Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
March 10, 2011

Topic: The committee discussed, in general, the use of historical-controlled trials for the approval of anticonvulsant monotherapy for seizures of partial origin for antiepileptic drug products that are already approved for adjunctive therapy. The committee also discussed how this may specifically apply to the approval of the supplemental new drug application (sNDA) 022115/S-006, LAMICTAL XR (lamotrigine extended-release tablets), sponsored by SmithKline Beecham Corporation d/b/a GlaxoSmithKline, for monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED).

These summary minutes for the March 10, 2011 Peripheral and Central Nervous System Drugs Advisory Committee meeting were approved on March 25, 2011.

I certify that I attended the March 10, 2011Peripheral 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*_____
Britt Anderson, M.D., Ph.D.
(Chair)

Summary Minutes of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting
March 10, 2011

The following is the final report of the Peripheral and Central Nervous System Drugs Advisory Committee meeting held on March 10, 2011. 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/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm235850.htm

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 March 10, 2011, at the Hilton Washington DC/Silver Spring, The Ballrooms, 8727 Colesville Road, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA and GlaxoSmithKline. The meeting was called to order by Britt Anderson, M.D., Ph.D. (Acting Chair). The conflict of interest statement was read into the record by Diem-Kieu H. Ngo, Pharm.D., BCPS (Designated Federal Officer). There were approximately 100 people in attendance. There was one Open Public Hearing (OPH) speaker.

Issue: The committee discussed, in general, the use of historical-controlled trials for the approval of anticonvulsant monotherapy for seizures of partial origin for antiepileptic drug products that are already approved for adjunctive therapy. The committee also discussed how this may specifically apply to the approval of the supplemental new drug application (sNDA) 022115/S-006, LAMICTAL XR (lamotrigine extended-release tablets), sponsored by SmithKline Beecham Corporation d/b/a GlaxoSmithKline, for monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED).

Attendance:
Peripheral and Central Nervous System Drugs Advisory Committee members present (voting): Jeffrey A. Cohen, M.D.; Dean D. Kindler, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members not present (voting): Nathan B. Fountain, M.D.; Samuel A. Frank, M.D. (Consumer Representative); Pooja Khatri, M.D.; Ellen J. Marder, M.D; Jason W. Todd, M.D.

Peripheral and Central Nervous System Drugs Advisory Committee members present (non-voting): Roy Twyman, M.D. (Industry Representative)

Temporary Members (voting): Britt Anderson, M.D., Ph.D. (Acting Chair); Lily Jung Henson, M.D., M.M.M., FAAN (Acting Consumer Representative); Marshall S. Balish, M.D., Ph.D.; Kevin E. Chapman, M.D.; Robert R. Clancy, M.D.; Thomas R. Fleming, Ph.D.; Andrew C. Leon, Ph.D.; Eli Mizrahi, M.D.; Phillip L. Pearl, M.D.; William H. Theodore, M.D.; David M. Treiman, M.D.; Hongyu Zhao, Ph.D.

Guest Speakers (non-voting): Jacqueline A. French, M.D.; Nancy R. Temkin, Ph.D.

FDA Participants (non-voting): Russell G. Katz, M.D.; Norman Hershkowitz, M.D., Ph.D.; Steven Dinsmore, D.O.; Xiang Ling, Ph.D.

Open Public Hearing Speakers: John M. Pellock, M.D. (American Epilepsy Society)

The agenda was as follows:

Call to Order and Opening Remarks	***Britt Anderson, M.D., Ph.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 Officer*
FDA Introductory Remarks	***Russell Katz, M.D.*** *Director, Division of Neurology Products (DNP)* *Office of Drug Evaluation I (ODE-I)* *Office of New Drugs (OND), CDER, FDA*
GUEST SPEAKER PRESENTATION	
Historical Control: Withdrawal to Monotherapy	***Jacqueline A. French, M.D.*** *Professor, Department of Neurology* *Director, Clinical Trials Consortium* *New York University Comprehensive Epilepsy Center*
Historical Control for Epilepsy Conversion to Monotherapy: Methodology	***Nancy R. Temkin, Ph.D.*** *Professor, Biostatistics and Neurological Surgery* *University of Washington*
Clarifying Questions	
BREAK	
INDUSTRY PRESENTATION	
Overview of Epilepsy and Lamotrigine	***Thomas Thompson, M.D.*** *Director, Neurosciences Medicine Development Center* *Physician Project Leader for Lamotrigine* *GlaxoSmithKline LLC*
Brief Review of the Historical Control Studies	***John Messenheimer, M.D.*** *Epilepsy Consultant* *John Messenheimer, PLLC*
LAM30055 – Design, Efficacy, and Safety Results	***John Messenheimer, M.D.***

Comparisons Between LAM30055, US30/31, and the Historical Control Studies	***John Messenheimer, M.D.***
Summary and Conclusions	***Thomas Thompson, M.D.***
Statistical Considerations	***Eugene M. Laska, Ph.D.*** *Research Professor, Biostatistics* *New York University Medical Center*
Clarifying Questions	

FDA PRESENTATION

Lamictal® XR™ (lamotrigine) Historical Control Trial	***Xiang Ling, Ph.D.*** *Mathematical Statistician* *Division of Biostatistics 1, Office of Biostatistics* *Office of Translational Science, CDER, FDA*
Clarifying Questions	

LUNCH

. *Open Public Hearing*

Panel Discussion/Questions

BREAK

Panel Discussion/Questions

Adjournment

Questions to the Committee:

1. Does the Committee believe that placebo-controlled monotherapy studies in patients with partial seizures are ethically acceptable? YES/NO/ABSTAIN

   Committee Discussion: *Note: a vote was not taken for this question. The committee agreed that long-term outpatient placebo-controlled or pseudo placebo-controlled trials of the sort demonstrated by the historical control studies presented by French et al. would be ethically problematic in general but there may be an appropriate subset of patients who suffer from diseases with no available treatment or study types such as the short-term inpatient setting where a placebo or pseudo-placebo may be considered.. Please see the transcript for details of the Committee discussion.*

2. If the answer to Question 1 is "NO", does the Committee believe that a historical control approach, of the sort proposed by French et al., can be acceptable under the specific circumstances in which a drug is known to be effective as adjunctive treatment? YES/NO/ABSTAIN

   YES: 14 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee unanimously agreed that a historical control approach, of the sort proposed by French et al., can be acceptable under the specific circumstances in which a drug is known to be effective as adjunctive treatment. Please see the transcript for details of the Committee discussion.*

3. If the answer to Question 2 is "YES", please discuss the specific methodology utilized by French et al. (e.g. the propriety of combining the eight control groups into a single historical control, the specific statistical approach used to combine the groups, the appropriateness of using a prediction interval and the specific prediction interval used to establish effectiveness) and whether it is acceptable.

   Committee Discussion: *The committee voiced concerns regarding the heterogeneity of the pseudo-placebo groups utilized by French et al to construct the historical control group., but concurred that it is acceptable as long as the inherent irregularities are addressed. Additionally, some of the committee members felt that it may have been problematic for the escape rates to be pooled into one aggregate rate. Please see the transcript for details of the Committee discussion.*

4. If the methodology is considered acceptable, what elements of a study using this approach are critical to consider, for example:
   a. Matching demographics (age, race, duration/severity of epilepsy, nationality, etc.)
   b. Initial concomitant antiepileptic drugs (AEDs)
   c. Differences in conversion methods
   d. Temporal trends in response
   e. Dropouts
   f. Any other elements

   Committee Discussion: *The committee agreed that all of the following elements are important: matching demographics, initial concomitant antiepileptic drugs, differences in conversion methods, temporal trends in response, and dropouts The committee also noted that investigators should match any proposed study sample to the known characteristics of the historical control populations. Additionally, it was noted that the five Stuart Pocock criteria for acceptability of historical control (Journal of Chronic Disease, 1976) should be met. Please see the transcript for details of the Committee discussion.*

5. Does the study under consideration fulfill the necessary criteria to allow for a determination of effectiveness? Specifically, please discuss:
   a. Potential for bias due to the fact that all patients are receiving active treatment
   b. Potential bias due to under-reporting of study endpoints
   c. Number of background AEDs
   d. The comparability of exit criteria in this study and in the historical control
   e. United States (US) data vs. foreign data

   Committee Discussion: *It was noted that a drug effect was evident despite the uncertainties that were inherent due to the open label bias, heterogeneity in the controls and the statistical adjustments which were made (prediction interval and lower limit 95% confidence interval). However, it was also noted that it is questionable if there is a drug effect if a need for preservation of effect of any previously approved drug is required. Please see the transcript for details of the Committee discussion.*

6. Has the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures? YES/NO/ABSTAIN

   YES: 10 NO: 2 ABSTAIN: 1

   a. If "YES", please discuss whether or not the fact that Lamictal **IR** is approved for monotherapy was critical to the decision.

   Committee Discussion: *Note: one committee member was not present for the vote. The majority of the committee agreed that the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures. All of the committee members who voted "YES" stated that the fact that Lamictal IR is approved for monotherapy was critical to their vote. Please see the transcript for details of the Committee discussion.*

7. *Based on the discussions that transpired, the following question was added during the meeting:* Assuming there is a very good match between the active treatment group and the historical controls, could you consider approval for a monotherapy indication for a drug that had adjunctive efficacy demonstrated but had not been examined in monotherapy using a different formulation?

   Committee Discussion: *The committee agreed that they could recommend approval of a drug that had efficacy demonstrated for adjunctive therapy but had not been evaluated for monotherapy (using a different formulation) if there was a good match between the active treatment group and the historical controls. Please see the transcript for details of the Committee discussion.*

The meeting was adjourned at approximately 5:05 p.m.