CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEUROSCIENCE
DIVISION of NEUROLOGY 2 (DN2)

NDA #: 217684
Products: Vigafyde (vigabatrin) oral solution
APPLICANT: Pyros Pharmaceuticals, Incorporated
FROM: Alice T.D. Hughes, M.D.
DATE: June 17, 2024

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (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 [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;

(B) The seriousness of the disease or condition that is to be treated with the drug;

(C) The expected benefit of the drug with respect to such disease or condition;

(D) The expected or actual duration of treatment with the drug;

(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;

(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS that includes elements to assure safe use is necessary for Vigafyde (vigabatrin) oral solution to ensure that the benefits of the drug outweigh the risk of vision loss associated with vigabatrin. In reaching this determination, we considered the following:

A. Estimates of the incidence and prevalence of infantile spasms vary. It has been estimated that infantile spasms have an incidence of 1.6 to 4.5 per 10,000 live births.[1,2,3,4]

   A systematic review and meta-analysis estimated a pooled incidence of infantile spasms in the United States of 0.134/1000 live births (95% CI 0.076–0.225),[5] or approximately 491 infants born in the United States each year (based on number of live births in 2022[6]).

B. Infantile spasms are an age-specific epileptic disorder of infancy and early childhood. Children with infantile spasms have an elevated mortality rate and are at risk for the development of difficult-to-control epilepsy and long-term neurodevelopmental disability. Some children with infantile spasms, however, have a favorable long-term outcome with seizure freedom and good cognitive outcomes.[7]

C. The efficacy of Vigafyde for infantile spasms was established by demonstration of bioequivalence to the listed drug Sabril. The efficacy and safety of Sabril was demonstrated in two multicenter trials. In Study 1A, patients were randomized to receive either low-dose (18-36 mg/kg/day, n=114) or high-dose (100-148 mg/kg/day, n=107) vigabatrin. Seventeen patients in the high dose group achieved spasm freedom (the primary endpoint) compared with 8 patients in the low dose group. This difference was statistically significant (p=0.0375). Study W019 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial consisting of a pre-treatment (baseline) period of 2-3 days, followed by a 5-day double-blind treatment phase during which patients were treated with vigabatrin (initial dose of 50 mg/kg/day with titration allowed to 150 mg/kg/day) or placebo. Although no statistically significant reduction in seizures was observed in the primary endpoint of seizure freedom over a 2-hour EEG epoch, a trend was noted. When a longer 24-hour window was examined, using clinical observation as an endpoint, a statistically significant (p=0.030) difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) was observed.

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[1] Trevathan E et al. The descriptive epidemiology of infantile spasms among Atlanta children. Epilepsia. 1999;40(6):748.
[2] Sidenvall R, Eeg-Olofsson O. Epidemiology of infantile spasms in Sweden. Epilepsia. 1995;36(6):572.
[3] Lúthvígsson P et al. Epidemiologic features of infantile spasms in Iceland. Epilepsia. 1994;35(4):802.
[4] Pellock JM et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51(10):2175.
[5] Jia et al. Latitudinal differences on the global epidemiology of infantile spasms:systematic review and meta-analysis. Orphanet Journal of Rare Diseases (2018) 13:216.
[6] In 2022, a total of 3,667,758 births occurred in the United States. From National Vital Statistics Reports. 2024; 73 (2).
[7] Riikonen R. Infantile Spasms: Outcome in Clinical Studies. Pediatric Neurology 108 (2020) 54-64.

D. If approved for infantile spasms, treatment with Vigafyde is expected for up to 2 years in patients who show clinical benefit. The Vigafyde Prescribing Information will recommend that Vigafyde be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within two to four weeks of initiation, or sooner if treatment failure becomes obvious, because of the risk of vision loss.

E. Vigafyde is associated with a risk of vision loss. In adults, vigabatrin causes progressive permanent bilateral concentric vision loss in 30 percent or more of patients. Vision loss can range in severity from mild to severe, including tunnel vision to within about 10 degrees of visual fixation, which can result in disability. It also appears that close monitoring can limit damage in many (but not all) cases. Vigabatrin can sometimes damage the central retina and may decrease visual acuity; therefore, visual acuity should also be monitored. The time to onset of vision loss from vigabatrin is unpredictable. It can occur within weeks of starting treatment or may occur long after treatment begins, even after months or years. Monitoring throughout use is therefore essential.

   Permanent vision loss may also occur in infants and children treated with vigabatrin, but assessing visual field defects is especially difficult in children, and the frequency and extent of vision loss in infants and children is poorly characterized. In infants and children, vision loss may not be detected until it is severe. Nonetheless, monitoring vision in this population is recommended. The onset and progression of vision loss from vigabatrin is unpredictable, and it may occur or worsen between assessments. Once detected, vision loss due to vigabatrin is not reversible. It is expected that even with frequent monitoring, some patients treated with vigabatrin will develop severe vision loss. It is possible that vision loss can worsen despite discontinuation of vigabatrin.

F. Vigafyde is not a new molecular entity.

The elements of the REMS will be elements to assure safe use (ETASU), including that healthcare providers have particular experience or training, or are specially certified, that pharmacies, practitioners, or health care settings that dispense the drug are specially certified, and that the drug is dispensed to patients with evidence or other documentation of safe-use conditions, an implementation system, and a timetable for submission of assessments of the REMS.

The shared system Vigabatrin REMS was approved on April 27, 2017. Upon approval, Vigafyde will be joining this shared system 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
06/17/2024 08:55:41 AM

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	217684
PDUFA Goal Date	June 17, 2024
Nexus TTT#	2023-6030
Reviewer Name(s)	May L. Chan-Liston, PharmD, MPH, Risk Management Analyst (DRM) Anahita Tavakoli, MA, Health Communication Analyst (DRM) Judine Berlus, PharmD, MPH, REMS Assessment Analyst (DMAMES)[a]
Team Leader(s)	Barbara Bergquist, PharmD (DMAMES) Jacqueline Sheppard, PharmD (DRM)
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	June 14, 2024
Subject	REMS Review
Established Name	Vigabatrin
Trade Name	Vigafyde
Name of Applicant	Pyros Pharmaceuticals, Inc.
Therapeutic Class	antiepileptic
Formulation(s)	oral solution, 100 mg/mL
Dosing Regimen	Infantile Spasms Initiate at a daily dose of 50 mg/kg (25 mg/kg twice daily); increase total daily dose every 3 days, in increments of 25 mg/kg/day to 50 mg/kg/day, up to a maximum daily dose of 150 mg/kg (75 mg/kg twice daily).

[a]DMAMES: Division of Mitigation Assessment and Medication Error Surveillance

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Vigafyde (vigabatrin) New Drug Application (NDA) 217684 submitted by Pyros Pharmaceuticals, Inc. (hereafter referred to as the Applicant) on August 17, 2023 and last amended June 13, 2024. Vigafyde is being proposed as a 505(b)(2) product with a new dosage form (100 mg/mL oral solution) of vigabatrin. The reference listed drug is Sabril (vigabatrin), NDA 022006.

Vigafyde is an antiepileptic proposed for 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. This application is under review in the Office of New Drugs in the Division of Neurology 2 (DN2).

All approved vigabatrin products use the Vigabatrin Shared System (SS) REMS to mitigate the risk of vision loss and the Applicant intends to have Vigafyde join the Vigabatrin SS REMS upon approval. In order to incorporate Vigafyde into the SS REMS, information pertaining to Vigafyde's indication, drug concentration, and dosing and administration are being added to the Vigabatrin SS REMS. These changes do not affect the goals or the requirements of the Vigabatrin SS REMS. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The REMS ETASU include prescriber certification (ETASU A), pharmacy certification (ETASU B), and documentation of safe use conditions (ETASU D).

The proposed Vigabatrin REMS submitted on June 13, 2024 is acceptable for approval. The REMS proposed by the Applicant will replace the Vigabatrin SS REMS upon approval of Vigafyde. The Vigabatrin SS REMS uses a Type V Drug Master File (DMF) 034825 with the Vigabatrin REMS Group (VRG) for which Pyros is already a member. The VRG will need to submit a REMS modification to align with the updates in the Vigabatrin SS REMS. If Vigafyde is approved, the Agency will issue a REMS Modification Notification Letter to the Vigabatrin SS REMS members to get the SS REMS into full compliance.

This review also includes the Division of Mitigation Assessment and Medication Error Surveillance's (DMAMES) evaluation of the proposed REMS Assessment Plan. DMAMES found that the proposed REMS Assessment Plan aligns with the approved Vigabatrin SS REMS Assessment Plan and is acceptable.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Vigafyde (vigabatrin), NDA 217684, a 505(b)(2) product, submitted by Pyros Pharmaceuticals, Inc. (hereafter referred to as the Applicant) on August 17, 2023. The reference listed drug is Sabril (vigabatrin), NDA 022006.[1]

Vigafyde is an antiepileptic proposed for 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. This application is under review in the Office of New Drugs in the Division of Neurology 2 (DN2).[2]

Vigabatrin products approved for infantile spasms are subject to the Vigabatrin Shared System (SS) REMS to mitigate the risk of vision loss. The Applicant proposes to have Vigafyde join the Vigabatrin SS REMS upon approval.[1]

2. Background

2.1. Product Information

Vigafyde (vigabatrin) is an antiepileptic drug with an unknown precise anti-seizure mechanism. Vigabatrin is believed to have its action due to its irreversible inhibition of γ-aminobutyric acid transaminase (GABA-T), the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA which leads to increased levels of GABA in the central nervous system.[2,3]

Vigafyde is proposed as a solution of 100 mg/mL of vigabatrin intended for oral use only. Compared to other reconstituted solutions of vigabatrin powder for oral solution (50 mg/mL), Vigafyde is a concentrated solution and the required volume of Vigafyde solution dosed for patients will be lower than previously prescribed vigabatrin oral products. Vigafyde does not require additional reconstitution or dilution prior to administration.[3]

2.2. Vigabatrin REMS

2.3. Regulatory History

The following is a summary of the regulatory history for NDA 217684 relevant to this review:

- 08/08/2023: The Applicant communicated that they intend on submitting a stand-alone REMS due to medication errors risk in addition to the risk of vision loss due to vigabatrin. The Applicant was advised in a pre-submission Type C WRO (Written Responses Only) communication that even though a stand-alone REMS to mitigate the risks of vision loss and medication errors could be proposed, it would be possible to include the Applicant's product in the Vigabatrin Shared System (SS) REMS.
- 08/17/2023: The Applicant submitted NDA 217684 for monotherapy for pediatric patients with infantile spasms one month to two years of age. The submission included a stand-alone REMS proposal (single-product REMS). The REMS proposal was to mitigate the risks of vision loss and potential medication errors. The Applicant also communicated they were amenable to having their NDA product join the approved Vigabatrin SS REMS.[1,2]
- 12/20/2023: An Information Request was sent to the Applicant stating that the potential medication error risk due to the differences in the concentration between Vigafyde (vigabatrin oral solution, 100 mg/mL) and the approved vigabatrin for oral solution (50 mg/mL following reconstitution) did not need to be identified as a specific risk in the REMS. However, the differences in the concentrations of Vigafyde and vigabatrin for oral solution can be included in REMS materials.[4]
- 01/05/2024: The Applicant communicated that they reached out to the Vigabatrin REMS Group (VRG) of the Vigabatrin SS REMS and proposed to amend the REMS submission for NDA 217684 with proposed edits/updates to the Vigabatrin SS REMS documents. The Applicant intends on providing the proposed updates to the Vigabatrin REMS Group (VRG) for review.[5]
- 02/12/2024: The Agency sent an IR agreeing that the Applicant may submit the proposed updated Vigabatrin SS REMS amendment to NDA 217684. The Applicant was informed they may choose to update and reach agreement with the VRG with any proposed modifications to the Vigabatrin SS REMS.[6]
- 03/14/2024: The Applicant submitted a REMS amendment that updated the REMS document and incorporated the Vigafyde indication statement and dosing information into the REMS Materials.[7]

- 05/09/2024: Updated labeling was provided to the Applicant.[8]

- 05/28/2024: Interim REMS comments were sent to the Applicant. The comments consisted of revising the REMS Document to conform to the *REMS Format Technical Guidance Document* by including sections on risk and required ETASU. In addition, the Applicant was requested to include clarifying indication statements and dosing and administration information for the approved vigabatrin for oral solution products to the *Patient Guide* and *REMS Website*.[9]

- 05/30/2024: The Applicant sent an email stating that they are concerned that the VRG may not be able to review and approve the FDA requested changes sent on May 28, 2024. The Applicant requests to only update the REMS Document and Materials with the FDA changes that the Applicant deems may be made without VRG consortium approval.[10]

- 05/31/2024: An IR response was sent to the Applicant agreeing that the Applicant may proceed with their planned REMS amendment submission and that the Applicant provide anticipated timelines to obtain VRG consortium approval on deferred updates to REMS materials.[11]

- 06/03/2024: The Applicant submitted a REMS amendment that only included changes necessary to incorporate Vigafyde into the SS REMS. These included updates to the indication statements and dosing information of vigabatrin oral solution products into the REMS Materials. The Applicant stated that the other outstanding FDA edits will be discussed at a VRG consortium meeting on June 10, 2024.[12]

- 06/12/2024: REMS comments were sent to the Applicant requesting revisions to the proposed REMS Website. The materials currently include the old indication statement section (obsolete) and well as the revised indication statement section.[13]

- 06/13/2024: The Applicant submitted a REMS amendment that updated the REMS Website.[14]

3. Benefit Assessment

Vigafyde (vigabatrin), based on the similarities to Sabril (vigabatrin) for oral solution, was submitted as a 505(b)(2) product. Because the reference product and the proposed Vigafyde product are both solutions at the time that they are administered to patients, the Applicant requested a waiver of in-vivo Bioavailability Studies. The Biopharmaceutics Review Team concluded from the submitted data that the proposed drug product does not have a significant impact of differences in dosing volumes, osmolality results, and excipients. Therefore, the Applicant was granted a waiver of in-vivo Bioavailability Studies. This waiver allows the Vigafyde application to rely on FDA's previous findings of safety and efficacy along with applicable literature to act as a bridge to Sabril (vigabatrin) for oral solution as the Reference Listed Drug (RLD).[3,15]

4. Risk Assessment & Safe-Use Conditions

4.1. Vision Loss

As a product that contains vigabatrin, Vigafyde will be subject to a REMS intended to mitigate the risk of vision loss and to inform participants of the need for periodic visual monitoring.

Since the proposed indication (treatment of infantile spasms) and proposed dosage of Vigafyde is the same for the already approved Vigabatrin for oral solution, the risks addressed by the Vigabatrin SS REMS apply equally to the proposed product and to the currently approved product.[3,15]

5. Expected Postmarket Use

Vigafyde is seeking approval for the treatment of infantile spasms. The Applicant is not seeking indication for the treatment of patients with refractory complex partial seizures. Due to the complex nature of the proposed indication, it is expected that Vigafyde (similar to other vigabatrin products) will be prescribed by specialists such as neurologists and epileptologists. As Vigafyde is provided as a different concentration, caregivers who switch from one formulation to another should be counseled on the differences between the products and given instructions on appropriate administration.

6. Risk Management Activities Proposed by the Applicant

6.1. Review of the Applicant's Proposed REMS

The Vigabatrin SS REMS was approved on April 27, 2022. The Applicant intends for Vigafyde to join the SS REMS upon NDA approval. The Applicant proposed the Vigabatrin SS REMS with additional clarifying indication statements and dosing and administration information for the approved vigabatrin oral solution products. The Applicant's amended proposed REMS submitted on June 13, 2024 is the subject of this review.

6.1.1. REMS Goals

The goal of the Vigabatrin REMS Program is to mitigate the risk of vision loss associated with vigabatrin by:

1. Ensuring that healthcare providers are educated about the risk of vision loss, the need to counsel patients about the risk, and the need for periodic visual monitoring.

2. Ensuring that vigabatrin is only dispensed to patients with documentation that patients are informed about the risk of vision loss associated with vigabatrin and the need for periodic visual monitoring.

Reviewer Comment: *The REMS goal and objectives in the REMS Document are acceptable and are the same as in the Vigabatrin REMS.*

6.1.2 REMS Document

The Applicant proposed changes to the REMS Document included updating the requirement to make the REMS website fully operational and REMS materials available within 90 calendar days of the REMS modification approval. No other changes were made.

Reviewer Comment: *The REMS Document is acceptable.*

6.1.3 REMS Elements

The required elements remain the same as those in the approved Vigabatrin SS REMS:

- Healthcare providers who prescribe the drug are specially certified. (ETASU A)

- Pharmacies that dispense the drug are specially certified. (ETASU B)
- The drug is dispensed to patients with evidence or other documentation of safe-use conditions (ETASU D)

ETASU A: Prescriber Certification

Healthcare providers who prescribe Vigafyde must become certified in the Vigabatrin REMS. To become certified to prescribe, each prescriber must review the prescribing information and enroll in the REMS by submitting a completed P*rescriber Enrollment and Agreement Form* to the REMS.

Before a patient initiates treatment, prescribers must agree to counsel the patient on the risks associated with vigabatrin, including vision loss, and the need for periodic visual monitoring, provide the patient with the *Patient Guide*, and enroll the patient by completing and submitting the *Patient/Parent/Legal Guardian-Physician Agreement Form* to the REMS. Prescribers must assess the patient's vision including ophthalmologic assessments described in the prescribing information and prescribers are required to report the REMS adverse events suggestive of vision loss.

ETASU B: Pharmacy Certification

Pharmacies (outpatient and inpatient) that dispense Vigafyde must become certified in the Vigabatrin REMS.

To become certified to dispense Vigafyde, outpatient and inpatient pharmacies must designate an authorized representative who will carry out the certification process and oversee implementation and compliance with the REMS on behalf of the pharmacy. The authorized representative must enroll in the REMS by submitting the *Pharmacy Enrollment Form* to the REMS and train all relevant staff involved in dispensing on the REMS requirements. Certified pharmacies must comply with audits carried out by Vigabatrin Applicants, or a third party acting on behalf of the Vigabatrin Applicants to ensure that all processes and procedures are in place and are being followed.

Certified inpatient pharmacies, in addition, must establish processes and procedures to verify the patient is enrolled in the REMS before dispensing and to verify that within 15 days of inpatient admission, a certified prescriber authorizes continuing treatment for an enrolled patient. Inpatient pharmacies must not dispense more than a 15 days' supply.

ETASU D: Documentation of Safe Use

Vigafyde is dispensed to patients with evidence or other documentation of safe-use conditions. Before dispensing Vigafyde, certified outpatient pharmacies obtain authorization to dispense each prescription by contacting the REMS to verify the prescriber is certified. Certified inpatient pharmacies must verify the patient is enrolled and document the patient identification number through the processes and procedures established as a requirement of the REMS. Within 15 days of inpatient admission, they must also obtain authorization to continue dispensing by contacting the REMS to verify (and document the patient identification number and authorization code) that a certified prescriber authorizes continuing vigabatrin for an enrolled patient.

Reviewer Comment: *The proposed elements remain the same as the Vigabatrin SS REMS.*

6.1.4. Implementation System

The proposed REMS Document states that the *REMS Website* must be operational and all REMS materials available through the *Vigabatrin REMS Website* or REMS Coordinating Center within 90 calendar days of the REMS modification approval.

Reviewer Comment: *The proposed REMS Implementation System is acceptable.*

6.1.5. Timetable for Submission of Assessments

The Applicant proposed to submit REMS Assessments every two years beginning on 4/27/2022.

Reviewer Comment: *The Applicant's proposed timetable for submission of REMS assessments is the same as the approved Vigabatrin SS REMS and is acceptable.*

6.1.6. REMS Materials

The following materials in the proposed Vigabatrin REMS are unchanged from the currently approved SS REMS: *Patient/Parent/Legal-Guardian-Physician Agreement Form* and *Pharmacy Enrollment Form*. Only the REMS materials with proposed changes are described below.

6.1.6.1. Prescriber Enrollment and Agreement Form

The Applicant proposed to remove the indications that apply to currently approved vigabatrin products.

Reviewer Comment: *The proposed Prescriber Enrollment and Agreement Form is acceptable.*

6.1.6.2. Patient Guide

The Applicant added indication statements, which include: a) the Infantile Spasm (IS) and Refractory Complex Partial Seizures (CPS) indications for Sabril (vigabatrin) and its approved generics and b) the IS indication for Vigafyde. Content within the *Patient Guide* was revised to include and align with Vigafyde labeling. This includes instructions for caregivers to administer Vigafyde to infants and to further describe the differences in the oral solution concentrations between Vigafyde and other approved vigabatrin oral solution products.

Reviewer Comment: *The proposed Patient Guide is acceptable.*

6.1.6.3. REMS Website

The Applicant revised the indication statements to include: a) the Infantile Spasm (IS) and Refractory Complex Partial Seizures (CPS) indications for Sabril (vigabatrin) and its approved generics and b) the IS indication for Vigafyde.

Reviewer Comment: *The proposed REMS Website is acceptable.*

7. REMS Supporting Document

The REMS Supporting Document, last amended on June 3, 2024, contains information on stakeholders' responsibilities in the REMS, how they carry out those responsibilities, and how the REMS will be implemented. The Supporting Document also includes the REMS Assessment Plan.

The Applicant included the Vigafyde product information and differences in concentration with the currently approved vigabatrin for oral solution products. The Applicant also updated the requirement to make the *REMS Website* fully operational and the REMS materials available within 90 calendar days of the REMS modification approval.

7.1. REMS Assessment Plan

The proposed REMS Assessment Plan is the same as the approved Vigabatrin SS REMS Assessment Plan. The REMS Assessment Plan includes metrics that fall within the assessment categories of Program Implementation and Operations, Knowledge, and an Overall Assessment of the REMS Effectiveness.

Reviewer Comments: The proposed REMS Assessment Plan is acceptable. The REMS Assessment Plan is in Appendix 11 and will be included in the approval letter.

8. Discussion

Infantile Spasms are a rare type of epilepsy that can lead to significant and severe cognitive impairment. Vigafyde is being proposed for use in pediatric patients as a 100 mg/mL oral solution which allows dosing using a smaller volume of fluid as compared to other vigabatrin products. The clinical reviewer recommends approval of Vigafyde based on the efficacy and safety information provided in the application.[15]

Upon approval, Vigafyde will join the Vigabatrin SS REMS. The goal of the Vigabatrin SS REMS Program is to mitigate the risk of vision loss. All approved vigabatrin products carry the same risks and therefore are subject to the same REMS requirements. The Applicant's proposed REMS consists of elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments.

The concentration of the Vigafyde oral solution (100 mg/mL) is twice the concentration of the already approved vigabatrin for oral solution products (50 mg/mL following reconstitution). Although DRM and DN2 determined that the potential risk of medication errors due to the difference in concentration between Vigafyde and other approved vigabatrin for oral solution products did not require a REMS to mitigate this risk, the team determined that it would be prudent to acknowledge the differences in the concentrations between Vigafyde and the other approved vigabatrin oral solution products in the REMS materials. One other difference between Vigafyde and the other vigabatrin products is that the Applicant is not seeking the complex partial seizures indication.

The REMS materials have been updated to address the difference in indication statement and dosing and administration. Within Vigafyde product labeling, the following sections provide dosing information and administration instructions for the prescriber: *Important Dosing and Administration Instructions, Switching Between Other Vigabatrin Products*, and *Patient Counseling Information*. The Vigafyde Medication Guide and Instructions for Use also provide dosing information and administration instructions in lay language for caregivers of patients. This caregiver-directed language was also included in the REMS *Patient Guide*.

During the course of this review, DRM and DMAMES directed the Applicant to update the REMS with revisions that enhance readability and functionality but are not necessary for the safe use of Vigafyde. These changes included updating the requirement of annual auditing of wholesalers-distributors that have made at least one commercial distribution in the previous 12 months and aligning the REMS Document and subsequent REMS Materials with FDA Technical Guidance "*Format and Content of a REMS Document: Guidance for Industry*." Due to the inability of the Applicant to obtain VRG consortium approval to incorporate these changes prior to the scheduled action date of this submission, the Agency agreed to delay the incorporation of the updates until the next Vigabatrin SS REMS modification, post-NDA approval.

The proposed Vigabatrin REMS submitted by the Applicant, if approved, will become the approved Vigabatrin REMS. The Vigabatrin SS REMS uses a Type V Drug Master File (DMF) 034825 with the

Vigabatrin REMS Group (VRG) for which the Applicant is already a member. Shortly after the approval of Vigafyde, the Agency will issue a REMS Modification Notification Letter to the Vigabatrin SS REMS members to get the SS REMS into full compliance. The VRG members will be directed to submit their proposed modified REMS to DMF 034825 as a cross-reference submission, Changes-Being-Effected 30 days (CBE-30) supplement, to their individual applications.

9. Conclusion & Recommendations

DRM finds the proposed Vigabatrin REMS to be acceptable and recommends approval of the REMS as submitted on June 13, 2024.

10. References

1. Pyros Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Vigafyde (vigabatrin). August 17, 2023.
2. Pyros Pharmaceuticals, Inc. Proposed Prescribing Information for Vigafyde (vigabatrin). August 17, 2023.
3. Pyros Pharmaceuticals, Inc. Clinical Overview: Vigabatrin Oral Solution 100 mg/mL. August 17, 2023.
4. Little, Josephine. Information Request. December 20, 2023.
5. Little, Josephine. Information Request Response from Pyros Pharmaceuticals, Inc. January 5, 2024.
6. Little, Josephine. Information Request. February 12, 2024.
7. Pyros Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Vigafyde (vigabatrin) amendment. March 14, 2024.
8. Little, Josephine. Division of Neurology I. Labeling Discussion Comments. May 9, 2024.
9. Chan-Liston, May. Division of Risk Management. REMS Review Interim Comments. May 28, 2024.
10. Pyros Pharmaceuticals, Inc. REMS Correspondence. May 30, 2024.
11. Little, Josephine. Information Request. May 31, 2024.
12. Pyros Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Vigafyde (vigabatrin) Amendment. June 3, 2024.
13. Little, Josephine. REMS Review Interim Comments. June 12, 2024.
14. Pyros Pharmaceuticals, Inc. Risk Evaluation and Mitigation Strategy for Vigafyde (vigabatrin) Amendment. June 13, 2024.
15. VanLandingham, Kevan. Division of Neurology 2. Vigafyde NDA 217684 Draft Clinical Review. June 14, 2024.

11. Appendix

REMS Document

Prescriber Enrollment and Agreement Form

Patient/Parent/Legal-Guardian-Physician Agreement Form

Pharmacy Enrollment Form

Patient Guide

REMS Website

REMS Assessment Plan

25 Page(s) of Draft REMS have been Withheld in Full as B4 (CCI/ TS) immediately following this page

Vigabatrin REMS Assessment Plan

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 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.

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/

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