July 9, 2012

Division of Dockets Management
Attn: Ms. Gloria Ortega
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

2012 JUL 11 A 9:41

Re: Citizen Petition seeking FDA rejection or issue a CRL to Vivus' Qnexa drug candidate.

CITIZEN PETITION

A. ACTION REQUESTED

The undersigned submits this petition under 21 C.F.R. § 10.30 to request that the Honorable Dr. Margaret A. Hamburg, M.D., Commissioner of the Food and Drug Administration, respectfully reject or, alternatively, issue a CRL to Vivus' New Drug Application for obesity drug candidate "Qnexa" for the reasons stated herein.

B. INTERESTS OF PETITIONER

Petitioner is consumer advocacy law firm. Petitioner does not have any interest in Vivus, Inc., and the drug candidate "Qnexa."

C. STATEMENT OF GROUNDS -

The FDA must not approve Qnexa with incomplete information. At a minimum, a CRL is necessary to assess unanswered risks. A review of the February 22, 2012, Qnexa Advisory Committee documents reveal serious concerns over adverse cardiovascular effects and an insufficient assessment of Qnexa's teratogenic potential as some serious safety reasons for not approving the application. Vivus has not provided sufficient information to address the potential strengths and weaknesses of the proposed teratogenicity risk management strategy for PHEN/TPM. The FDA briefing documents show the applicant proposed to mitigate the risk of teratogenicity by contraindicating use for women of childbearing potential (WOCBP), and

implement a RISK Evaluation and Mitigation Strategy (REMS) using restricted distribution to enforce this contraindication. The FDA correctly observed the contraindication is too broad, and does not agree that, should Qnexa be approved, the risk of teratogenicity would outweigh Qnexa's benefits for every woman capable of becoming pregnant. Secondly, although it might be feasible to restrict use of Qnexa, such a restriction would not preclude use of the individual components of Qnexa by WOCBP for weight loss. Since the resubmission of the application, Vivus, Inc., and the FDA have discussed possible approaches to mitigating the risk of teratogenicity. Given the availability of the separate ingredients of Qnexa, an ideal risk mitigation strategy does not appear to be practical.

In a recent published abstract, attached hereto as Exhibit A, it was determined that "in topiramate-exposed pregnancies, the rate of all malformations has been 4.2 to 4.9%, with an increase in oral clefts with and without other anomalies." The risks of OCs (oral clefts) and MCMs (major congenital malformations) associated with TPM use in the first trimester of pregnancy have not been fully answered in the interim report of the FORTRESS study due to the limited sample size in the TPM monotherapy subcohort, the pending study results using the entire SMP cohort, and the poor data quality issues with the analysis for MCMs.

Noteworthy, even excerpts from the Vivus' own briefing documents raise serious concerns about the analysis of data on all major congenital malformations in process. Vivus represented the FORTRESS data will be made available once final validated results have been obtained. Vivus' briefing documents also indicated the study will be completed in the second half of 2012. To date, Vivus has not provided the FORTRESS study data. It is believed that the final results from the FORTRESS study are expected to provide a more statistically precise

estimate of effect than previous studies. At a minimum, the FORTRESS study should be required before a REMS is developed or QNEXA drug approval can be properly considered. The FDA should not accept interim and insufficient results as final proof of Qnexa's safety profile.

Vivus' FORTRESS (Fetal Outcome Retrospective Topiramte Exposure Study) is preliminary because no data validation was performed on the results. Furthermore, the FDA set the sample size for topiramate-exposed mother/baby pairs at 2,300 and 16,000 for unexposed mother/baby pairs but the study only used 1,945 and 13,614 cases for exposed and non-exposed pairs so they did not follow FDA's mandate (the results by the way show that the pair exposed in the first trimester are 6.46 times more likely to be born with OC than the non-exposed pairs. A CRL is appropriate to allow Vivus to complete the FORTRESS study and provide the actual scientific conclusions. As noted in the briefing documents, 34 pregnancies occurred during the clinical trials. As stated by the FDA reviewer, "the occurrence of 34 pregnancies in a controlled clinical development program where enrollment required agreement for use of double barrier or oral contraceptive plus single barrier methods, as well as a negative pregnancy test at each study visit, underscores the large potential for pregnancy exposure with PHEN/TPM if approved for weight loss."

Moreover, it is unlikely that an effective balance can be achieved with a risk management approach for Qnexa that does not have unintended consequences with current or future users of Topiramate or that encourages prescribers to approximate Qnexa by prescribing the individual ingredients to circumvent the requirements of a REMS specific only to Qnexa. The approval of Qnexa should be delayed until the impact study on Topiramate users can be adequately done and addressed. In addition, a delay would be appropriate until effective mechanisms are identified

that would actively discourage use of Qnexa's individual ingredients.

It is critically important that patient care is kept in the forefront of the FDA's concerns when evaluating a potential REMS program, especially in the face of dangerous clinical evidence. It is unclear what metrics are being proposed or will be used to measure the impact of the REMS on the benefit-risk ratio for Qnexa. Under the FDAAA, evaluation of the success or failure of any REMS is required. Therefore, knowing the metrics will be critical. The briefing documents are replete with references that better science and data is needed to assess both the risks and the benefits of Qnexa. All proposed Qnexa REMS programs outlined in public documents to date fall short of the proper means for effectively safeguarding unborn children from dangerous exposure to Topiramate. QNEXA could be broadly used within the large WOCBP patient segment and any initial vigilance on the part of the medical community will be overrun by prescriber responsiveness to WOCBP demand.

A serious concern is glaringly obvious because the potential high demand by patients could lead to relaxed adherence to the potential REMS program and education. Thus, there could be an increased number of pregnancies going undetected for months while on Qnexa. The FORTRESS data was inconclusive and incomplete regarding birth defects.

Approval of Qnexa would directly authorize the Topiramate and Phentermine ingredients to be used in combination as weight loss agents. There is real concern about the abuse potential for Physicians to logically prescribe the ingredients to save patients money. The FDA recognized this abuse potential exists for physicians' in the following excerpt taken from the briefing document:

"It is unlikely that some prescribers would prescribe the individual ingredients in an amount that would approximate Qnexa capsules to circumvent the requirements of the REMS."

Qnexa's impact on heart rate. An increase in heart rate that was consistent across subgroups was observed over 2 years with Qnexa. Furthermore, there has not been an adequate characterization of Qnexa's increase in heart rate in higher risk cardiovascular populations. Categorical heart rate change in 1 and 2 year cohorts, point to a consistent increase with Qnexa compared to placebo. Out in the market place, Qnexa will be viewed as a highly efficacious product that will be prescribed to obese patients with multiple comorbidities, including various forms of heart disease. The EMDAC agreed that the observed increase in heart rate was a significant concern over a long period of time. The two year safety cohort did nothing to dispel the consistent and sustained increase in heart rate caused by Qnexa. Without greater numbers of higher risk patients studied, it is unclear how the label could adequately guide prescribers to use Qnexa in a safe manner. At the February 22, 2012, advisory committee meeting, cardiologists who participated concluded that clarity has not yet been provided in Vivus's response to the 2010 CRL on this topic. The FDA should delay approval of Qnexa to determine how prescribers should address heart rate increases in high risk populations.

In addition, Qnexa's response to the 2010 CRL provides insufficient data in high risk populations as well. **REMS is not a substitute for an incomplete or unfinished study**. An unfair and ill-advised precedent would be set if the FDA were to approve a drug on the basis that access would be restricted since the company has not fully demonstrated the prevalence of a well-known and negative side effect of TPM use. Th FDA recently approved Lorcaserin/Belviq, and therefore, the FDA has afforded the indicated population a safe and effective obesity medicine.

D. The Importance of Obesity Medicines. The importance of obesity medicines is well known. Obesity medicines play an essential role in health care system. According to the Center for Disease Control Publication, health effects associated with obesity include, but are not limited to, the following:

1. High blood pressure - Additional fat tissue in the body needs oxygen and nutrients in order to live, which requires the blood vessels to circulate more blood to the fat tissue. This increases the workload of the heart because it must pump more blood through additional blood vessels. More circulating blood also means more pressure on the artery walls. Higher pressure on the artery walls increases the blood pressure. In addition, extra weight can raise the heart rate and reduce the body's ability to transport blood through the vessels.
2. Diabetes - Obesity is the major cause of type 2 diabetes. This type of diabetes usually begins in adulthood but, is now actually occurring in children. Obesity can cause resistance to insulin, the hormone that regulates blood sugar. When obesity causes insulin resistance, the blood sugar becomes elevated. Even moderate obesity dramatically increases the risk of diabetes.
3. Heart disease - Atherosclerosis (hardening of the arteries) is present 10 times more often in obese people compared to those who are not obese. Coronary artery disease is also more prevalent because fatty deposits build up in arteries that supply the heart. Narrowed arteries and reduced blood flow to the heart can cause chest pain (angina) or a heart attack. Blood clots can also form in narrowed arteries and cause a stroke.
4. Joint problems, including osteoarthritis - Obesity can affect the knees and hips because of the stress placed on the joints by extra weight. Joint replacement surgery, while

commonly performed on damaged joints, may not be an advisable option for an obese person because the artificial joint has a higher risk of loosening and causing further damage.

5. Sleep apnea and respiratory problems - Sleep apnea, which causes people to stop breathing for brief periods, interrupts sleep throughout the night and causes sleepiness during the day. It also causes heavy snoring. Respiratory problems associated with obesity occur when added weight of the chest wall squeezes the lungs and causes restricted breathing. Sleep apnea is also associated with high blood pressure.
6. Cancer - In women, being overweight contributes to an increased risk for a variety of cancers including breast, colon, gallbladder, and uterus. Men who are overweight have a higher risk of colon and prostate cancers.
7. Metabolic syndrome - The National Cholesterol Education Program has identified metabolic syndrome as a complex risk factor for cardiovascular disease. Metabolic syndrome consists of six major components: abdominal obesity, elevated blood cholesterol, and elevated blood pressure, insulin resistance with or without glucose intolerance, elevation of certain blood components that indicate inflammation, and elevation of certain clotting factors in the blood. In the US, approximately one-third of overweight or obese persons exhibit metabolic syndrome.
8. Psychosocial effects - In a culture where often the ideal of physical attractiveness is to be overly thin, people who are overweight or obese frequently suffer disadvantages. Overweight and obese persons are often blamed for their condition and may be considered to be lazy or weak-willed. It is not uncommon for overweight or obese conditions to result in persons having lower incomes or having fewer or no romantic

relationships. Disapproval of overweight persons expressed by some individuals may progress to bias, discrimination, and even torment.

9. Obesity is the number one cause of Type-2 diabetes. Type-2 diabetes is the leading cause of kidney disease that often leads to kidney failure and very expensive transplants or dialysis as treatments.

E. ADVERSE CONSEQUENCES FOR FDA CRL OR REJECTION OF QNEXA.

Qnexa does not address an unmet medical need since Lorcaserin/Belviq has been approved. Qnexa's ingredients, Phentermine and Topiramate, are separate drug components that have been available to physicians for years. The FDA recently provided physicians with Lorcaserin/Belviq to address their diverse group of patients and the health problems they face with their patient needs, and medication tolerance levels, in their endeavor to treat obesity patients.

F. ECONOMIC IMPACT:

The FDA's recent approval of Lorcaserin/Belviq filled an unmet medical need. Qnexa will not fill an unmet medical need for obesity medications. Although, obesity has a far-ranging negative effect on health, Qnexa's safety issues will add an unnecessary financial burden to the healthcare system. The Qnexa REMS program will also be an enormous financial burden on the healthcare system to manage. The FDA's risk evaluation and mitigation strategy program is intended to ensure the drug benefits outweigh the risks. The Center for Healthcare Supply Chain Research and its partner of the Healthcare Distribution Management Association (HDMA), indicates unsurprisingly that REMS requirements are costly to the supply chain. It also recognizes that hidden, unforeseen, and unreimbursed costs can tax the drug distribution system. REMS will also be a costly and time consuming burden on the healthcare system. REMS was

devised out of growing concerns that safety signals were insufficiently handled before and after drug approvals, for example, Merck's Vioxx painkiller is an often cited example. If a REMS program can be devised for Qnexa, it would be advisable to consider Pilot testing. The FDA has recognized, in past cases, that without 100% compliance with the REMS across all stakeholders, physicians are likely to change their prescribing practices based upon whichever drug is the least burdensome option.

However, it is well known that obesity-related diseases account for nearly 10 percent of all US medical spending, or an estimated $147 Billion Dollars each year and cause an estimated 300,000 premature deaths in the US. See Finkelstein, EA, Trogdon, JG, Cohen, JW, and Dietz, W. Annual medical spending attributable to obesity. Health Affairs 2009; 28(5): w822-w831. Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. Obesity Research. 1998; 6(2):97-106. See also CDC Obesity Publications – Obesity, Saving Lives, Protecting People, Saving Money through Prevention. The recent Gallop Poll found that Obesity costs cities an estimated $80 billion a year in healthcare costs.

CONCLUSION:

Based upon the facts and scientific evidence, Qnexa is not safe and should not be approved by the FDA without the FORTRESS study data and analysis. A Qnexa REMS is impractical and will be a costly and time consuming burden on the healthcare system based upon the information presently known.

G. CERTIFICATION

The undersigned certifies that, to the best of the knowledge and belief of the undersigned, this Petition includes all information and views on which this Petition relies, both positive and negative, and that it includes all representative data and information known to the petitioner.

Respectfully submitted,

By: _____.

Joseph Dedvukaj (P51335)
The Joseph Dedvukaj Firm, P.C.
Attorneys & Counselors at Law
1277 West Square Lake Road
Bloomfield Hills, Michigan 48304
Office#(248) 352-2110
Facsimile#(248) 352-0880
Email: jdlawfirm@aol.com
Website: www.jdlawfirm.org

THE JOSEPH DEDVUKAJ FIRM, P.C.

Attorneys & Counselors at Law

1277 West Square Lake Rd. • Bloomfield Hills, MI 48302 • Tel. 248-352-2110 • Fax 248-352-0880

jdlawfirm@aol.com

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Re: Citizen Petition seeking FDA rejection or issue a CRL to Vivus' Qnexa drug candidate.

Dear Ms. Ortega:

Enclosed, please find the Citizen Petition my office is filing regarding the Vivus New Drug Application for Qnexa. Please file in your usual manner and provide a copy to my office.

Thank you, in advance, for your anticipated cooperation.

Sincerely,

Joseph Dedvukaj

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