CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	June 17, 2024
From	Philip H. Sheridan, MD Paul R. Lee, MD, PhD, MA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	NDA 217684
Applicant	Pyros Pharmaceuticals, Inc.
Date of Submission	August 17, 2023
PDUFA Goal Date	June 17, 2024
Proprietary Name	Vigafyde
Established or Proper Name	Vigabatrin Oral Solution
Dosage Form(s)	Oral solution, 100 mg/mL
Applicant Proposed Indication/Population	VIGAFYDE is indicated 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.
Applicant Proposed Dosing Regimen	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)
Recommendation on Regulatory Action	Approval
Recommended Indication/Population	VIGAFYDE is indicated 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.
Recommended Dosing Regimen	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)

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment
This New Drug Application (NDA), which was submitted via the 505(b)(2) pathway, for Vigafyde (vigabatrin oral solution) for the treatment of infantile spasms (IS) in pediatric patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss. This 505(b)(2) NDA does not include efficacy data, and, therefore, the determination of benefit and risk depends on a demonstration of an adequate scientific bridge from Vigafyde to the listed drug (LD), Sabril (vigabatrin powder for oral solution), and on the previous findings of effectiveness and safety for the LD. The FDA determined that an in-vivo bioequivalence and bioavailability study comparing Vigafyde to the LD could be waived based on a rigorous comparison of the constituents of the two drugs. The LD, Sabril, was approved on August 31, 2009, based on two adequate and well-controlled trials and the endorsement of an external advisory committee. Sabril has been marketed in the United States for the treatment of IS since 2009. It is marketed under a risk evaluation and management strategy (REMS) because of retinal toxicity which may cause permanent visual loss. IS is a severe age-specific epilepsy syndrome of infancy and the most common epileptic encephalopathy in this age group. The incidence of IS has been estimated at 0.25 to 0.60 per 1000 live births. IS classically presents with epileptic spasms, hypsarrhythmia on electroencephalography (EEG), and cognitive impairment. There are more than 200 known etiologies for this syndrome; potential etiologies include symptomatic prenatal (e.g., central nervous system congenital malformations, tuberous sclerosis and other neurocutaneous syndromes, chromosomal abnormalities such as trisomy 21, epilepsy-associated genetic variants, and inborn errors of metabolism), symptomatic perinatal (e.g., congenital infection, hypoxia-ischemia, intraventricular hemorrhage, perinatal stroke, sinus venous thrombosis), and symptomatic postnatal (e.g. hypoglycemia and acquired brain injuries). About 10 to 20 % of patients with IS have an unknown (cryptogenic) etiology. The epileptic spasms occur frequently each day and are distressing and disruptive to the basic daily functions of the patients and caregivers. Most antiseizure medications have very limited efficacy in eliminating or even just suppressing the spasms. A successful treatment response, according to the 2004 American Academy of Neurology practice parameters, is defined as complete cessation of spasms confirmed by video-EEG and abolition of hypsarrhythmia on prolonged EEG. The two drugs that have demonstrated efficacy by these criteria and are approved for the treatment of IS are intramuscular ACTH and oral vigabatrin. Both approved treatments have risks of severe adverse reactions (particularly the risk of vision loss associated with vigabatrin due to retinal toxicity), but the benefit of these treatments is regarded as justifying these risks because of the profound neurological and developmental consequences of untreated IS. Factors associated with a better prognosis for patients with IS are a short latency between the onset of spasms and effective treatment, cryptogenic etiology, normal neurodevelopment prior to the onset of spasms, absence of asymmetries on EEG, and a quick and sustained response to treatment. Unfortunately, despite the important relief from the disabling spasms provided by effective treatments, most children with IS will have lifelong cognitive impairment and progress to other seizure syndromes later in childhood, such as Lennox-Gastaut syndrome or focal epilepsy.

Tuberous sclerosis complex is estimated to be the underlying cause of IS in 10 to 30% of patients with IS. For these patients, the efficacy of vigabatrin appears to be superior to that of ACTH.

Based on this benefit-risk assessment, and the demonstration of an adequate scientific bridge, it is recommended that Vigafyde be approved for the treatment of IS in pediatric patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss. However, because of the established risk of visual loss associated with vigabatrin exposure, Vigafyde must be subject to the same REMS as the LD (Sabril) and all generic formulations of vigabatrin.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Infantile spasms (IS) is a severe age-specific epilepsy syndrome of infancy. • The epileptic spasms of IS typically occur frequently each day and are distressing and disruptive of the infant's daily basic functioning. • Early recognition and prompt effective treatment of the spasms soon after their onset are associated with a better prognosis. • The goal of treatment of IS is the complete cessation of spasms, confirmed by video electroencephalogram (EEG), and the abolition of hypsarrhythmia on an EEG.	Early effective treatment gives the infant patient the best chance for eradication or control of the frequent epileptic spasms and for meaningful future neurodevelopment.
Current Treatment Options	Two drugs are currently approved for the treatment of IS: • Vigabatrin oral solution 50 mg/100 ml (proprietary name Sabril) was approved on August 31, 2009, for patients (b) (4) to 2 years of age. • Acthar Gel was approved for the indication of IS on October 15, 2010, for patients (b) (4) to 2 years of age.	Although the syndrome of IS is not responsive to most seizure medications, there are two approved treatments of IS. One of these approved effective treatments is Sabril, the LD for this 505(b)(2) application. There is a continued need for new formulations of effective medications to treat IS especially for patients who may have compliance or tolerability issues with existing formulations.
Benefit	• Efficacy and safety were not directly assessed in the development program for Vigafyde because the Vigafyde NDA submission utilized the 505(b)(2) pathway and relied on the previous findings of safety and effectiveness for the listed drug (LD), Sabril. • Efficacy for Sabril was established on the basis of two adequate and well-controlled studies, and the finding of effectiveness in the treatment of IS was endorsed by an external advisory committee.	Based on adequate scientific bridging of Vigafyde to the LD (Sabril), Vigafyde may rely on the findings of the safety and efficacy of the LD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	➢ Study 1 (N=221) was a multicenter, randomized, low-dose/high-dose, parallel-group study. The primary efficacy endpoint of this study was the proportion of patients who were spasm-free for 7 consecutive days beginning within the first 14 days of vigabatrin therapy. Seventeen patients in the high-dose group achieved spasm freedom compared with 8 patients in the low dose group (p=0.0375). ➢ Study 2 (N=40) was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. No statistically significant differences were observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc efficacy analysis, using a 24-hour clinical evaluation window found a statistically significant difference in the overall percentage of reductions in spasms between the vigabatrin group (68.9%) and the placebo group (17.0%) (p=0.030). • Vigafyde was deemed adequately bridged to the LD per 21 CFR 320.24(b)(6). The FDA determined that an in vivo bioequivalence and bioavailability study comparing Vigafyde to the LD could be waived. The waiver request provided a full discussion of the differences between the LD and Vigafyde including the potential impact of differences in dosing volumes, osmolality results, and excipients.	
Risk and Risk Management	• There were no clinical studies submitted to this NDA; therefore, the primary assessment of safety depends on the previous findings of safety for the LD. • The adverse reaction of greatest concern for vigabatrin is the progressive and permanent bilateral visual field constriction due to retinal toxicity that has been observed in some adults and older children receiving vigabatrin for the treatment of complex partial	Based on adequate bridging to the LD, Sabril, Vigafyde would have the same safety risks as the LD, including the risk of vision loss. As with the LD, the risk of vision loss with Vigafyde is justified because of the serious consequences of untreated IS. Given this potential for vison loss, a REMS is required to ensure that the benefits of Vigafyde outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	seizures. This toxicity could result in permanent vision loss. The marketing of the LD and Vigafyde requires a REMS to mitigate this risk. • Based on post hoc analyses of the two adequate and well controlled safety and efficacy trials for the LD (Sabril) and subsequent reported clinical experience, vigabatrin appears to result in a better treatment response than ACTH for IS associated with tuberous sclerosis complex.	Vigabatrin appears to be the preferred treatment for IS associated with tuberous sclerosis complex.

2. Background

This is a 505(b)(2) application (NDA 217684) for Vigafyde (vigabatrin oral solution) using Sabril (vigabatrin powder for oral solution, NDA 022006) as the listed drug (LD). The proposed indication is 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, which is an indication that the LD Sabril is approved to treat.

The LD, Sabril, has been marketed in the United States since its approval for IS on August 21, 2009. Sabril requires a boxed warning in its labeling and a risk evaluation and mitigation strategy (REMS) because of the risk of vision loss from drug-induced retinal toxicity.

The key regulatory history for Vigafyde is as follows:

- Type B, pre-IND meeting request (Written Response Only [WRO]) to discuss the development plan for PIND 157997 dated November 23, 2021 (WRO issued on January 21, 2022): The Agency informed the Applicant that the proposed product was considered a new dosage form due to the increased concentration compared to that of the LD, Sabril.
- An Initial Pediatric Study Plan that indicated a plan to request a waiver of pediatric studies was received on August 9, 2022, then closed on October 30, 2022, because Orphan Designation had been granted on October 12, 2022).
- Type C meeting request (WRO) received on November 1, 2022 (WRO issued on January 13, 2023): This meeting request included questions related to Chemistry, Manufacturing, and Controls (CMC). The lack of a need for additional nonclinical and clinical data was agreed upon by FDA. FDA did not agree that the results of a human factors (HF) validation study could be used to demonstrate the increased safety/clinical superiority of Vigafyde compared to Sabril because an HF validation study is not comparative in nature.
- Type C meeting request (WRO) under NDA 217684 to obtain feedback on the adequacy of a planned NDA submission, dated May 25, 2023 (WRO issued on August 8, 2023): FDA provided input on the eCTD organization and possible differences in osmolality and bioavailability of the oral solution formulation. The Applicant was again informed that data obtained from a HF study was incapable, by design, of providing an acceptable basis for a claim of clinical superiority over the LD.
- The Applicant submitted NDA 217684 for monotherapy for pediatric patients with infantile spasms one month to two years of age to the FDA on August 17, 2023. The submission included a standalone REMS proposal (single-product REMS). The REMS proposal included risks of vision loss and potential medication errors. The Applicant also communicated they were amenable to having their NDA product join the approved Vigabatrin Shared System REMS.

3. Product Quality

The technical lead for the product quality review team was Dr. Martha Heimann, and the reviewers were Dr. Jeffrey Medwid (drug substance), Dr. Venkateswara Pavuluri (drug product/labeling), Dr. Yan Xu (manufacturing), Dr. Jia Yu (biopharmaceutics), Dr. Susan Tripathi (microbiology), and Erica Keafer (regulatory business process manager).

The Office of Product Quality (OPQ) review team notes that, as both the LD and Vigafyde are solutions when administered to patients, the Applicant could request a waiver of in-vivo bioavailability studies. The waiver request included a full discussion of the differences between the LD and Vigafyde, including the potential impact of differences in dosing volumes, osmolality results, and excipients. The OPQ review team acknowledged the Biopharmaceutics team's review that accepted the waiver request and concluded that the proposed drug product is adequately bridged to the LD per 21 CFR 320.24(b)(6).

The OPQ review team concluded that the Applicant had provided adequate information in NDA 217684 to ensure that the Applicant can consistently manufacture a product that was suitable for use by the intended patient caregivers to treat patients with IS.

The OPQ review team recommends approval of NDA 217684 for Vigafyde (vigabatrin) oral solution 100 mg/ml.

4. Nonclinical Pharmacology/Toxicology

No nonclinical data were submitted in this application; no nonclinical issues arose during review of this application. Therefore, a nonclinical pharmacology/toxicology review was not conducted.

5. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) review was written by Dr. Ramakrishna Samala (primary reviewer) and by Dr. Gopichand Gottipati (secondary reviewer).

The OCP team notes that the Applicant did not conduct any clinical pharmacology studies and instead submitted a biowaiver request, along with supporting justification. Therefore, the OCP team deferred to the Biopharmaceutics team regarding a biowaiver determination to support demonstration of an adequate scientific bridge to the LD.

The Biopharmaceutics review was written by Dr, Jia Leo (primary reviewer), Dr. Ta-Chen Wu (secondary reviewer), and Dr. Okponanabofa Eradiri (tertiary reviewer). While evaluating the waiver request, they noted that the Applicant provided data and justifications that there would be no significant impact on the absorption of vigabatrin by the exclusion of povidone and the inclusion of four new excipients, and that there would be no significant impact on the absorption and bioavailability of vigabatrin due to the higher osmolality of the proposed drug product. The concentration of the active pharmaceutical ingredient, vigabatrin, in Vigafyde is double that in the LD after reconstitution, which explains, at least in part, the osmolality difference. The conclusion of the Biopharmaceutics review team was that the differences in osmolality and some excipients would be unlikely to significantly impact the in vivo absorption and bioavailability of the proposed drug product. Therefore, the Biopharmaceutics review team concluded that the data and information submitted by the Applicant established scientific bridging of Vigafyde to the LD after reconstitution per 21 CFR 320.24(b)(6).

The OCP review team and the Biopharmaceutics review team recommend approval of this NDA submission.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No efficacy data were submitted since the application relies on the previous finding of effectiveness for the LD, Sabril, and on the determination of the comparative bioavailability of Vigafyde to the reconstituted LD. As discussed in Sections 3 and 5 of this review, the Applicant provided adequate evidence that, despite being a different formulation, their vigabatrin product has similar bioavailability to the LD after reconstitution which constitutes an adequate scientific bridge to the reconstituted LD.

8. Safety

Dr. Kevan VanLandingham wrote the clinical safety review of this application. No safety data were submitted since the application relies on the previous finding of safety for the LD, Sabril, and on the determination of the comparative bioavailability of Vigafyde to the reconstituted LD.

Dr. VanLandingham recommends approval of this NDA.

9. Advisory Committee Meeting

There was no advisory committee for this 505(b)(2) application because the efficacy and safety of Vigafyde have been established through determination of the comparative bioavailability to the reconstituted LD (Sabril).

10. Pediatrics

Because Vigafyde has orphan drug designation for the treatment of IS, the Pediatric Research Equity Act (PREA) is not triggered.

11. Other Relevant Regulatory Issues

The Office of Prescription Drug Promotion (OPDP) reviewed the proposed Prescribing Information, as well as the proposed carton and container labeling. The OPDP team provided comments during the labeling negotiations with the Applicant.

OPDP and Division of Medical Policy Programs (DMPP) wrote a combined review for the proposed Medication Guide/Instructions For Use (IFU), and their recommendations were included in the labeling negotiations with the Applicant.

The Division of Medication Error Prevention and Analysis 2 (DMEPA2) review (based on its evaluation of the proposed Prescribing Information, Medication Guide, IFU, and carton/container labeling) provided specific recommendations to include in negotiations with the Applicant.

12. Labeling

Refer to the final negotiated product labeling. The labeling for Vigafyde relies on the previous findings of efficacy and safety for the LD, Sabril. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management (DRM) interim review (issued May 28, 2024) evaluated the proposed REMS for Vigafyde. This interim review notes that the Applicant is proposing to add its NDA to the approved Shared System (SS) Vigabatrin REMS Program.

The primary goal of the Shared System (SS) Vigabatrin REMS Program is to mitigate the risk of vision loss. Because all previously approved vigabatrin products carry the same risks, they are subject to the same REMS. The Applicant's proposed REMS consists of the same elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments) as does the existing approved Shared System (SS) Vigabatrin REMS Program.
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The Applicant submitted a REMS amendment that addressed the comments from the interim review on Monday, June 3, 2024. The Applicant responded to an information request from DRM on June 13, 2024. With these revisions, the REMS was considered acceptable by DRM as reflected in the REMS memorandum of June 17, 2024.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

There will be no postmarketing requirements nor commitments for this NDA.

14. Recommended Comments to the Applicant

See the action letter.

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/s/

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