Summary Minutes of the
Endocrinologic and Metabolic Drugs Advisory Committee
Location: Hilton Washington DC North/Gaithersburg
620 Perry Road, Gaithersburg, Maryland.
July 15, 2010

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

These summary minutes for the July 15, 2010 Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration were approved on October 18, 2010

I certify that I attended the July 15, 2010 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
Paul T. Tran, RPh.
Designated Federal Official, EMDAC

/s/
Kenneth Burman, M.D.
Committee Acting Chair

The Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 15, 2010 at The Hilton Washington DC/North Gaithersburg, Maryland. Prior to the meeting, the members and the invited consultants had been provided the background material from the FDA. The meeting was called to order by Kenneth Burman, M.D. (Acting Chair); the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Official). There were approximately 250 persons in attendance. There were 9 speakers for the Open Public Hearing session.

Attendance:

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Voting):
Thomas Bersot, M.D., Ph.D., David Capuzzi, M.D., Ph.D., Allison Goldfine, M.D., Abraham Thomas, M.D., M.P.H., Lamont Weide, M.D., Ph.D.

Endocrinologic and Metabolic Drugs Advisory Committee Members Present (Non-voting):
Enrico Veltri, M.D. (Industry Representative)

Drug Safety and Risk Management Advisory Committee Member Present (Voting):
Elaine Morrato, Dr.PH, M.P.H.

Cardiovascular and Renal Drugs Advisory Committee Member Present (Voting):
Sanjay Kaul, M.D.

Special Government Employee Consultants Present (Voting):
Kenneth Burman, M.D. *(Acting Chair)*, Melanie Coffin *(Patient Representative)*, Jessica Henderson, Ph.D. *(Acting Consumer Representative)*, Susan Heckbert, M.D., Ph.D., Ed Hendricks, M.D., Michael Rogawski, M.D., Ph.D.

Special Government Employee Consultant Not Present (Voting):
Jules Hirsch, M.D.

Regular Government Employee Consultants Present (Voting):
Janet Cragan, M.D., M.P.H., Katherine Flegal, Ph.D., Michael Proschan, Ph.D.

FDA Participants:
Curtis Rosebraugh, M.D., M.P.H., Eric Colman, M.D., Mary Roberts, M.D.

Open Public Hearing Speakers:
Lynn McAfee, Council on Size & Weight Discrimination, Director, Medical Advocacy
Dr. James McKenney, Chief Executive Officer, National Clinical Research-Richmond, Inc
Gloria Elliott

Kelly L. Close, Editor in Chief, diaTribe
Caroline M. Apovian, M.D., F.A.C.P, F.A.C.N. (Speaking on behalf of the Obesity Society), Associate Professor of Medicine and Pediatrics, Boston University School of Medicine, Director, Center for Nutrition and Weight Management
Margaret (Peggy) I. Pence
Erin Aycock
Joseph Nadglowski, Jr., President and CEO, Obesity Action Coalition (OAC)
Sidney M. Wolfe M.D., Director, Health Research Group at Public Citizen

Designated Federal Official:
Paul Tran, R.Ph.

Issue: The committee discussed the safety and efficacy of new drug application (NDA) 22-580, proposed tradename QNEXA (phentermine/topiramate) Controlled Release Capsules, by VIVUS, Inc., as an adjunct to diet and exercise for weight management in patients with a body mass index equal to or greater than 30 kilograms (kg) per square meter, or a body mass index equal to or greater than 27 kg per square meter if accompanied by weight-related co-morbidities.

8:00 a.m.– 8:05 a.m.	Call to Order and Introductions	**Kenneth Burman, M.D.** *Committee Acting Chair* Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)
8:05 a.m. – 8:15 a.m.	Conflict of Interest Statement	**Paul Tran, R.Ph.** Designated Federal Official EMDAC
8:15 a.m. – 8:30 a.m.	Introduction/Background	**Eric Colman, M.D.** Deputy Director Division of Metabolism and Endocrinology Products (DMEP), Office of Drug Evaluation (ODE) II Office of New Drugs (OND) Center for Drug Evaluation and Research (CDER) FDA
8:30 a.m. – 10:00 a.m.	Sponsor Presentation	**Vivus, Inc.**
	Unmet Medical Need	**Louis Aronne, M.D.** Clinical Professor of Medicine Weill-Cornell Medical College
	Clinical Pharmacology and Efficacy	**Wesley Day, Ph.D.** Vice-President, Clinical Development VIVUS, Inc.
	Neuropsychiatric Safety	**Kishore Gadde, M.D.** Director of Obesity Clinical Trials Program DUKE University Medical Center

	Safety REMS, Phase IV Outcomes Trial Benefit/Risk	**Neil Gesundheit, M.D., M.P.H.** Associate Dean for Advising Associate Professsor of Medicine (Endocrinology) Stanford University School of Medicine
	Pregnancy	**Gideon Koren, M.D.** Director, The Motherisk Program The Hospital for Sick Children Professor of Pediatrics, Pharmacology, Pharmacy and Medical Genetics University of Toronto
10:00 a.m. – 10:15 a.m.	Clarifying Questions from the Committee to Sponsor	
10:15 a.m. – 10:30 a.m.	**Break**	
10:30 a.m. – 11:30 a.m.	FDA Presentation	**Mary Roberts, M.D.** Clinical Reviewer DMEP, ODE II, OND CDER, FDA
11:30 a.m. – 12:00 p.m.	Clarifying Questions from the Committee to FDA	
12:00 p.m. – 1:00 p.m.	**Lunch**	
1:00 p.m. – 2:00 p.m.	Open Public Hearing Session	
2:00 p.m. – 2:30 p.m.	Questions from Committee to Sponsor and FDA	
2:30 p.m. – 2:45 p.m.	**Break**	
2:45 p.m. – 5:00 p.m.	Discussion/Questions to the Committee	
5:00 p.m.	**Adjournment**	

Questions to the Advisory Committee:

1) Taking into account the results of the assessments made with the PHQ-9 and the Columbia Suicidality Severity Rating Scale (C-SSRS), please comment on the significance of the increased adverse event reports of depression, anxiety, and sleep disorders in subjects treated with Phentermine/Topiramate (PHEN/TPM).

   - If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

The committee agreed that the observed increase in depression levels was a serious concern, including the possibility that this could result in suicidal

ideation. There was a general consensus that the population studied is not an adequate representation of the "real world" and consequentially, the results gathered from the PHQ-9 and C-SSRS are likely not representative of results that would be observed in broader populations. In particular, there was a concern that the prevalence of adverse mental health effects may be significantly larger in at-risk groups such as patients with epilepsy and other medical illnesses. The lack of data concerning co-morbidity and the risks involved with co-administration with other medications were also cited as significant concerns. The committee specifically discussed the issue of co-administration as it relates to other psycho-active medications such as those taken for mental illnesses. In addition, the positive trend seen in quality of life measures was encouraging but the significance of these levels was debated.

Please see the transcripts for detailed discussion.

2) Please comment on the potential significance of the increased adverse event reports of disorders of attention, memory, language, and other cognitive disorders in subjects treated with PHEN/TPM.

   - If approved, please discuss need for monitoring and possible monitoring strategies.

Overall, the committee agreed that the cognitive effects of PHEN/TPM were subtle but of concern. The significance of the observed cognitive effects was debated, as several committee members noted that the data suggest these effects are reversible once the medication is stopped. Again, the committee expressed concern over the applicability of the available data to a broader population. The committee discussed the implications of cognitive impairment for job-performance and safety and agreed that the risks are more significant when compounded with the likelihood that some patients may abuse PHEN/TPM (the higher the dose, the more effects observed.)

Please see the transcripts for detailed discussion.

3) Please comment on the potential clinical significance of the metabolic acidosis determined by decreases in serum bicarbonate levels with PHEN/TPM treatment.

   - If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

The committee agreed that metabolic acidosis is a potentially serious side-effect of PHEN/TPM and one which warrants considerable attention. The applicability of the study results to a larger population was a concern, as a broad population would include individuals in significant risk groups. The risk groups discussed included women, who are generally at-risk for low bone density levels, and patients with co-morbid conditions that can cause acidosis such as a history of

kidney stones, renal failure, congestive heart failure, and GI abnormalities. The committee also noted that co-administration with other medications effecting acidosis could raise the potential for adverse effects. Laxatives were cited as a prime example as the committee considered the likely co-occurrence of PHEN/TPM and laxative use in patients abusing both agents to induce greater weight loss. Some committee members mentioned that bicarbonate levels should be monitored in certain patients, although it was also noted that bicarbonate levels routinely decrease for individuals on low-carbohydrate diets. Vitamin D levels were also proposed as an indication to be monitored, as the use of Topiramate in epileptic patients has been shown to affect these levels. However, the committee also considered the possibility for Vitamin D levels to be a confounding variable in evaluating PHEN/TPM-induced acidosis, as overweight patients often present with low serum levels. Overall, the committee agreed that the long-term clinical effects of PHEN/TPM-induced metabolic acidosis are unclear and should be further studied. The committee also agreed that should the product be approved, specific dosing recommendations would be needed in addition to clinical guidelines for monitoring at-risk populations.

Please see the transcripts for detailed discussion.

4) Please comment on the potential clinical significance of the increase in heart rate observed in PHEN/TPM treated individuals.

    - If approved, please discuss need for monitoring, possible monitoring strategies, and contraindications for use.

The committee agreed that the observed increased heart rate was a significant concern, as this poses a risk of atrial fibrillation and other cardiac abnormalities. They noted that the risk of adverse cardiovascular events is greater in patients with co-morbid conditions such as diabetes and obesity. The failure of the completed studies to adequately represent the expected broader PHEN/TPM-administered population was also a concern regarding cardiovascular effects, as it was for the adverse effects discussed in the preceding questions. Specifically, the committee called for comprehensive cardiovascular studies looking at continuous rather than intermittent heart rate monitoring.

Please see the transcripts for detailed discussion.

5) Given the doses of topiramate in PHEN/TPM, please comment on whether you believe PHEN/TPM poses a teratogenic risk to the target population for weight loss.

    - If you believe it does pose a risk, please comment on how this risk should be managed in women of child-bearing potential if PHEN/TPM is approved.

The committee highlighted the teratogenic risks associated with the administration of PHEN/TMP in women who are pregnant or may become pregnant. However, it was also noted that teratogenicity is a problem in obese patients in general and thus it may be appropriate for this to be considered a control. There was a discussion regarding the relationship, if any, between dosing and teratogenicity and the committee called for studies revealing more data on this as well as the overall risk of teratogenicity with the administration of PHEN/TPM. Several committee members were particularly interested in the results of the breast lactation study which had not yet been released.

Please see the transcripts for detailed discussion.

6) Based on the current available data, do you believe the overall benefit-risk assessment of PHEN/TPM (QNEXA) is favorable to support its approval for the treatment of obesity in individuals with a BMI ≥30 kg/m2 or ≥27 kg/m2 with weight-related co-morbidities?

Vote: Yes: 6 No: 10 Abstain: 0

If voting yes:

- Please discuss the basis for this recommendation
- Please discuss any labeling recommendations
- Please discuss whether additional studies should be conducted post-approval

If voting no:

- Please discuss basis for this recommendation
- Please discuss what additional studies would be necessary to address an outstanding deficiency/deficiencies

After the formal vote was cast, one committee member immediately indicated that he had selected the incorrect button; the chair allowed the member to correct his vote from "Yes" to "No". The vote tally was modified to the results noted above.

The majority of the committee agreed that the data available were insufficient to warrant approval. Those who voted against approval highlighted the need for studies representing a broader population as well as data which provide for a more comprehensive assessment of the risks. Specifically, several committee members cited the need for a better assessment of cognitive effects, citing that the studies conducted only examined behaviors after a 10-month period. In addition some "no" voters expressed an agreement that the public health consequences were too great to warrant approval, considering the risks associated with PHEN/TPM and the likelihood that the heavy demand for weight loss pharmacotherapy will result in many patients exceeding dosing limitations to maximize weight loss. Further, the use of this medication would likely be broader than utilized in the premarketing trials.

In general, committee members who voted in favor of approval focused on the demonstrated efficacy of Qnexa. Many of those explaining the rationale behind their "yes" vote agreed that, considering the risks associated with obesity, the public health benefits of PHEN/TPM outweigh the risks. Several "yes" voters also stated that they were concerned with the lack of data but felt that adequate data could only be gathered once the product has been on the market and is used by a broader population.

Additionally, several members who voted in favor of approval mentioned that both Phentermine and Topiramate are already approved and marketed individually for other indications. They argued that given the wide availability, there is a high likelihood that these drugs are and will continue be used together regardless of Qnexa approval. They further concluded that it would be more favorable to have the combination presented to the public in a manner in which dosing and risk mitigation strategies are clear.

Please see the transcripts for detailed discussion.