DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022580/S-004

SUPPLEMENT APPROVAL

Vivus, Inc.
Attention: Malcolm McKay, Ph.D.
Vice President, Regulatory Affairs and Compliance Officer
1172 Castro Street
Mountain View, CA 94040

Dear Dr. McKay:

Please refer to your Supplemental New Drug Application (sNDA) dated and received October 16, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qsymia (phentermine and topiramate extended-release) capsules CIV.

We also refer to your amendments dated April 15, 2013, and your risk evaluation and mitigation strategy (REMS) assessment dated January 14, 2013.

This supplemental new drug application proposes a modification to the approved REMS for Qsymia (phentermine and topiramate extended-release) capsules.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter and is appended. In addition, as acknowledged in our April 4, 2013 letter, we have found the REMS assessment to be complete.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling, with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Qsymia (phentermine and topiramate extended-release) capsules was originally approved on July 17, 2012 (and last modified on November 1, 2012). The REMS consists of a Medication Guide, elements to assure safe use (ETASU), implementation system, and a timetable for submission of assessments of the REMS. Your proposed modification to the REMS consists of:

- A revised Medication Guide to clarify dosing and administration instructions
- A revised pharmacy certification ETASU expanding pharmacy enrollment requirements
- A revised implementation system

The timetable for submission of assessments of the REMS will remain the same as that approved on July 17, 2012.

The revised REMS assessment plan should include, but is not limited to, the following:

1. An assessment of females of reproductive potential's (FRP) understanding of:
    a. The increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
    b. Their ability to become pregnant
    c. The importance of pregnancy prevention for FRP receiving Qsymia therapy
    d. The need to promptly discontinue Qsymia therapy in the event of a pregnancy
    e. The existence and purpose of the Qsymia Pregnancy Surveillance Program

2. An assessment of the receipt, reading and understanding by FRPs of the Qsymia Medication Guide and *Risk of Birth Defects with Qsymia* Patient Brochure.

3. An assessment of contraceptive use by FRPs including, but not limited to, the type and patterns of use.

4. Assessment of FRP's receipt of counseling about pregnancy prevention and effective contraceptive use, including
    a. Counseling provider (i.e., prescriber, office nurse, pharmacist)
    b. Duration of time spent counseling
    c. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia)
5. An assessment of prescribers understanding of:
    a. The increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
    b. The determination of reproductive status of female patients
    c. The need to exclude a pregnancy in a FRP before initiating Qsymia therapy
    d. The need for a FRP to consistently use effective contraception
    e. Highly effective and acceptable combination contraceptive methods as outlined in the Qsymia REMS
    f. The need to counsel FRPs about pregnancy prevention and effective contraceptive use at each visit while receiving Qsymia
    g. The need to promptly discontinue Qsymia therapy in the event of a pregnancy
    h. The existence and purpose of the Qsymia Pregnancy Surveillance Program

6. An assessment of HCP provision of counseling FRPs about pregnancy prevention and effective contraceptive use, including:
    a. Duration of time spent counseling
    b. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia)
    c. Use of materials to aid counseling (such as the *Healthcare Provider Counseling Tool for Females of Reproductive Potential*, the Qsymia *Prescriber Dosing and Management Checklist*, etc.)

7. A report on the periodic assessments of the distribution and dispensing of the Medication Guide in accordance with 21CFR 208.24 and *Risk of Birth Defects with Qsymia* Patient Brochure.

8. The following information regarding the Dear Healthcare Provider (DHCP) letter sent during the reporting period:
    a. The dates of the initial and subsequent mailings of the DHCP letter to HCPs and professional organizations
    b. The total number of recipients of the DHCP letter
    c. The source of the mailing list(s)
    d. A copy of all documents included in each distribution of the DHCP letter
    e. For DHCP letter sent via email
        i. Date, number, percent, and specialty of HCPs targeted
        ii. Number, percent, and specialty of HCPs who opened email
        iii. Number and percent of emails that were undeliverable
        iv. Number and percent of HCPs sent DHCP letter via hard copy if email was undeliverable

f. Number and percent of DHCP letters sent via hard copy
    i. Date, number, percent, and specialty of HCPs targeted
    ii. Number and percent of DHCP letters returned to sender
g. Number and percent of DHCP letters distributed by sales representatives
h. Names of professional organizations contacted to distribute the DHCP letter to members
    i. Number, percent, and names of professional organizations who accepted and redistributed DHCP letter
    ii. Number, percent, names of professional organizations who declined to accept or redistribute DHCP letter and reason why

9. The following information regarding prescriber training for each reporting period and cumulatively:
    a. Number of HCPs who have prescribed Qsymia
    b. Number of HCPs who have completed training
    c. Number of HCPs who have completed training and prescribed Qsymia
    d. Number and percent of HCPs prescribing Qsymia by medical specialty
    e. Number and percent of HCPs who have prescribed Qsymia but who have not completed training
        i. Number and percent contacted by VIVUS within REMS specified timeframe to become trained
            1. Number and percent trained after contact
    f. Number and percent of HCPs trained on-line, in person, or using print modules
    g. An assessment of strategies that have been employed during the reporting period to encourage prescribers to undergo educational training

10. The following information regarding certified pharmacies for each reporting period and cumulatively:
    a. Number and type (mail-order, chain, independent) of pharmacy certified
        i. For each chain indicate the number of dispensing locations certified
    b. Number and type of pharmacy decertified and the reason for decertification
    c. Number and percent of prescriptions submitted through the switch provider
    d. Number and percent of prescriptions rejected and the reason for rejection
    e. A summary of the quarterly compliance reports that are provided to VIVUS by the corporate chain and mail-order pharmacies

11. A report of the number and percent of patients receiving Qsymia by dose.

12. A summary of REMS Call Center and Qsymia REMS Pharmacy Support Center activity including frequently asked questions and frequently reported problems.

13. The number of unique hits for each page of the QsymiaREMS website.

14. With respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

NDA 022580 REMS CORRESPONDENCE
(Insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT METHODOLOGY)

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 022580 REMS ASSESSMENT

NEW SUPPLEMENT FOR NDA 022580
PROPOSED REMS MODIFICATION

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022580
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised package labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above or by fax to 301-847-8444.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call Pooja Dharia, Pharm.D., Regulatory Project Manager, at (301) 796-5332.

Sincerely,

{See appended electronic signature page}

Amy G. Egan, M.D., M.P.H.
Deputy Director for Safety
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURES:
Package Insert
Medication Guide
REMS

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY G EGAN
04/16/2013