NDA 022580/S-024

SUPPLEMENT APPROVAL

VIVUS, LLC
Attention: Maryam Azizi
Senior Director, Regulatory Affairs
900 East Hamilton Avenue
Suite 550
Campbell, CA 95008

Dear Maryam Azizi:

Please refer to your supplemental new drug application (sNDA) dated and received August 9, 2023, and your amendments, submitted pursuant to section 505(b)(2) 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).

We have completed our review of this supplemental application, as amended. It is approved effective on the date 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 May 9, 2023. 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 consist of changes to align the REMS with updated labeling from the prior approval supplement (S-023), which revised Qsymia labeling to be consistent with Topamax (topiramate) labeling.

The goal of the REMS was changed to: The goal of the Qsymia REMS is to inform certified pharmacies and patients of reproductive potential about:

1. The increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA) in a fetus exposed to Qsymia during the first trimester of pregnancy
2. The importance of pregnancy prevention for patients of reproductive potential receiving Qsymia

3. The need to discontinue Qsymia immediately if pregnancy occurs

In addition, the following changes were made to the REMS:

- The REMS Document was updated to remove unnecessary instances of the term "program," add a requirement for maintaining pharmacy certification, add a requirement for wholesaler-distributors to comply with audits, add a requirement to ensure the Medication Guide is made available for dispensing with each Qsymia prescription, revise audit language for certified pharmacies and wholesalers-distributors, include the risk the REMS mitigates in Section I: Administrative Information, and include a new Section VI: Statutory Elements.
- Changes to the REMS materials including the Pharmacy Training, Risk of Birth Defects with Qsymia Patient Brochure, and REMS Website to update the risk description of embryo-fetal toxicity to include major congenital malformations and small for gestational age (SGA).
- The Pharmacy Enrollment Form was revised to add, "closed system" as a pharmacy type.
- Title change from "REMS Program Website" to "REMS Website" in the REMS document and materials.
- The Medication Guide was revised to include the word, "major," in front of birth defects (on page 1 in the first bullet point) to align with the Prescribing Information approved with S-023.

Your proposed modified REMS, submitted on August 9, 2023, amended and appended to this letter, is approved.

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:

For each metric, provide the two previous, current, and cumulative reporting periods (if applicable or relevant) unless otherwise noted.

Program Implementation and Operations

1. **REMS Certification and Enrollment Statistics**

   a. Pharmacies
      i. Number of certified pharmacies stratified by pharmacy type (i.e., mail order, chain, independent)
      ii. Number and percentage of newly certified pharmacies stratified by pharmacy type (i.e., mail order, chain, independent)
      iii. Number and percentage of active certified pharmacies (i.e., have dispensed Qsymia within the reporting period) stratified by pharmacy type (i.e., mail order, chain, independent)

b. Distributors
   i. Number of authorized distributors
   ii. Number and percentage of newly authorized distributors
   iii. Number and percentage of active authorized distributors (i.e.,have shipped Qsymia within the reporting period)

2. **REMS Utilization Data**

a. Patient Demographics
   i. Unique number of all patients who received Qsymia stratified by gender
   ii. Unique number of patients of reproductive potential receiving Qsymia grouped by the following age ranges (years)
      1. 12 - < 18
      2. 18 - < 25
      3. 25 - < 45
      4. 45 - < 53
      5. 53+
   iii. Average duration of Qsymia treatment among patients of reproductive potential based on patient age outlined above

b. Prescription Data
   i. A table that includes the following for the overall population and another table for patients of reproductive potential based on patient age as outlined above:
      a. Total number of unique patients
      b. Number and percentage of total prescriptions dispensed
      c. Number and percentage of total prescriptions dispensed for new prescriptions and refills
      d. Number and percentage of total prescriptions dispensed by dosage strength

3. **REMS Compliance**

a. Audits
   i. A report of audit findings for each stakeholder including but not limited to:
      1. A copy of the audit plan for each stakeholder
      2. Number of audits expected and performed
      3. The number and type of deficiencies (e.g., critical, major, or minor findings) noted for audited stakeholders
      4. Report of the number of those with deficiencies noted that successfully completed a corrective and preventative action (CAPA) plan within the timeline specified in the audit plan
      5. Actions taken for those that did not complete the CAPA within the timeframe specified in the audit plan
      6. Unique identifiers for stakeholders that had deviations to track deviations by stakeholders over time

7. Documentation of completion of training for relevant staff
8. Verification of the existence of documented processes and procedures for complying with the REMS
9. Comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. Non-compliance
   i. A summary of the non-compliance identified, including but not limited to:
      1. A copy of the non-compliance plan which addresses the criteria for non-compliance for each stakeholder, actions taken to address non-compliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS
      2. Summary of non-compliance events identified per pharmacy and distributors including any CAPAs and status of corrective actions
      3. Number of instances of non-compliance accompanied by a description of each instance and the reason for the occurrence (if provided); for each instance of non-compliance report the following:
         a. Unique identifier of the stakeholder(s) associated with the non-compliance event or deviation to enable tracking over time
         b. Source of the non-compliance data
         c. Results of the root cause analysis
         d. Action(s) taken in response and whether any follow-up is planned
      4. Number and type of pharmacy decertified and the reason for decertification
      5. Summary of annual compliance reports provided to VIVUS by corporate chains, mail order pharmacies, and contracted distributors

c. 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
   i. Pharmacist Materials Distribution Survey
      1. 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

Health Outcomes and/or Surrogates of Health Outcomes

4. **Safety Surveillance**
   a. Summary of pregnancy cases associated with Qsymia, including the following:
      i. Event identification number
      ii. Source of the report
      iii. Contraceptive methods used
      iv. Pregnancy outcome
      v. Age of patient

vi. Cases of congenital malformations for each exposed pregnancy

b. Follow-up of outstanding pregnancy reports from the previous assessment reporting period
c. Root cause analysis of each reported pregnancy to determine the reason the REMS failed to prevent the pregnancy exposure; the root cause analysis should include patient interviews as a component. Include the protocol utilized to conduct this root cause analysis
d. Overall summary and discussion of whether the data warrants further detailed assessment, labeling changes, and/or communication.

Knowledge

5. Evaluation of Knowledge of the Qsymia REMS and Risks of Qsymia
   a. An assessment of patients of reproductive potentials' understanding of:
      i. Increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts) and of being small for gestational age (SGA), in a fetus exposed 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
      iv. The receipt, reading, and understanding by patients of reproductive potential of the Qsymia Medication Guide and Risk of Birth Defects with Qsymia patient brochure
      v. Patients of reproductive potential receipt of counseling about pregnancy prevention and effective contraceptive use including:
         1. Counseling provider (i.e., prescriber, office nurse, pharmacist)
         2. Duration of time spent counseling
         3. Frequency of patient counseling (each visit while receiving Qsymia; first time prescribed Qsymia)
   b. An assessment of pharmacists' understanding of:
      i. Increased risk of embryo-fetal toxicity with major congenital malformations, including but not limited to cleft lip and/or cleft palate (oral clefts), and of being small for gestational age (SGA), in a fetus exposed 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
      iv. 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

6. 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 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.

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 NDA 022580

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

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

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
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Medication Guide
- 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
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