CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215904Orig1s000

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	215904
PDUFA Goal Date	March 20, 2022
OSE RCM #	2021-1472
Reviewer Name	Yasmeen Abou-Sayed, PharmD
Team Leader	Jacqueline Sheppard, PharmD
Division Director	Cynthia LaCivita, PharmD
Review Completion Date	March 7, 2022
Subject	Evaluation of Need for a REMS
Established Name	Ganaxolone
Trade Name	Ztalmy
Name of Applicant	Marinus Pharmaceuticals, Inc
Therapeutic Class	Neuroactive steroid (epalon)
Formulation	Oral suspension 50mg/ml
Dosing Regimen	(b) (4)

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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 Ztalmy (ganaxolone) is necessary to ensure the benefits outweigh its risks. Marinus Pharmaceuticals, Inc. submitted a New Drug Application (NDA 215904) for ganaxolone with the proposed indication for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD). No serious risks that warrant a REMS are associated with the use of ganaxolone. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and DN1 have determined that a REMS is not needed to ensure the benefits of ganaxalone outweigh its risks. CDD is rare serious disease for which there are no FDA-approved treatments available. The analysis of the safety data for ganaxolone indicated that there are no serious risks associated with ganaxolone that would require a REMS. Labeling will include standard class labeling for antiepileptic drugs with warnings and precautions for somnolence and sedation suicidal behavior and ideation and withdrawal of antiepileptic drugs (AEDs).

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) Ztalmy (ganaxolone) is necessary to ensure the benefits outweigh its risks. Marinus Pharmaceuticals, Inc submitted a New Drug Application (NDA) 215904 for ganaxolone with the proposed indication for the treatment of seizures associated with Cyclin-dependent kinase-like 5 deficiency disorder (CDD).[1] This application is under review in the Division of Neurology 1. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Ztalmy (ganaxolone), a new molecular entity[a], is a neuroactive steroid that modulates gamma-aminobutyric acid A (GABA) receptors in the central nervous system, proposed for the treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD). It is the first of a new class of drugs, the epalons, and has a distinctive mechanism of action that differentiates it from currently approved modulators of GABA receptors such as benzodiazepines and barbiturates. Ganaxolone is proposed as 50 mg/ml oral suspension to be given three times daily for chronic therapy.[b] The weight-based titration schedule is detailed in Tables 1 and 2 below. Ganaxolone is not currently approved in any jurisdiction.

[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.*

Table 1 - ZTALMY Recommended Titration Schedule for Patients Weighing 28 kg or Less

Dosage	Total Daily Dosage	Days
6 mg/kg three times daily	18 mg/kg/day	1 to 7
11 mg/kg three times daily	33 mg/kg/day	8 to 14
16 mg/kg three times daily	48 mg/kg/day	15 to 21
21 mg/kg three times daily	63 mg/kg/day	22 to ongoing

Table 2 - ZTALMY Recommended Titration Schedule for Patients Weighing More Than 28 kg

Dosage	mL per Dose	Total Daily Dosage	Days
150 mg three times daily	3	450 mg	1 to 7
300 mg three times daily	6	900 mg	8 to 14
450 mg three times daily	9	1350 mg	15 to 21
600 mg three times daily	12	1800 mg	22 to ongoing

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 215904 relevant to this review:

- 6/28/2017: Orphan Drug Designation granted for ganaxolone for the treatment of cyclin-dependent kinase-like 5 gene-related early-onset infantile epileptic encephalopathy
- 7/20/2022: NDA 215905 submission for treatment of seizures associated with cyclin-dependent kinase-like 5 deficiency disorder (CDD) received
- 2/8/2022: A Late-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 ganaxalone

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a developmental encephalopathy caused by mutations in the CDKL5 gene. This rare disease disorder is characterized by early infantile onset refractory epilepsy (usually by age 3 months, but as early as the first week of life), hypotonia, developmental intellectual and motor disabilities, and cortical visual impairment.[c,2,3,4] CDD is severe condition with seizure frequency and intensity that is refractory to current therapy as well as severe cognitive and motor developmental delays. It is linked to the X chromosome and affects the female gender four times more often than males. Although rare, the occurrence could be between 1/40,000 and 1/60,000 live births.[5,d]

3.2. Description of Current Treatment Options

There currently is no FDA approved treatment for CDD. Current treatment is symptom based and no specific anti-seizure medication is particularly associated with improved symptom control for CDD patients; epilepsy in this population is highly refractory. The most commonly prescribed anti-seizure medications for patients with CDD are broad spectrum agents including levetiracetam, topiramate, clobazam, and phenobarbital. Off-label use of FDA-approved cannabidiol (Epidiolex) has also been seen in CDD treatment regimens. Pharmacologic agents used and their various safety issues are summarized in Appendix A. The ketogenic diet may also provide some benefit in CDD patients, but there is not sufficient data to support is use. There remains an unmet medical need for treatment options for CDD.

4. Benefit Assessment

The pivotal trial (Study 3001, National Clinical Trial [NCT] 03572933) supporting efficacy of ganaxolone for the treatment of seizures associated with CDKL5 deficiency disorder consisted of a double blind, randomized, placebo-controlled, global study.[6] The trial was designed with a 6-week baseline period to collect seizure data, followed by a 17-week treatment phase, and then follow by a long-term open label phase. Key inclusion criteria included:

- Subjects between the age of 2 to 21 years
- Failure to control seizures despite appropriate trial of 2 or more anti-seizure medications at therapeutic doses
- Have at least 16 seizures of the primary seizure types (bilateral tonic, generalized tonic-clonic, bilateral clonic, atonic/drop or focal to bilateral tonic-clonic) per 28 days in the 2 months prior to screening

[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.*

- Be on a stable regimen of 0-4 anti-seizure medications for ≥ 1 month prior to the screening visit

A total of 101 patients were randomized, with 95 completing the 17-week treatment phase of the study. Patients received ganaxolone or placebo and dosed according to the titration schedules previous described in Tables 1 and 2 of this review.

The primary efficacy endpoint of Study 3001 is the percent change in 28-day primary seizure frequency through the end of the 17-week treatment phase relative to the 6-week baseline period. Participants completed a daily seizure calendar, noting seizure type and frequency, to determine ganaxolone' s effect on seizures. At the end of the treatment phase, there was a statistically significant difference in the median percent change from baseline in seizure frequency between treatment groups, -30.7% for subjects in the ganaxolone group and -6.9% for subjects in the placebo (p = 0.0036).[e]

5. Risk Assessment & Safe-Use Conditions

The safety database for ganaxolone for the treatment of seizures associated with CDD includes all patients (n=101) from Study 3001 and from the long-term open label study that followed (Study 0900, NCT 04678479).[7] Eighty-three patients had exposure to ganaxolone over 6 months, and 50 patients over 12 months. The most common adverse event seen in ganaxolone treatment are extensions of the drug's central nervous system effects, including somnolence (36%), dizziness (16%), and gait disturbance (4%). These adverse events are frequently seen in anti-epileptic drugs and are reversible upon discontinuation of treatment.[f] Labeling will include standard class labeling for antiepileptic drugs with warnings and precautions for somnolence and sedation, suicidal behavior and ideation, and withdrawal of antiepileptic drugs (AEDs).[8]

One death occurred on day 381 of Study 0900 in [redacted] (b) (6) due to severe meningococcal sepsis which was assessed to be unlikely related to study drug. No other serious adverse events that would warrant a REMS were associated with the use of ganaxolone.

6. Expected Postmarket Use

The proposed indication for ganaxolone is for treatment of seizures associated with CDD. Due to the refractory nature of the epilepsy associated with CDD and the need for adjunctive treatments, most CDD patients are being diagnosed, receiving care, and prescribed ganaxolone by neurologists, pediatric neurologists and epileptologists familiar with managing anti-epileptic drugs,

7. Risk Management Activities Proposed by the Applicant

[e] 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.*

[f] 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.*

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

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of ganaxolone on the basis of the efficacy and safety information currently available.[9] CDD is a rare serious disease that manifests in infancy, one if its hallmarks being intractable seizures. The availability of ganaxolone for treatment of seizures in patients with CDD will address an unmet medical need in this rare disease population where no specific anti-seizure medication is particularly associated with improved symptom control for CDD patients.

The analysis of the safety data for ganaxolone indicated that there are no serious safety concerns that warrant a REMS. Based on its mechanism of action in the central nervous system, the most commonly observed adverse events were somnolence and dizziness. These adverse events are frequently seen in anti-epileptic drugs and are reversible upon discontinuation of treatment. The label for ganaxolone will include warnings and precautions for these adverse events, along with standard class labeling for suicidal behavior and ideation and withdrawal of antiepileptic drugs. Based on the currently available data, DRM and DN1 concur that a REMS is not necessary to ensure the benefits of ganaxolone outweigh the risks.

9. Conclusion & Recommendations

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

10. Appendix

Appendix A – Non-FDA Approved Treatments for the treatment of CDD

Product Name **Approval Year**	**Approved Indication**	**Dosage**	**Safety Issues**
Keppra (levetiracetam) **1999**	Treatment of partial-onset seizures in patients 1 month of age and older	Oral: weight-based dosing in patients less than 16 years of age, twice daily. Twice daily for patient aged 16 years and older	• Behavior Abnormalities and Psychotic Symptoms • Suicidal Behavior and Ideation • Somnolence and Fatigue • Anaphylaxis and Angioedema • Serious Dermatological Reactions • Coordination Difficulties

Product Name Approval Year	Approved Indication	Dosage	Safety Issues
			• Hematologic Abnormalities • Increase in Blood Pressure
Topamax (topiramate) **1996**	Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older. adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox Gastaut syndrome in patients 2 years of age and older.	Oral: Monotherapy-Pediatric Patients 2 to 9 Years of Age; weight-based dosing twice daily. Adults and Pediatric Patients 10 Years of Age and Older; twice daily	• Acute Myopia and Secondary Angle Closure Glaucoma • Visual Field Defects • Oligohidrosis and Hyperthermia • Metabolic Acidosis • Suicidal Behavior and Ideation • Cognitive/Neuropsychiatric Adverse Reactions • Serious Skin Reactions • Hyperammonemia and Encephalopathy (Without and With Concomitant Valproic Acid [VPA] Use) • Kidney Stones • Hypothermia with Concomitant Valproic Acid (VPA) Use
Onfi (clobazam) **2011**	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age or older.	administered in divided doses twice daily (the 5 mg dose can be administered as single daily dose)	• Somnolence/Sedation • Withdrawal • Physical and Psychological Dependence • Suicidal Behavior and Ideation • Serious Skin Reactions
Phenobarbital **Identified as antiepileptic in 1912**	Anticonvulsant–For the treatment of generalized and partial seizures	Oral: 60 to 120mg/day	• CNS Depression • Respiratory Depression/Circulatory Collapse • Allergic/Hypersensitivity Reactions
Epidiolex (cannabidiol) **2018**	treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age	Oral: twice daily	• Hepatocellular Injury • Somnolence and Sedation • Suicidal Behavior and Ideation • Hypersensitivity Reactions • Withdrawal of Antiepileptic Drugs • Most frequent cause of discontinuations was transaminase elevation.

Product Name Approval Year	Approved Indication	Dosage	Safety Issues
	and older		

11. References

[1] Marinus Pharmaceuticals. New Drug Application (NDA) 205904 for Ztalmy (ganaxolone), July 20, 2021.

[2] Olson HE, et al. Cyclin-Dependent Kinase-Like 5 Deficiency Disorder: Clinical Review. Pediatr Neurol. 2019 Aug;97:18-25.

[3] Fehr S, Et al. The CDKL5 disorder is an independent clinical entity associated with early-onset encephalopathy. Eur J Hum Genet. 2013;21(3):266-273.

[4] Olson HE, et al. Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder: clinical review. Pediatr Neurol. 2019;97:18-25.

[5] Symonds JD, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: a prospective population-based national cohort. Brain. 2019;142(8):2303-2318.

[6] Marinus Pharmaceuticals. Clinical Summary of Efficacy for NDA 215904 Ztalmy (ganaxolone), July 20, 2021.

[7] Marinus Pharmaceuticals. Clinical Summary of Safety for NDA 215904 Ztalmy (ganaxolone), July 20, 2021.

[8] Marinus Pharmaceuticals. Draft Prescribing Information for NDA 215904 Ztalmy (ganaxolone), July 20, 2021.

[9] Dinsmore, S. Division of Neurology 1. Draft Clinical Review for NDA 215904 Ztalmy (ganaxolone), February 16, 2022.

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