NDA 217684/S-001

SUPPLEMENT APPROVAL

Pyros Pharmaceuticals, Incorporated
Attention: Raenel Gibson, RAC
Regulatory Affairs Executive Director
2001 Route 46, Suite 310
Parsippany, NJ 07054

Dear Raenel Gibson:

Please refer to your supplemental new drug application (sNDA) dated and received July 16, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vigafyde (vigabatrin) oral solution.

This Prior Approval sNDA provides for proposed modifications to the approved Shared System (SS) REMS for vigabatrin, of which Vigafyde (vigabatrin) is a member.

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 Shared System (SS) REMS for vigabatrin products, of which Vigafyde is a member, was originally approved on April 27, 2017, and the most recent REMS modification was approved on June 17, 2024. The SS REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your proposed modifications to the REMS consist of:

- REMS Document
  - Changes to align with the REMS Document Technical Conformance Guide
  - Changes to the audit requirements for pharmacies and wholesalers-distributors

- REMS Materials
  - Global changes to materials
    - Updates to align with changes to the REMS Document
  - Patient Guide
    - Change the name of material from “What You Need to Know About Vigabatrin Treatment: A Patient Guide” to “Patient Guide”
    - Remove instructions to healthcare providers

Your proposed modified REMS, submitted to Drug Master File (DMF) (b) (4) on July 12, 2024, amended and appended to this letter, is approved.

This shared system REMS, known as the Vigabatrin SS REMS, currently includes products listed on the FDA REMS website.[1]

Other products may be added in the future if additional NDAs or ANDAs are approved.

The timetable for submission of assessments of the REMS remains the same as that approved on October 12, 2022.

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 (where applicable), unless otherwise noted.

Program Implementation and Operations

1. REMS Certification and Enrollment

    a. Certification of healthcare providers (HCPs)

        i. Number of new certifications of HCPs stratified by degree and specialty indicating whether previously certified or not.

        ii. Number of active HCP (have prescribed vigabatrin at least once during the reporting period) in outpatient pharmacy settings stratified by degree and specialty.

    b. Certification of pharmacies

        i. Number of new certified inpatient and outpatient pharmacies.

        ii. Number of active certified outpatient pharmacies (have filled or ordered at least one prescription for vigabatrin during the reporting period).

        iii. For certified inpatient pharmacies, the number of orders shipped during the assessment period.

    c. Patient enrollment

        i. Number of new patients enrolled stratified by age groups.

[1] https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm

ii. Number of active patients (have received at least one shipment of vigabatrin during the reporting period) in outpatient pharmacy settings stratified by age groups.

2. REMS Utilization

   a. Number of prescriptions by patient age for each reporting period and cumulatively.

   b. Number of prescriptions by pharmacy type for each reporting period and cumulatively.

3. REMS Infrastructure and Performance (per reporting period)

   a. Vigabatrin REMS Contact Center

      i. Number of contacts by stakeholder type (patient/parent/legal guardian, prescriber, pharmacy, other).

      ii. Summary of frequently asked questions (FAQ) by stakeholder type.

         1) Adverse events should be a separate category.

         2) Complaints/concerns about the REMS should include a description of the complaint/concern.

4. REMS Compliance

   a. Audits: Summary of audit findings for audits conducted during the reporting period by pharmacy type, including any corrective and preventive actions (CAPA).

   b. Number of prescribers and pharmacies de-certified and reasons for decertification.

   c. Number and percentage of outpatient prescriptions written by a certified prescriber.

   d. Number and percentage of patients who received vigabatrin from an outpatient pharmacy who are enrolled.

   e. Number and percentage of patients who received vigabatrin from an inpatient pharmacy who are enrolled.

   f. For vigabatrin prescriptions dispensed that were written by non-certified prescribers or for non-enrolled patients, a root-cause analysis of each event, including associated unique pharmacy number, actions taken to prevent

future occurrences (e.g., provision of educational program materials, prescriber became certified), and a monitoring plan to determine the success of actions taken.

g. Number of inpatient pharmacies that continued to dispense vigabatrin beyond 15 days of inpatient admission without properly documenting that a certified prescriber authorized continuing vigabatrin for an enrolled patient.

h. Number and percentage of patients who received vigabatrin beyond 15 days of an inpatient admission who had therapy authorized by a certified prescriber.

i. Number of prescriptions dispensed by non-certified pharmacies, a root-cause analysis of each event, including associated unique pharmacy number; actions taken to prevent future occurrences (e.g., provision of educational program materials, pharmacy staff re-education), and a monitoring plan to determine the success of actions taken.

j. Number of times certified pharmacies either bypassed REMS authorization processes and dispensed vigabatrin OR did not receive authorization from the REMS to dispense the drug but dispensed it anyway.

k. Number of shipments sent to non-certified pharmacies, sources of report, and actions taken to prevent future occurrences.

l. Summary of any additional non-compliance, source of report, resulting corrective and preventive actions (CAPA).

Knowledge

5. Evaluation of knowledge through Knowledge, Attitude and Behavior (KAB) surveys (per reporting period)

    a. Prescribers

        i. An evaluation of stakeholder knowledge of certified prescribers of the increased risk of vision loss, the need to counsel patients and parents/legal guardians about the risk, and the need for periodic visual monitoring.

        ii. An evaluation of prescriber practice or behavior with regards to:

            1) Counseling patients and parents/legal guardians about the increased risk of vision loss, and the need for periodic visual monitoring.

            2) Documentation of counseling.

3) Mitigation of potential vision loss (such as referring patients for periodic vision monitoring).

b. Patients

i. An evaluation of knowledge of patients or parents/legal guardians of the increased risk of vision loss, and the need for periodic visual monitoring.

ii. An evaluation of patients' or parents'/legal guardians' recall of counseling by prescriber on the risk of vision loss and the need for periodic visual monitoring as well as patients' recall of the frequency of their vision monitoring.

Overall Assessment of REMS Effectiveness

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 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 217684 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 217684 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR NDA 217684 / S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217684 / S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR NDA 217684 / 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 217684 / 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 217684

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.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

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, contact Josephine Little, Regulatory Project Manager, via email at Josephine.Little@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Alice T.D. Hughes, MD
Deputy Director for Safety
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- 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/

ALICE HUGHES
09/12/2024 07:53:59 AM