkas, M.D., Ph.D.; Norman Hershkowitz, M.D.

Open Public Hearing Speakers: Patricia A. Gibson, MSSW, ACSW; Mark Veasey; Jim Hable; Richard H. Mattson, M.D.; Joyce Cramer; Scott L. Crossland; Philip Gattone, M.Ed.; Cormac O'Donovan, M.D., FRCPI; Steven C. Schachter, M.D.

The agenda was as follows:

8:00 a.m.	Call to Order and Opening Remarks	**Larry B. Goldstein, M.D.** Acting Chair Peripheral and Central Nervous System Drugs Advisory Committee
	Introduction of Committee	
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Designated Federal Official
8:15 a.m.	FDA Introductory Remarks	**Russell Katz, M.D.** Director, Division of Neurology Products Office of Drug Evaluation I, OND, CDER, FDA

INDUSTRY PRESENTATION

8:30 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *Introduction*	**Tim Cunniff, Pharm.D.** VP, Global Regulatory Affairs, Pharmacovigilence, and Clinical Quality Assurance Ovation Pharmaceuticals, Inc.
8:35 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *An Unmet Need for Therapies*	**R. Edward Faught, M.D.** Professor and Vice Chair, Department of Neurology University of Alabama School of Medicine University of Alabama at Birmingham Director, UAB Epilepsy Center
8:40 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *Efficacy and General Safety*	**Christopher Silber, M.D.** VP, Clinical Affairs Ovation Pharmaceuticals, Inc.
8:55 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *Peripheral Visual Field Defect (pVFD) Consequences & Monitoring*	**Robert C. Sergott, M.D.** Director of Neuro-Ophthalmology Professor of Ophthalmology and Neurology Wills Eye Institute, Thomas Jefferson University

9:15 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *Peripheral Visual Field Defect (pVFD) Characterization*	**Steven Sagar, M.D.** Medical Director Ovation Pharmaceuticals, Inc.
9:45 a.m.	Sabril (vigabatrin) Tablets and Powder for Oral Solution – *Risk Evaluation and Mitigation Strategy (REMS)*	**Tim Cunniff, Pharm.D.** VP, Global Regulatory Affairs, Pharmacovigilence, and Clinical Quality Assurance Ovation Pharmaceuticals, Inc.
9:55 a.m.	Sabril (vigabatrin) Tablets for Refractory Complex Partial Seizures – *Benefit/Risk Assessment*	**Roger J. Porter, M.D.** Adjunct Professor of Neurology University of Pennsylvania, Philadelphia, PA Adjunct Professor of Pharmacology Uniformed Services University of the Health Sciences Bethesda, MD
10:00 a.m.	Clarifying Questions	
10:15 a.m.	**BREAK**	

FDA PRESENTATION

10:30 a.m.	Ophthalmic Findings in Adults	**Ronald Farkas, M.D, Ph.D.** Clinical Reviewer, Division of Neurology Products Office of Drug Evaluation I, OND, CDER, FDA
11:30 a.m.	Vigabatrin – Risk Evaluation and Mitigation Strategies (REMS)	**Joyce Weaver, Pharm.D., BCPS** Senior Drug Risk Management Analyst Office of Surveillance and Epidemiology, CDER, FDA
11:45 p.m.	Clarifying Questions	
12:00 p.m.	**LUNCH**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Questions/Clarifications	
3:30 p.m.	**BREAK**	
3:45 P.M.	Panel Discussion/Questions	
5:30 PM	**ADJOURNMENT**	

Questions to the Committee:

1. Vigabatrin has been shown to cause irreversible visual loss (central and/or peripheral).

    a. Does the committee believe that continued treatment results in a clinically meaningful loss of vision in some patients? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The majority of the committee agreed that continued treatment results in clinically meaningful loss of vision in some patients. (See Transcript for Complete Discussion)

    b. Has the sponsor shown that this visual loss can be detected before it becomes clinically meaningful? YES/NO/ABSTAIN

The committee rephrased question #1b to the following: Are there data to show that the visual defect can be detected before it is clinically meaningful?

YES: 14 NO: 7 ABSTAIN: 3

Committee Discussion:
The majority of the committee agreed that the visual loss can be detected before it becomes clinically meaningful. The Ophthalmologists on the panel noted that this can theoretically be done based on their clinical experience. The committee noted that no one ophthalmologic test will work reliably for everyone. (See Transcript for Complete Discussion)

    c. Has the sponsor adequately shown that discontinuation of treatment halts the progression of the visual loss? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The committee agreed that the sponsor has not adequately shown that discontinuation of treatment halts the progression of the visual loss. (See Transcript for Complete Discussion)

    d. The sponsor asserts that vigabatrin does not cause central visual loss. Does the committee think that the sponsor has adequately shown this? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The committee agreed that the sponsor has not adequately shown that vigabatrin does not cause central visual loss. (See Transcript for Complete Discussion)

2. Can the committee envision any combination of patient population and conditions of use that would support approval? YES/NO/ABSTAIN

YES: 24 NO: 0 ABSTAIN: 0

Committee Discussion:
The committee did not agree with the sponsor's definition of "refractory" being failure of only 2 other anticonvulsant drugs. Panel members agreed that it is difficult to determine the appropriate patient population for this drug. Additionally, it was noted that Sabril (vigabatrin) has not been

shown to be more effective than other anticonvulsant drugs; additionally, there is no data showing how effective this drug is in refractory patients. (See Transcript for Complete Discussion)

3. If yes to question 2, then:

    a. What is the appropriate population (e.g., standard population of patients with epilepsy or some subset [e.g., candidates for surgery or intractable patients who are not surgical patients])?

    b. If Sabril is to be approved for use in a refractory population, should additional effectiveness (comparative) data be obtained specifically in this population? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that no additional effectiveness (comparative) data in the refractory population are needed prior to approval of Sabril (vigabatrin). The committee concluded that it is difficult to define "refractory" since individual epileptologists may define this differently. The committee agreed that Sabril (vigabatrin) should be reserved for patients with complex partial seizures who are refractory to good trials of several anticonvulsants. (See Transcript for Complete Discussion)

4. If yes to question 2, under what circumstances could Sabril (vigabatrin) be approved? For example, should it be available only under a Risk Evaluations and Mitigation Strategy (REMS)? Following is a partial list of potential components of a REMS:

    a. Should it be made available only under restricted conditions (e.g., certain practitioners, restricted distribution, an educational campaign, special training program for practitioners, registry, etc.)? YES/NO/ABSTAIN

    b. Should continued access to the drug be linked to results of ophthalmologic monitoring? YES/NO/ABSTAIN

    c. Other?

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that Sabril (vigabatrin) should be made available only under restricted conditions and continued access to the drug should be linked to results of ophthalmologic monitoring. (See Transcript for Complete Discussion)

5. Is there sufficient evidence to support specific recommendations on the schedule of ophthalmologic monitoring? YES/NO/ABSTAIN

    a. Should there be a requirement for periodic ophthalmologic monitoring? YES/NO/ABSTAIN

    b. If so, is the sponsor's plan for monitoring adequate? YES/NO/ABSTAIN

    c. If the sponsor's plan is not adequate, does the committee have any proposal?

    Committee Discussion:
    A formal vote was not taken for this question. Based on the committee's discussion of question #1, the committee agreed that there should be a requirement for periodic ophthalmologic monitoring and that the sponsor's plan for monitoring is not adequate. The committee recommended the following

ophthalmologic monitoring be performed: at baseline (may need several visual field perimetry tests to determine baseline), at 3 months, every 4-6 months thereafter, and for a period (undefined) after discontinuation of Sabril (vigabatrin). (See Transcript for Complete Discussion)

6. Is there additional data related to the visual loss that should be obtained prior to approval of Sabril (vigabatrin)? YES/NO/ABSTAIN

    a. If yes, what data?

    Committee Discussion:
    A formal vote was not taken for this question. The majority of the committee agreed that no additional data related to the visual loss should be obtained prior to approval of Sabril. The committee noted that studies of visual loss should be conducted as a post-marketing requirement. (See Transcript for Complete Discussion)

7. Does the Committee believe that the intramyelinic edema seen in animals has any clinical consequences in adults? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that there is no data to address this question. (See Transcript for Complete Discussion)

8. If yes to number 7, should there be additional clinical requirements (e.g., additional monitoring, additional analyses, additional data)? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that no additional clinical requirements are needed before approval. (See Transcript for Complete Discussion)

9. Given the data in hand, does the committee recommend that Sabril (vigabatrin) be approved for the treatment of refractory complex partial seizures in adults? YES/NO/ABSTAIN

    YES: 24 NO: 0 ABSTAIN: 0

    Committee Discussion:
    Dr. Katz clarified that individuals above 16 years old are considered "adults" since the regulatory definition of "pediatrics" is $\leq$ 16 years old. The sponsor stated that there were no patients below the age of 18 in either of the pivotal studies. Some committee members were concerned about access of Sabril (vigabatrin) by minor children with refractory complex partial seizures or by adults with other types of seizures. The sponsor stated that access will not be limited to individuals over the age of 18 with refractory complex partial seizures and that the REMS will be modified to address off-label use by minors. (See Transcript for Complete Discussion)

The meeting was adjourned at approximately 5:45 p.m.