NDA 022580/S-020

SUPPLEMENT APPROVAL

Vivus, Inc.
Attention: Santosh T. Varghese, MD
Chief Medical Officer
900 East Hamilton Ave
Suite 550
Campbell, CA 95008

Dear Dr. Varghese:

Please refer to your supplemental new drug application (sNDA) dated and received July 30, 2021, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Qsymia (phentermine and topiramate extended-release) capsules.

This Prior Approval sNDA provides for proposed modifications to the approved Qsymia risk evaluation and mitigation strategy (REMS).

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

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 FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the 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.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include 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 Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), 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 (REMS) REQUIREMENTS

The REMS for Qsymia was originally approved on July 17, 2012, and the most recent REMS modification was approved on March 31, 2021. The REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS. Your proposed modifications to the REMS are to convert the REMS document to the new standardized format and provide the Applicant's name change throughout the REMS Document and REMS materials. This modification also removes ETASU A, prescriber training, as an element of the REMS, updates the goals to reflect the removal of ETASU A, and removes the REMS materials associated with prescriber training.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS and that an element of the REMS is no longer necessary to ensure the benefits of the drug outweigh the risk:

Elements to Assure Safe Use: We have determined that ETASU A, prescriber training, is no longer necessary in this REMS to ensure that the benefits of the drug outweigh the risks. Removal of this ETASU is supported by data showing adequate knowledge of the risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy, the importance of pregnancy prevention for patients of reproductive potential receiving Qsymia, and the need to discontinue Qsymia immediately if pregnancy occurs among cohorts of prescribers who are trained and those who are not yet trained. In addition, removing ETASU A would decrease the burden of the pharmacy to report prescriber data to the REMS program.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Finally, removing ETASU A also removes the REMS materials associated with prescriber training.

Your proposed modified REMS, initially submitted on July 30, 2021, amended and appended to this letter, is approved. The modified REMS consists of a Medication Guide, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

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

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

Program Implementation and Operations (per reporting period and cumulatively)

1. Pharmacy Enrollment Statistics
   a. Number and type (mail order, chain, independent) of pharmacies certified
   b. Number of chain dispensing locations certified

2. REMS Compliance
   a. Number and type of pharmacy decertified and the reason for decertification
   b. Summary of annual compliance reports provided to VIVUS by corporate chains, mail order pharmacies, and contracted distributors
   c. Copy of the audit plan for each stakeholder including the criteria for non-compliance (noncompliance plan)
   d. Number of audits expected and performed
   e. Summary report of deviations found, associated corrective and preventative actions and status of corrective actions

3. 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
   a. Pharmacist Materials Distribution Survey (beginning with the 11-year (12th) REMS assessment)
      i. Assessment of pharmacists' compliance with the Qsymia REMS dispensing requirements, specifically the provision of a Medication Guide and Risk of Birth Defects with Qsymia patient brochure with each dispensing of Qsymia

4. Patient Demographics and Prescription Data

a. Patient Demographics
   i. Unique number of patients received Qsymia stratified by gender
   ii. Unique number of patients of reproductive potential receiving Qsymia stratified by age groups (12-17, 18-29, 30-39, 40-49, and >50)
   iii. Average duration of Qsymia treatment among patients of reproductive potential

b. Prescription Data
   i. Provide a table that includes the following for the overall population and another table for patients of reproductive potential :
      a. Total number of unique patients
      b. Number and percentage of total prescriptions dispensed
      c. Number and percentage of total prescriptions dispensed for new and refill
      d. Number and percentage of total prescriptions dispensed by dosage strength

Knowledge (per reporting period and cumulatively)

5. Patients of reproductive potential (beginning with the 11-year (12th) REMS assessment)
   a. Assessment of patients of reproductive potential understanding of:
      i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
      ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy
      iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy
   b. Assessment of the receipt, reading, and understanding by patients of reproductive potential of the Qsymia Medication Guide and Risk of Birth Defects with Qsymia patient brochure
   c. Assessment of patients of reproductive potential receipt of counseling about pregnancy prevention and effective contraceptive use including:
      i. Counseling provider (i.e., prescriber, office nurse, pharmacist)
      ii. Duration of time spent counseling
      iii. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia

6. Pharmacists (beginning with the 11-year (12th) REMS assessment)

a. Assessment of pharmacists' understanding of:
   i. Increased risk of congenital malformation (specifically orofacial clefts) to infants with exposure to Qsymia during the first trimester of pregnancy
   ii. Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia therapy
   iii. Need to promptly discontinue Qsymia therapy in the event of a pregnancy

b. Assessment of pharmacists' awareness and understanding of the need to provide a Medication Guide and Risk of Birth Defects with Qsymia patient brochure with every Qsymia prescription dispensed

Health Outcomes and/or Surrogates of Health Outcomes

7. Safety Surveillance
   a. Summary of pregnancy cases associated with Qsymia, including the source of the report, pregnancy outcome, and cases of congenital malformations for each exposed pregnancy
   b. Overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

8. The requirements for assessments of an approved REMS under section 505-1(g)(3) include 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.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that 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. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing REMS modifications*, provide a rationale for why the REMS does not need to be modified.

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 ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

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.

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.

Prominently identify any 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

or

NEW SUPPLEMENT FOR NDA 022580/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022580/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 022580/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 022580/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR NDA022580

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

FDA can accept the REMS document in Structured Product Labeling (SPL) format. If you intend to submit the REMS document in SPL format, as soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in SPL format using the FDA automated drug registration and listing system (eLIST).

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

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, call Martin White, Regulatory Project Manager, at 240-402-6018.

Sincerely,

{See appended electronic signature page}

Monika Houstoun, Pharm.D., M.P.H.
Deputy Director for Safety (Acting)
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Medication Guide (included in REMS enclosure)
- REMS

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MONIKA A HOUSTOUN
03/08/2022 11:48:43 AM