NDA 217684

NDA 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 new drug application (NDA) dated and received on August 17, 2023, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vigafyde (vigabatrin) oral solution.

This NDA provides for the use of Vigafyde (vigabatrin) oral solution as monotherapy for the treatment of infantile spasms in pediatric patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.

APPROVAL & LABELING

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

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 Prescribing Information, Instructions for Use, and Medication Guide) 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 *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

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

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on June 6, 2024, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217684**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Vigafyde (vigabatrin) oral solution shall be 24 months from the date of manufacture when stored at 20°C to 25°C.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Vigafyde to ensure the benefits of the drug outweigh the risk of vision loss associated with vigabatrin.

Your proposed REMS must also include the following:

Elements to assure safe use: Pursuant to 505-1(f)(1), we have determined that Vigafyde can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risk of vision loss associated with vigabatrin listed in the labeling of the drug.

Your REMS includes the following elements to mitigate this risk:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies, practitioners, or health care settings that dispense the drug are specially certified
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions

Implementation System: The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure safe use (outlined above) that require pharmacies, practitioners, or health care settings that dispense the drug be specially certified and the drug be dispensed to patients with documentation of safe use conditions.

You propose to use a shared system for the elements to assure safe use and the REMS assessments. This shared system, known as the Vigabatrin REMS, includes the products listed on the FDA REMS website available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm.

Your proposed REMS, submitted on August 17, 2023, amended, and appended to this letter, is approved.

The REMS consists of elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Vigafyde into interstate commerce.

The 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.

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 Program 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 program 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 regard 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success.

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)**

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). 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, proposed 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 the 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 a REMS modification*, provide a rationale for why the REMS does not need to be modified.

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 REVISION 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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

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

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[6].

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}

Paul R. Lee, MD, PhD, MA
Director (Acting)
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use
- REMS

[6] https://www.uspnf.com/

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/

PAUL R LEE
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