Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
January 8, 2009

Topic: The committee discussed NDA 22-006, vigabatrin, Ovation Pharmaceuticals, Inc., for the proposed indication of treatment of infantile spasms.

These summary minutes for the January 8, 2009 Peripheral and Central Nervous System Drugs Advisory Committee meeting were approved on January 23, 2009.

I certify that I attended the January 8, 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 8, 2009

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on January 8, 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 8, 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 14 Open Public Hearing (OPH) speakers.

Issue: January 8, 2009, the committee discussed NDA 22-006, vigabatrin, Ovation Pharmaceuticals, Inc., for the proposed indication of treatment of infantile spasms.

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 X. Repka, M.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.; Karl Kieburtz, 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.; Philip Sheridan, M.D.

Open Public Hearing Speakers: Rachel Macri; Karen Johnson-Wenger; Joyce Cramer; Eric H. Kossoff, M.D.; Vicky H. Whittemore, Ph.D.; Laura Kozisek; Rebecca Anhang Price; Robin Krantz; Diane Edquist Dorman; Danielle Foltz; Elizabeth Thiele, M.D., Ph.D.; Tim Zirkel; Jeff Buchhalter, M.D., Ph.D.; Steven C. Schachter, M.D.; Anna Wulick.

The agenda was as follows:

7:30 a.m.	Call to Order	**Larry B. Goldstein, M.D.** Acting Chair Peripheral and Central Nervous System Drugs Advisory Committee
	Conflict of Interest Statement	**Diem-Kieu H. Ngo, Pharm.D., BCPS** Designated Federal Official

INDUSTRY PRESENTATION

7:45 a.m.	Sabril (vigabatrin) for Oral Solution for Infantile Spasms – *Introduction*	**Tim Cunniff, Pharm.D.** VP, Global Regulatory Affairs, Pharmacovigilence, and Clinical Quality Assurance Ovation Pharmaceuticals, Inc.
7:55 a.m.	Sabril (vigabatrin) for Oral Solution for Infantile Spasms – *Unmet Need and Disease Background*	**W. Donald Shields, M.D.** Professor of Neurology and Pediatrics Mattel Children's Hospital at UCLA
8:10 a.m.	Sabril (vigabatrin) for Oral Solution for Infantile Spasms – *Efficacy and General Safety*	**Steven Sagar, M.D.** Medical Director Ovation Pharmaceuticals, Inc.
8:50 a.m.	Intramyelinic Edema: Knowledge From Animal Studies	**D. Reid Patterson, D.V.M., Ph.D.** Diplomate: ABT, ACVP, ACLAM Fellow: ATS, IATP Reid Patterson Consulting, Inc
8:55 a.m.	Sabril (vigabatrin) for Oral Solution for Infantile Spasms – *Clinical MRI Abnormalities*	**James W. Wheless, M.D.** Professor and Chief, Department of Pediatric Neurology The University of Tennessee Health Science Center Director, Neuroscience Institute & LeBonheur Comprehensive Epilepsy Program LeBonheur Children's Medical Center Clinical Chief & Director of Pediatric Neurology St. Jude Children's Research Hospital, Memphis, TN

9:10 a.m.	Sabril (vigabatrin) for Oral Solution for Infantile Spasms – *Benefit/Risk Assessment*	**John M. Pellock, M.D.** Professor and Chairman Division of Child Neurology Virginia Commonwealth University
9:15 a.m.	Clarifying Questions	
9:30 a.m.	**BREAK**	

FDA PRESENTATION

9:45 a.m.	Ophthalmic Findings in Pediatrics	**Ronald Farkas, M.D., Ph.D.** Clinical Reviewer, Division of Neurology Products Office of Drug Evaluation I, OND, CDER, FDA
10:15 a.m.	Clinical Studies in Infantile Spasms	**Philip Sheridan, M.D.** Clinical Reviewer, Division of Neurology Products, Office of Drug Evaluation I, OND, CDER, FDA
11:00 a.m.	Nonclinical Central Nervous System Pathological Findings	**Larry C. Schmued, Ph.D.** Director, Neurohistochemistry Laboratory Division of Neurotoxicity National Center for Toxicological Research, FDA
11:30 a.m.	Clarifying Questions	
12:00 p.m.	**LUNCH**	
1:00 p.m.	Open Public Hearing	
2:00 p.m.	Questions/Clarifications	
3:00 p.m.	**BREAK**	
3:15 p.m.	Panel Discussion/Questions	
5:30 p.m.	**ADJOURNMENT**	

Questions to the Committee:

1. Has the sponsor provided substantial evidence for vigabatrin as a treatment of infantile spasms? YES/NO/ABSTAIN

   The committee rephrased question #1to the following: Has the sponsor provided sufficient evidence that vigabatrin is efficacious in the treatment of infantile spasms?

   YES: 25 NO: 0 ABSTAIN: 0

   Committee Discussion: *(See Transcript for Complete Discussion)*

2. Do the studies indicate efficacy in:

    a. Cessation of spasms? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The committee agreed that the studies indicate that Sabril is efficacious in the cessation of spasms. (See Transcript for Complete Discussion)

    b. Amelioration of the EEG? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The committee agreed that there is substantial evidence that treatment with Sabril can ameliorate the EEG. (See Transcript for Complete Discussion)

    c. Prevention of other seizures types later in life? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The majority of the committee did not feel that the studies indicate that Sabril prevents other seizure types later in life. (See Transcript for Complete Discussion)

    d. Improvement in long-term developmental outcome? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. Dr. Chugani commented that developmental delay is due to the underlying etiology and the spasms; thus, if the spasms are controlled, patients may still have developmental delay due to the underlying etiology. The majority of the committee did not feel that the studies indicate that Sabril improves long-term developmental outcome. (See Transcript for Complete Discussion)

3. There is a view that current unapproved treatments (ACTH or steroids) can provide long-term protection against infantile spasms with a short duration course of treatment (e.g., about two weeks). The sponsor has proposed that vigabatrin be given chronically but has not provided evidence from controlled trials that treatment with vigabatrin chronically provides an additional benefit beyond a brief treatment course. Should the sponsor be required to adequately study this question? YES/NO/ABSTAIN

Committee Discussion:
A formal vote was not taken for this question. The committee agreed that the sponsor should be required to adequately study (post-approval) whether chronic treatment with vigabatrin provides an additional benefit beyond a brief treatment course. Some committee members proposed that the sponsor should conduct a randomized withdrawal study at some point post-approval. There was discussion regarding the design of a withdrawal study but the committee did not arrive at a consensus regarding the design of such a study. The Biostatisticians commented that data from a patient registry will not be adequate to study this question. (See Transcript for Complete Discussion)

4. Vigabatrin has been shown to cause irreversible visual damage, and the sponsor has proposed that monitoring with ERG can adequately detect this damage at an acceptably early stage.

    a. Has the sponsor provided evidence that ERG is a reliable way to detect lesions in the pediatric population before they become clinically meaningful? YES/NO/ABSTAIN

    b. Has the sponsor presented any other methods to detect lesions sufficiently early? YES/NO/ABSTAIN

    c. If the committee concludes that the sponsor has identified an adequate method to detect visual damage sufficiently early, is there evidence to support a monitoring regimen over time that will detect damage sufficiently early? YES/NO/ABSTAIN

    d. If there is inadequate evidence to support a monitoring regimen, should the sponsor be required to develop that evidence? YES/NO/ABSTAIN

    e. If the committee concludes that the sponsor has not identified an adequate method to detect damage sufficiently early, should the sponsor be required to develop one? YES/NO/ABSTAIN

    f. Has the sponsor adequately shown that the visual loss will not progress if the treatment is discontinued once visual damage has been detected? YES/NO/ABSTAIN

    g. Has the sponsor provided adequate evidence about the functional consequences of treatment with vigabatrin on the developing visual system and overall function, especially against the background of preexisting neurological abnormalities? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for any subparts of question #4. The Ophthalmologists on the panel agreed that there is no method to practically and reliably predict or detect the lesion with the tests currently available. Additionally, it was agreed upon that ophthalmologic testing can not detect the visual defects any better than observations by the Pediatric Neurologists evaluating the patient. It was commented that visual defects can occur and can be severe and irreversible; thus, families need to be informed but also cautioned that visual testing may not prevent the occurrence of visual defects. (See Transcript for Complete Discussion)

5. Has the sponsor presented adequate evidence that central visual loss does not occur in pediatric patients? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that data have not been presented to answer this question. (See Transcript for Complete Discussion)

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

    Committee Discussion:
    The committee felt that this question was a moot point based on the discussions that have transpired throughout the day. (See Transcript for Complete Discussion)

7. If yes to question 6, then:

    a. What is the appropriate population (e.g., all patients with infantile spasms, only age-specific subsets, etiologic subsets such as tuberous sclerosis, patients who have failed other treatments)?

    b. If Sabril (vigabatrin) is to be approved for use in a specific subset of patients, should additional effectiveness data in this subset be obtained? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for this question. The committee agreed that Sabril should not be approved for use in any specific subset of patients, but rather be approved for all patients with infantile spasms. Patients who may have pre-existing visual conditions should be cautioned about the adverse effects but Sabril should not be contraindicated in any patient population. The committee also agreed that additional efficacy studies are not needed in any subset of patients. (See Transcript for Complete Discussion)

8. If yes to question 6, 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 any subparts of this question. The committee agreed that Sabril (vigabatrin) should only be available under a REMS. Based on the discussions during the January 7, 2009 meeting on Sabril for the treatment of refractory complex partial seizures in adults, the committee concurred that Sabril for the treatment of infantile spasms should also be made available only under restricted conditions. The committee recommended that the REMS for the refractory complex partial seizure indication should be different than the REMS for the infantile spasms indication. (See Transcript for Complete Discussion)

9. Given alternative off-label therapy (ACTH, valproic acid, etc.), do the safety concerns preclude marketing even if efficacy has been demonstrated? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for any subparts of this question. Dr. Katz clarified that "marketing" means "approval" in this context. The committee agreed that the safety concerns should not preclude approval of Sabril (vigabatrin). (See Transcript for Complete Discussion)

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

    Committee Discussion:
    A formal vote was not taken for this question. It was commented that intramyelinic edema seen in animals does not seem to correlate with MRI changes. The committee agreed that no data is available to answer this question. (See Transcript for Complete Discussion)

11. What is the clinical significance, if any, of the observation of neuropil vacuolation in young animals?

    a. Are these related to newly appreciated MRI findings in children revealing grey matter lesions? YES/NO/ABSTAIN

    b. If the committee does not believe that the MRI findings in children are related to the neuropil vacuolation in animals, are they of clinical concern nonetheless? YES/NO/ABSTAIN

    Committee Discussion:
    A formal vote was not taken for any subparts of this question. The committee agreed that no data is available to answer this question. (See Transcript for Complete Discussion)

12. Should additional safety data be obtained prior to approval for Sabril as a treatment for infantile spasms? YES/NO/ABSTAIN

    a. If so, what data?

    Committee Discussion:
    A formal vote was not taken for this question. The committee did not recommend that additional safety data should be obtained prior to approval of Sabril. (See Transcript for Complete Discussion)

13. Given the data in hand, does the committee recommend that Sabril (vigabatrin) should be approved for treatment of infantile spasms? YES/NO/ABSTAIN

    YES: 23 NO: 0 ABSTAIN: 0

    Committee Discussion:
    Dr. Jung and Dr. West were absent for this question. (See Transcript for Complete Discussion)

The meeting was adjourned at approximately 4:45 p.m.