CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217026Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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	217026
PDUFA Goal Date	March 10, 2023
OSE RCM #	2022-418
Reviewer Name(s)	Sarah K. Holman, PharmD, BCPS
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 9, 2023
Subject	Evaluation of Need for a REMS
Established Name	Trofinetide
Trade Name	Daybue
Name of Applicant	Acadia Pharmaceuticals, Inc.
Therapeutic Class	Synthetic analog of the tripeptide glycine-proline-glutamate (GPE)
Formulation(s)	200 mg/mL oral solution
Dosing Regimen	Weight-based dose administered orally or via gastrostomy tube twice daily Dose range 5 g – 12 g

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Daybue (trofinetide) is necessary to ensure the benefits outweigh its risks. Acadia Pharmaceuticals Inc. submitted a New Drug Application (NDA) 217026 for trofinetide with the proposed indication for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. The risks associated with trofinetide include diarrhea and weight loss. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Neurology 1 (DN1) have determined that a REMS is not needed to ensure the benefits of trofinetide outweigh its risks. Rett syndrome is a severe progressive neurodevelopmental disorder with no FDA-approved therapies available for treatment. The healthcare providers who are likely to prescribe trofinetide are specialized clinicians who are typically part of a multi-disciplinary care team and should be able to manage the risks associated with trofinetide. The risks of diarrhea and weight loss will be communicated through Section 5: Warnings and Precautions of the labeling.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Daybue (trofinetide) is necessary to ensure the benefits outweigh its risks. Acadia Pharmaceuticals Inc. (hereafter referred to as the Applicant) submitted a New Drug Application (NDA) 217026 for trofinetide with the proposed indication for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.[1] This application is under review in the Division of Neurology 1 (DN1). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Daybue (trofinetide), a new molecular entity[a], is a synthetic analog of the tripeptide glycine-proline-glutamate (GPE), a product of the naturally occurring cleavage of insulin-like growth factor 1. The mechanism in the treatment of Rett syndrome is unclear, however, trofinetide is hypothesized by the Applicant to enhance neuronal synaptic function and morphology. Trofinetide is proposed for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.[2]

Trofinetide is proposed for chronic use[b] and will be supplied as a 200 mg/ml oral solution. The proposed dosing of trofinetide is weight-based (dose range 5 g-12 g) administered orally or via gastrostomy tube twice daily. If diarrhea occurs, the trofinetide dose may be reduced to half of the recommended dose or

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

temporarily interrupted until diarrhea improves.[2] Trofinetide is likely to be administered in the outpatient setting. Trofinetide was granted fast track designation in June 2013, orphan drug designation in February 2015, and rare pediatric disease designation in March 2020. Trofinetide is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 217026 relevant to this review:

- **11/20/2012:** IND 114319 submitted for trofinetide
- **06/04/2013**: Fast Track designation granted
- **02/11/2015**: Orphan Drug designation granted
- **03/02/2020**: Rare Pediatric Disease designation granted
- **07/12/2022**: NDA 217026, Daybue (trofinetide) submission for treatment of Rett syndrome in adults and pediatric patients 2 years of age and older received[1]
- **11/03/2022**: A Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for trofinetide.[3]

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Rett syndrome is a severe progressive neurodevelopmental disorder that occurs almost exclusively in females.[4] Rett syndrome is typically caused by loss-of-function mutations of the *methyl CpG binding protein 2* (*MECP2)* gene on the X chromosome.[4,5] The severity of the disease is determined by the location, type, and severity of the *MECP2* mutation and can range from mild to severe.[6] Infants with Rett syndrome generally develop normally until 6 to 18 months of age, after which they often lose acquired language, fine motor, and gross motor skills.[5] A characteristic finding of Rett syndrome is the development of stereotypic repetitive hand movements.[4] Other clinical manifestations of Rett syndrome include impaired control of voluntary movement, autistic-like behaviors, breathing dysregulation, feeding and swallowing difficulties, growth retardation, osteoporosis, scoliosis, constipation, and seizures.[c,4-6]

Rett syndrome is a rare disease affecting an estimated 1 in 10,000 girls in the United States by age 12.[d,6] Rett syndrome is the second most common cause of severe intellectual disability after Down

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

syndrome.[5,6] Patients with Rett syndrome typically survive into adulthood with greater than 70% surviving beyond 45 years of age.[7]

3.2. Description of Current Treatment Options

There are no FDA-approved therapies for the treatment of Rett syndrome. Treatment of Rett syndrome consists of symptom management and supportive care. Symptoms necessitating treatment may include seizures, anxiety, sleep disturbance, breathing impairment, spasticity, muscle rigidity, and gastrointestinal abnormalities. Supportive care may include nutritional supplementation and gastrostomy tube placement.[4] Individuals with Rett syndrome often require occupational, physical, behavioral, and speech therapy and a multi-disciplinary approach to care.[5,6] Given the lack of available treatment options, treatment of Rett syndrome represents an unmet medical need.

4. Benefit Assessment

The primary evidence for efficacy of trofinetide for the treatment of Rett syndrome is supported by one phase 3 pivotal trial, Study ACP-2566-003 (National Clinical Trial [NCT] 04181723, hereafter referred to as Study 003).[8] Study 003 was a double-blind, placebo controlled, parallel-group, multicenter study which evaluated 187 females aged 5-20 years (trofinetide group=91, placebo group=93)[e] with *MECP2*-Rett syndrome. Subjects were randomized to receive trofinetide or placebo twice daily orally or via gastrostomy tube over a 12-week treatment period. Trofinetide dosing was based on four weight ranges summarized in Table 1 below. Until the week 6 visit, the dose could be decreased for poor tolerability and up to four doses could be withheld.

Table 1. Trofinetide Dosing Schedule Based on Weight at Baseline[8]

Weight	Dose
12- 20 kg	6 g (30 mL) twice daily
>20-35 kg	8 g (40 mL) twice daily
>35-50 kg	10 g (50 mL) twice daily
>50 kg	12 g (60 mL) twice daily

The study population in Study 003 had a mean age of 10.9 years, mean body weight of 29.7 kg, and was predominantly White (91.8%). The baseline demographics were well-balanced between study groups. The co-primary endpoints were change in baseline to week 12 of Rett Syndrome Behavior Questionnaire

[e] In Study 003, although 187 subjects were randomized, efficacy analyses were performed using the Full Analysis Set (study population 184 subjects). The Full Analysis Set consisted of subjects who were randomized, received at least one dose of study drug, and had both a baseline value and at least one postbaseline value for the RSBQ total score, or had at least one CGI-I score after taking the study drug.

(RSBQ) score[f] and Clinical Global Impression-Improvement (CGI-I) score[g]. The trofinetide treatment group had a statistically significant improvement in RSBQ score and CGI-I score at week 12 as outlined in Tables 2 and 3 below.

Table 2. RSBQ Total Score Change from Baseline to Week 12[8]

	Placebo (N=93)	Trofinetide (N=91)
Least squares mean (SE)	-1.7 (0.90)	-4.9 (0.94)
Least squares mean difference (SE) [95% CI]	-3.1 (1.3) [95% CI: -5.7, -0.6]	
2-sided p-value	0.0175	

Table 3. CGI-I Score in Participants with Rett syndrome at Week 12[8]

	Placebo (N=93)	Trofinetide (N=91)
Least squares mean (SE)	3.8 (0.07)	3.5 (0.07)
Least squares mean difference (SE) [95% CI)	-0.3 (0.10) [95% CI: -0.5, -0.1)	
2-sided p-value	0.003	

In Study 003, there was a higher dropout rate observed in the trofinetide arm compared with the placebo arm (24.7% vs 9.6%) which was evaluated by the statistical reviewer for its impact on conclusions regarding efficacy of trofinetide. The statistical reviewer concluded that the higher observed dropout rate in the trofinetide arm in Study 003 had a minimal impact on the results of the study.[9]

Study ACP-2566-009 (NCT04988867, hereafter referred to as Study 009) is an open-label ongoing study evaluating use of trofinetide in female subjects with Rett Syndrome aged 2-5 years. Study 009 is a bridging study to evaluate pharmacokinetics, safety, and tolerability of trofinetide and is supportive of efficacy of trofinetide in this population.[8]

[f] The Rett Syndrome Behavior Questionnaire (RSBQ) is a 45-item questionnaire completed by caregivers which assesses symptoms of Rett syndrome. Each item in the RSBQ is rated from 0 to 2 with a higher score indicating greater severity or frequency of the symptom. RSBQ total score ranges from 0 to 90.

[g] The Clinical Global Impression-Improvement (CGI-I) scale is an assessment of patients' global functioning completed by a clinician. The clinician rates the patient's improvement on a 7-point scale (1=very much improved; 7=very much worse) when compared to baseline status.

The clinical reviewer concluded that the Applicant provided evidence of effectiveness based on the results of Study 003.[10,h]

5. Risk Assessment & Safe-Use Conditions

The primary safety population consists of all subjects in the randomized population who received trofinetide in the pivotal phase 3 trial, Study 003 (NCT04181723). Data from trials Neu-2566-RETT-001, Neu-2566-RETT-002, ACP-2566-004 (ongoing), and ACP-2566-005 (ongoing) provide additional supportive safety data for subjects aged 5 years and older. Study 009 (ongoing) provides supportive safety data for subjects with Rett syndrome aged 2-5 years.[11]

The primary safety population includes 93 subjects randomized to trofinetide and 94 subjects randomized to placebo. The mean duration of drug exposure was 81.5 days in the placebo group and 73.5 days in the trofinetide group. Early discontinuation from the study occurred more frequently in the trofinetide group compared with placebo (24.7% vs 9.6%) with the most common reason being adverse events occurring in 17.2% of subjects who received trofinetide. The most common adverse events were diarrhea, vomiting, pyrexia, seizure, anxiety, somnolence, nasopharyngitis, and decreased appetite.[2,11] Although not common, weight loss is an adverse event of concern given the primarily pediatric patient population and baseline growth challenges in patients with Rett syndrome. See Sections 5.2.1 and 5.2.2 for additional discussion on diarrhea and weight loss, respectively.

5.1. Serious Adverse Events

5.1.1. Serious Adverse Events

During the pivotal study, Study 003, there were 8 serious adverse events[i] (SAEs) reported in 6 subjects (3 in the placebo group and 3 in the trofinetide group)[j]. In the placebo group, SAEs included constipation, pneumatosis intestinalis, and respiratory distress occurring in 1 subject each. In the trofinetide group, COVID-19 pneumonia and seizure occurred in 1 subject each while one subject experienced bacteremia, bronchiolitis, and urinary tract infection. Bacteremia, urinary tract infection, and seizure were considered related to study drug with seizure leading to

[h] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[i] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[j] Section 505-1 (a) of the FD&C Act: *FDAAA factor (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.*

drug discontinuation in 1 subject.[11] The clinical reviewer concluded that many of the serious adverse events that were reported in the study appeared compatible with chronic complications of Rett Syndrome. However, the adverse effect of vomiting with trofinetide may increase the risk of aspiration and the diarrhea associated with trofinetide may increase the risk of developing urinary tract infections in this population.[10]

5.1.2. Deaths

There were 2 deaths in the long-term open-label Study ACP-2566-005. The first subject was a 15-year-old female with past medical history of vomiting and gastroesophageal reflux disease who was receiving trofinetide 40 mL twice daily. The subject underwent G-tube placement in preparation for planned tooth extraction and, two days after the surgery, vomited during sleep leading to aspiration and death. The vomiting and aspiration were considered severe treatment-emergent adverse events (TEAEs) unrelated to trofinetide.[11] The second death occurred in a 17-year-old female receiving trofinetide 40 mL twice daily. The subject experienced a perforated peptic ulcer believed to be caused by prolonged ibuprofen use. The perforation was surgically repaired, however 2 months later, the subject experienced a bleeding ulcer that led to asystole and death. The gastric ulcer perforation and hemorrhaging were considered severe TEAEs not related to trofinetide.[12] The clinical reviewer concluded that the 2 deaths among the trials were unlikely related to the use of trofinetide.[10]

5.2. Adverse Events of Special Interest

5.2.1. Diarrhea

In Study 003, diarrhea was the most common TEAE occurring in 80.6% of trofinetide-treated subjects vs 19.1% of placebo-treated subjects. The majority of the diarrhea was mild to moderate in severity. However, diarrhea was a frequent cause for study withdrawal leading to 12.9% of subjects in the trofinetide treatment group to withdraw from the study. Of the subjects in the trofinetide group with a TEAE of diarrhea, 1 subject had concurrent dehydration and 3 subjects had concurrent weight loss.[11]

In Study 003, a diarrhea management plan was introduced which included stopping all laxatives, increasing fiber intake, and using loperamide to treat the diarrhea. Antipropulsives including loperamide were used in 50.5% of subjects in the trofinetide group vs 3.2% of subjects in the placebo group. Investigators could hold up to four doses of study drug and decrease the assigned study dose up to 50% before the Week 6 visit. The dose was then increased as tolerated with the aim to return to the originally assigned dose. Dose reduction was more common in subjects treated with trofinetide compared with placebo (35.5% vs 5.3%).[11]

The clinical reviewer recommends the risk of diarrhea be communicated in labeling, Section 5 – Warnings and Precautions. Labeling will include that patients should stop laxatives before

starting trofinetide. Labeling will also include recommendations to interrupt, reduce the dose, or discontinue trofinetide should diarrhea occur.[10]

5.2.2. Weight Loss

In Study 003, weight loss of >7% compared to baseline occurred in 12.9% of trofinetide-treated subjects compared to 4.7% of placebo-treated subjects.[13] Given the primarily pediatric population of the study and the co-occurrence of feeding and growth difficulties in patients with Rett syndrome at baseline, the effect of trofinetide on patient weight may be of concern. Although diarrhea can contribute to weight loss or lack of appropriate weight gain, the majority of trofinetide-treated subjects that experienced diarrhea did not have weight loss.

The clinical reviewer recommends the risk of weight loss be communicated in labeling, Section 5 – Warnings and Precautions, including monitoring weight and discontinuation of trofinetide if significant weight loss occurs.[10]

6. Expected Postmarket Use

Trofinetide is to be administered orally or via gastrostomy tube by a caregiver in the outpatient setting or in an inpatient setting, and is likely to be prescribed by specialists, such as pediatricians or neurologists. As Rett syndrome is a rare and progressive disease, patients are typically managed closely by experienced clinicians who should be able to monitor and manage the risks associated with trofinetide.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for trofinetide beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of trofinetide for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older on the basis of the available efficacy and safety information.[10]

Rett syndrome is a severe progressive neurodevelopmental disorder primarily occurring in females that can lead to loss of language and motor skills, feeding difficulties, breathing dysregulation, and seizures. There are no FDA-approved therapies for the treatment of Rett syndrome, treatments available primarily focus on symptom management and supportive care. Given the lack of available treatment options, treatment of Rett syndrome represents an unmet medical need.

The benefits of treatment of Rett syndrome with trofinetide were demonstrated in a Phase 3, double-blind, placebo-controlled trial. In the trofinetide treatment group, there was a statistically significant improvement in the co-primary endpoints of RSBQ score and CGI-I at week 12 when compared with placebo.

The safety profile for trofinetide is favorable with no serious adverse events requiring risk mitigation beyond labeling.

Given the complexity of the disease and need for a multi-disciplinary approach to management, healthcare providers who are likely to prescribe trofinetide should be able to monitor and manage the risks associated with trofinetide. Therefore, based on the data currently available, this reviewer is not recommending a REMS for the management of the risks of trofinetide therapy.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for trofinetide to ensure the benefits outweigh the risks. At the time of this review, labeling negotiations were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

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8. Acadia Pharmaceuticals Inc. Daybue (trofinetide). NDA 217026. Module 2.7.3 - Summary of Clinical Efficacy. July 12, 2022.
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12. Acadia Pharmaceuticals Inc. Daybue (trofinetide). NDA 217026. 120-Day Safety Update Report. November 8, 2022.
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