DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022580/S-010
NDA 022580/S-011
NDA 022580/S-012

SUPPLEMENT APPROVALS

Vivus, Inc.
Attention: Santosh T. Varghese, M.D.
Vice President, Medical & Regulatory Affairs, Pharmacovigilance, and QA
351 East Evelyn Avenue
Mountain View, CA 94041

Dear Dr. Varghese:

Please refer to your Supplemental New Drug Applications (sNDAs) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qsymia (phentermine and topiramate extended-release) capsules, as follows:

NDA NUMBER:	022580	022580	022580
SUPPLEMENT NUMBER:	10	11	12
PRODUCT NAME:	Qsymia (phentermine and topiramate extended-release) capsules	Qsymia (phentermine and topiramate extended-release) capsules	Qsymia (phentermine and topiramate extended-release) capsules
DATE OF SUBMISSION:	December 30, 2013	January 3, 2014	April 30, 2014
DATE OF RECEIPT:	December 31, 2013	January 6, 2014	April 30, 2014
AMENDMENTS:	June 23, July 31, and August 22, 2014	June 23 and September 19, 2014	June 23 and September 19, 2014
PROVIDES FOR:	Proposed modifications to the approved risk evaluation and mitigation strategy (REMS) based on the final report for study OB-901, *Fetal Outcomes Retrospective Topiramate Exposure Study* (FORTRESS), submitted on May 29, 2013, and on Periodic Adverse Drug Event Reports (PADER) which contained events of acute angle closure glaucoma and increased intraocular pressure in patients taking Qsymia	Revisions to the Physician Insert and Medication Guide based on the final report for study OB-901, *Fetal Outcomes Retrospective Topiramate Exposure Study* (FORTRESS), submitted on May 29, 2013, and on Periodic Adverse Drug Event Reports (PADER) which contained events of acute angle closure glaucoma and increased intraocular pressure in patients taking Qsymia	Revisions to the Physician Insert to add “Suicidal ideation, Suicidal behavior” to Section 6.2 Postmarketing Experience.

These supplements are in response to our REMS Modification Notification and supplement request letter dated November 8, 2013, and our supplement request letter dated April 17, 2014.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text and with minor editorial revisions listed below:

Removal of Recent Major Changes from the Highlights of Prescribing Information section

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

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 (text for the package insert and Medication Guide), 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 via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications 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, 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 was originally approved on July 17, 2012, and REMS modifications were approved on November 1, 2012 and April 16, 2013. The REMS consists of a Medication Guide, elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS consist of:

- a change to the REMS document removing the requirement that The Dear Healthcare Provider letter be provided to MedWatch;
- changes to the REMS materials to conform to the changes being made to the package insert. Specifically, the changes include updated data in the Healthcare Provider Training Program [online and print] and the Pharmacy Training Program [online and print], based on the final report for study OB-901, *Fetal Outcomes Retrospective Topiramate Exposure Study* (FORTRESS), and;
- reformatting of the table in the Healthcare Provider Counseling Tool for Females of Reproductive Potential, the Healthcare Provider Training Program [online and print], and the Pharmacy Training Program [online and print], listing acceptable contraception methods for females of reproductive potential.

Your proposed modified REMS, submitted on August 22, 2014, and appended to this letter, is approved.

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

There are no changes to the REMS assessment plan described in our letter dated April 16, 2013.

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)

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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)

If you do not submit electronically, please send 5 copies of REMS-related submissions.

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/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. 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}

Jennifer Rodriguez Pippins, 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:
Physician 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/

JENNIFER R PIPPINS
09/26/2014