CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217684Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	217684
Priority or Standard	Standard
Submit Date(s)	August 17, 2023
Received Date(s)	August 17, 2023
PDUFA Goal Date	June 17, 2024
Division/Office	DN2/OND
Reviewer Name(s)	Kevan VanLandingham, MD, PhD Philip Sheridan, MD
Review Completion Date	June 17, 2024
Established/Proper Name	vigabatrin
(Proposed) Trade Name	Vigafyde
Applicant	Pyros Pharmaceuticals
Dosage Form(s)	Oral solution, 100 mg/mL
Applicant Proposed Dosing Regimen(s)	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)
Applicant Proposed Indication(s)/Population(s)	Infantile Spasms, infants 1 month to 2 years of age
Recommendation on Regulatory Action	Approval, 505(b)(2)
Recommended Indication(s)/Population(s) (if applicable)	Infantile Spasms - monotherapy in infants 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FAERS	FDA Adverse Event Reporting System
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GABA	gamma-aminobutyric acid
GABA-T	gamma-aminobutyric acid transaminase
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IFU	Instructions For Use
IND	Investigational New Drug Application
IS	Infantile Spasms
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

kg	kilograms
LD	listed drug
MedDRA	Medical Dictionary for Regulatory Activities
MG	Medication Guide
mg	milligrams
mITT	modified intent to treat
mL	milliliters
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
rCPS	refractory complex partial seizures
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
VGB	vigabatrin
WRO	written request only

1. Executive Summary

1.1. Product Introduction

Vigabatrin (VGB) is a selective and irreversible inhibitor of gamma-aminobutyric acid transaminase (GABA-T), which is the enzyme responsible for the metabolism of the central nervous system (CNS) inhibitory neurotransmitter gamma-aminobutyric acid (GABA). The mechanism of action is dose-dependent inhibition of GABA-T, and consequent increased levels of GABA in the CNS.

VGB is an oral antiseizure medication that was approved in the United Kingdom in 1989. Since then, it has been approved in over 50 countries. It was approved in the United States by FDA on 21-Aug-2009 as 500 mg tablets (NDA 020427) and 500 mg VGB for oral solution (NDA 022006), marketed since then under the brand name Sabril. VGB Oral Solution 500 mg must be reconstituted with 10 mL of water by parents or healthcare providers prior to use to obtain a 50 mg/mL solution of VGB. VGB is indicated as *monotherapy for pediatric patients with Infantile Spasms (IS) 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss*, and this is the indication that the Sponsor, Pyros, intends to pursue. VGB has also been approved in the US as an *adjunctive therapy for adults and pediatric patients 2 years of age and older with Refractory Complex Partial Seizures (rCPS) who have inadequately responded to several alternative treatments*. The Sponsor does not intend to pursue this indication. Based on the similarities to the VGB oral solution, the proposed product is being submitted via a 505(b)(2), relying on the previous findings of safety and efficacy along with applicable literature to act as a bridge to the Listed Drug (LD).

The initial daily dosing is 50 mg/kg/day given in two divided doses (25 mg/kg twice daily). Subsequent dosing can be titrated by 25 mg/kg/day to 50 mg/kg/day increments every 3-days, up to a maximum of 150 mg/kg/day given in 2 divided doses (75 mg/kg twice daily).

Orphan Drug Designation was granted to Vigafyde on October 12. 2022. In the grant letter, the Applicant was informed that "it is the active moiety or principal molecular structural features of the drug1 and not the formulation of the drug that is designated." "In order to obtain orphan-drug exclusivity upon approval, you will need to demonstrate that your drug is clinically superior to any already approved version of the same drug for the same indication. Failure to demonstrate clinical superiority over the already approved same drug(s) will result in your drug not receiving orphan-drug exclusivity. See 21 CFR 316.34(c)."

1.2. Conclusions on the Substantial Evidence of Effectiveness

As both the reference product and the proposed product are solutions when administered to patients, the Applicant requested a waiver of in-vivo bioavailability studies. FDA agreed that the biowaiver approach for the oral solution was feasible so long as the supporting information was found acceptable by FDA. As such, the waiver request included a full discussion of the differences between the reference product and the proposed product including the potential impact of differences in dosing volumes, osmolality results, and excipients. The Applicant provided data and justifications that there is 1) no significant impact on the absorption of VGB by the exclusion of povidone and the inclusion of four new excipients and 2) no significant impact on the absorption and bioavailability of VGB due to the higher osmolality of the proposed drug product. The Biopharmaceutics Review Team concluded that the proposed drug product is adequately bridged to the listed drug per 21 CFR 320.24(b)(6).

1.3. Benefit-Risk Assessment

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.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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. ➢ 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.	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
	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 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.	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. Vigabatrin appears to be the preferred treatment for IS associated with tuberous sclerosis complex.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Infantile spasms (IS) are an epileptic syndrome that begins in the first year of life, consisting of a sudden flexion of the baby's arms, legs. The spasms consist of a sudden flexion of the baby's arms, legs and head (Jai, 2018). An individual spasm typically lasts for less than 1 second to up to 5 seconds, and with clusters of 3-20 spasms typically occurring several times per day in untreated patients, often on awakening (Wong, 2001). They may occur as many as 100 times a day. IS may occur in the setting of extensive cortical dysgenesis, genetic mutations (comprising developmental epileptic encephalopathy), or tuberous sclerosis.

Incidence rates of IS range from approximately two to five per 10,000 live births, with a lifetime prevalence of IS at age 10 years has been estimated at 1.5 to 2 per 10,000 children (Wong, 2001). The consistently lower prevalence rates of IS among children compared with incidence can most likely be attributed to the relatively high mortality associated with IS, the evolution of spasms into other seizure types, and incomplete ascertainment in population-based studies of older children (Wong, 2001).

Early diagnosis and effective treatment may improve the prognosis for these infants, as early responders have shown better long-term seizure control and developmental outcomes.

Overall, the outcome in IS is poor, and patients have increased morbidity and mortality (Riikonen, 2020). The underlying etiology is the most important prognostic factor. In studies with a long follow-up (up to 50 years), a favorable cognitive outcome has been observed in approximately one quarter of patients and complete seizure freedom in one-third.

2.2. Analysis of Current Treatment Options

Current FDA approved treatments for IS include adrenocorticotropic hormone (ACTH) and VGB (Grinspan, 2021). VGB is the preferred choice of treatment for IS associated with Tuberous Sclerosis. Although not FDA approved, high dose oral prednisolone or prednisone have been used. The use of other anti-seizure medications, ketogenic diet or epilepsy surgery tend to have a worse outcome.

Table #: Summary of Treatment Armamentarium Relevant to Proposed Indication (FDA Approved Treatments for Infantile Spasms

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]					
VGB	Indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss	2009	Oral: The initial daily dosing is 50 mg/kg/day given in two divided doses (25 mg/kg twice daily); subsequent dosing can be titrated by 25 mg/kg/day to 50 mg/kg/day increments every 3 days, up to a maximum of 150 mg/kg/day given in 2 divided doses (75 mg/kg twice daily)	Study 1 (N=221) was a multicenter, randomized, low-dose high-dose, parallel-group, partially blind. 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 VGB 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	Permanent vision loss, MRI abnormalities in infants, intramyelinic edema, suicidal behavior and ideation, anemia, somnolence and fatigue, peripheral neuropathy, weight gain and edema.

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
				observed in the average frequency of spasms using the 2-hour evaluation window. However, a post-hoc alternative efficacy analysis, using a 24-hour clinical evaluation window found a statistically significant difference in the overall percentage of reductions in spasms between the VGB group (68.9%) and the placebo group (17.0%) (p=0.030).	
Acthar Gel	Indicated as monotherapy for the treatment of infantile spasms in infants and children under 2 years of age.	2010	Intramuscular Injection: The recommended dose is 150 U/m divided into twice daily of 75 U/m. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period.	The effectiveness of Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (Video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2-week course of treatment with Acthar Gel (75 U/m intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and	Infections, adrenal insufficiency, Cushing's Syndrome, masking symptoms of other diseases, gastrointestinal perforation and bleeding, behavioral and mood disturbances, worsening of comorbid diseases, ophthalmic effects (cataracts, glaucoma, infections), immunogenicity potential, negative effects on growth and physical development, and decrease in bone density.

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
				hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone ($p<0.002$). A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m once daily for 3 weeks, n=30) of Acthar Gel with low-dose, short duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Nonresponders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for	

Product(s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
				cessation of spasms but not for the resolution of hypsarrhythmia.	

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Based on a review of the Orange Book, there are currently no listed manufactures of a ready-made VGB oral solution. Lundbeck, the manufacture of the registered listed drug, Sabril, and 12 other manufacturers, produce VGB powder for oral solution, which requires reconstitution by the caregiver.

3.2. Summary of Presubmission/Submission Regulatory Activity

Significant interactions between FDA and the Applicant include the following:

- Type B, pre-IND meeting (WRO) to discuss the development plan for PIND 157997 November 23, 2021 (minutes issued January 21, 2022): Applicant asked 31 questions, not all of which were answered in this WRO. The Applicant was informed that the proposed product was considered a new dosage form due to the increased concentration from the Listed Drug. Several questions delt with demonstration of clinical superiority on a hypothetical basis, and that no additional clinical trials would be necessary, to which the FDA did not agree.
- Initial Pediatric Study Plan waiver request was received on August 9, 2022 (accepted on November 7, 2022, as Orphan Designation was granted on October 12, 2022: Orphan Disease Designation required that failure to demonstrate clinical superiority over the already approved same drug(s) would result in the drug not receiving orphan-drug exclusivity (21 CFR 316.34(c).
- Type B, pre-NDA meeting (WRO) September 9, 2022, to discuss the development plan for NDA 217684: Meeting was denied on September 21, 2022, as the meeting request contains twenty-four questions which proposed that the Division address in a sixty-minute teleconference meeting. This strategy was inconsistent with statement included in the draft Guidance for Industry, “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (Revision 2, March 2015)”.
- Type C meeting requests, received on October 4, 2022, and October 22, 2022: Meetings were denied on October 26, 2022, due to the NDA submission was not submitted in eCTD format.

- Type C Pre-Submission Meeting (WRO) received on November 1, 2022 (minutes issued January 13, 2023): Multiple questions regarding CMC were asked and answered. The lack of need additional nonclinical data or for module 5 was agreed. FDA did not agree that the results of a human factors (HF) validation study can be used to demonstrate the increased safety/clinical superiority of the proposed product as compared to Sabril because the design of an HF validation study is not comparative in nature.
- Type B, pre-NDA meeting (WRO) to discuss the plan for NDA 217684 May 25, 2023 (minutes issued August 8, 2023): FDA provided input on the organization of the eCTD NDA filing and possible differences in osmolality and bioavailability of oral solution formulation. The Applicant was informed that data obtained from a simulated use human factors (HF) study as proposed was incapable, by design, of providing an acceptable basis for a claim of clinical superiority over the Listed Drug. Additionally, the Applicant was asked to provide a rationale for proposing a "stand-alone REMS program" instead of having NDA 217684 join the currently approved Vigabatrin REMS.
- 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.1,2 The Applicant also communicated they were amenable to having their NDA product join the approved Vigabatrin Shared System REMS.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable.

4.2. 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.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable.

4.5. 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.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

No clinical data was provided with this submission.

6. Review of Relevant Individual Trials Used to Support Efficacy

No trials were conducted to support efficacy.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Based on the similarities to the VGB oral solution, the proposed product is being submitted via a 505(b)(2) pathway, relying on the previous findings of efficacy along with applicable literature to act as a bridge to the Listed Drug (LD).

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Not applicable.

7.3. Integrated Assessment of Effectiveness

As both the reference product and the proposed product are solutions when administered to patients, the Applicant requested a waiver of in-vivo bioavailability studies. Based on the preliminary information included in these meeting packages, FDA agreed that the biowaiver approach for the oral solution was feasible as long as the supporting information package was found acceptable by FDA. As such, the waiver request included a full discussion of the differences between the reference product and the proposed product including the potential impact of differences in dosing volumes, osmolality results, and excipients. The Applicant provided data and justifications that there is 1) no significant impact on the absorption of VGB by the exclusion of povidone and the inclusion of four new excipients and 2) no significant impact on the absorption and bioavailability of VGB due to the higher osmolality of the proposed drug product. The proposed drug product is deemed adequately bridged to the listed drug per 21 CFR 320.24(b)(6).

8. Review of Safety

8.1. Safety Review Approach

The Applicant did not provide datasets which allow for independent analysis to assess the safety of Vigafyde. The Applicant did provide 31 FDA Adverse Event Reporting System (FAERS) reports concerning currently marketed VGB oral solution, which were predominantly reports regarding patients with infantile/epileptic spasms, out of a total of 938 reports regarding VGB, involving a mix of reports of patients with focal epilepsy or infantile spasms. These FAERS adverse event reports consisted of incorrect product preparation or reuse of excess prepared solution or powder. No Adverse Event was noted in 30% of these reports. Data integrity could not be assessed.

8.2. Safety in the Post-market Setting

Annual Safety Reports have been reviewed. Based upon the review of information from these reports, and the published literature, no new safety concerns were identified. The benefit-risk assessment for Sabril remained unchanged.

8.3. Integrated Assessment of Safety

As both the reference product and the proposed product are solutions when administered to patients, the Applicant requested a waiver of in-vivo bioavailability studies. FDA agreed that the biowaiver approach for the oral solution was feasible as long as the supporting information was found acceptable by FDA. As such, the waiver request included a full discussion of the differences between the reference product and the proposed product

including the potential impact of differences in dosing volumes, osmolality results, and excipients. The Applicant provided data and justifications that there is 1) no significant impact on the absorption of VGB by the exclusion of povidone and the inclusion of four new excipients and 2) no significant impact on the absorption and bioavailability of VGB due to the higher osmolality of the proposed drug product. The proposed drug product is deemed adequately bridged to the listed drug per 21 CFR 320.24(b)(6).

9. Advisory Committee Meeting and Other External Consultations

There was no advisory committee for this 505(b)(2) application because the safety profile of Vigafyde is similar to that of the LD.

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 (MG)/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, MG, IFU, and carton/container labeling) provided specific recommendations to include in negotiations with the Applicant.

12. Labeling Recommendations

Refer to the final negotiated product label. Labeling negotiations with the Applicant have been completed, and the Applicant has accepted all recommended changes.

13. Risk Evaluation and Mitigation 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 VGB 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 the approved Shared System (SS) Vigabatrin REMS Program.

The Applicant submitted a REMS amendment addressing the comments from the interim review on Monday, June 3, 2024. With these revisions, the REMS was considered acceptable by DRM.

14. Postmarketing Requirements and Commitments

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

15. Appendices

15.1. References

Grinspan ZM, Knupp KG, Patel AD, et al (2021). Comparative Effectiveness of Initial Treatment for Infantile Spasms in a Contemporary US Cohort. Neurology 97(12): e1217-e1228.

Jai J, Chen S, Sivarajah V, et al (2018). Latitudinal differences on the global epidemiology of infantile spasms: systematic review and meta-analysis. Orphanet J of Rare Dis. 13:216 (https://doi.org/10.1186/s13023-018-0952-x)

Riikonen R (2020). Infantile Spasms: Outcome in Clinical Studies. Pediatr Neurol 108: 54-64.

Wong M and Trevathan E. Infantile Spasms. Pediatr Neurol 24: 89-98.

15.2. Financial Disclosure

Not applicable.

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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06/16/2024 09:26:28 PM
Review complete. Approval recommended

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