CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219876Orig1s000

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	219876
PDUFA Goal Date	August 18, 2025
Nexus TTT #	2025-12355
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader(s)	Naomi Boston, Pharm.D.
Acting Division Director	Laura Zendel, Pharm.D.
Review Completion Date	August 4, 2025
Subject	Evaluation of Need for a REMS
[Established/Proper] Name	dordaviprone
Trade Name	Modeyso
Name of Applicant	Chimerix, Inc.
Therapeutic Class	protease activator
Dosage Form(s)	125 mg capsule
Dosing Regimen	Adults: dordaviprone 625 mg orally once weekly Pediatric patients aged 1 to < 17 years who weigh at least 10 kg: • 10 kg to < 12.5 kg: dordaviprone 125 mg orally once weekly • 12.5 kg to < 27.5 kg: dordaviprone 250 mg orally once weekly • 27.5 kg to < 42.5 kg: dordaviprone 375 mg orally once weekly • 42.5 kg to < 52.5 kg: dordaviprone 500 mg orally once weekly • ≥ 52.5 kg: dordaviprone 625 mg orally once weekly

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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 Modeyso (dordaviprone) is necessary to ensure the benefits outweigh its risks. Chimerix, Inc. submitted a New Drug Application (NDA) 219876 for dordaviprone with the proposed indication (b) (4) The FDA approved indication will be for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy. The serious risks associated with dordaviprone include hypersensitivity, QTc interval prolongation, and embryo-fetal toxicity. The applicant did not submit a proposed REMS but submitted a risk management plan with routine pharmacovigilance activities.

DRM and Division of Oncology 2 (DO2) agree that a REMS is not necessary to ensure the benefits of dordaviprone outweigh its risks. The efficacy of dordaviprone was supported by an integrated efficacy population from studies ONC006, ONC013, ONC014, ONC016, and ONC018, in which the dordaviprone group had an overall response rate assessed by blinded independent central review according to Response Assessment in Neuro-Oncology 2.0 criteria of 22%. DO2 recommends accelerated approval based on the currently available data. The serious risks associated with dordaviprone of hypersensitivity, QTc interval prolongation, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with dordaviprone.

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)[a] Modeyso (dordaviprone) is necessary to ensure the benefits outweigh its risks. Chimerix, Inc. submitted a New Drug Application (NDA) 219876 for dordaviprone with the proposed indication (b) (4)

This application is under review in the Division of Oncology 2 (D02). The applicant did not submit a proposed REMS but submitted a risk management plan with routine pharmacovigilance activities.

2. Background

2.1. Product Information

Modeyso (dordaviprone), an NME, is proposed (b) (4)

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

Dordaviprone is a protease activator of the mitochondrial caseinolytic protease P and inhibits the dopamine D2 receptor. In-vitro, dordaviprone activated the integrated stress response, induced apoptosis, and altered mitochondrial metabolism leading to restored histone H3 K27 trimethylation in H3 K27M-mutant diffuse glioma models. Dordaviprone is proposed to be supplied as a 125 mg capsule.

The proposed dosing regimen in adults is dordaviprone 625 mg orally once weekly.

The proposed dosing regimen in pediatric patients aged 1 to < 17 years old who weigh at least 10 kg is:

- 10 kg to < 12.5 kg: dordaviprone 125 mg orally once weekly
- 12.5 kg to < 27.5 kg: dordaviprone 250 mg orally once weekly
- 27.5 kg to < 42.5 kg: dordaviprone 375 mg orally once weekly
- 42.5 kg to < 52.5 kg: dordaviprone 500 mg orally once weekly
- ≥ 52.5 kg: dordaviprone 625 mg orally once weekly

Dordaviprone is continued until disease progression or unacceptable toxicity.[b]

Dordaviprone is not currently approved in any jurisdiction. Dordaviprone was designated as an orphan product and received fast track designation. If approved, the indication will be approved under accelerated approval based on response rate and duration of response.[c]

2.2. Regulatory History

The following is a summary of the regulatory history for dordaviprone NDA 219876 relevant to this review:

- 06/04/2018: Orphan drug designation granted
- 11/05/2018: Fast track designation granted
- 12/18/2024: NDA 219876 submission (b) (4)
- 04/23/2025: A Post 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 dordaviprone

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

[c] The proposed label includes language that this indication is approved under accelerated approval based on response rate and duration of response, and overall survival and progression free survival have not been demonstrated.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Diffuse midline glioma harboring an H3 K27M mutation is a rare brain tumor subtype, defined by somatic mutations in genes encoding the histone H3 protein.[2] The 2021 WHO Classification of CNS Tumors defines these tumors as a pediatric-type diffuse high grade glioma (WHO Grade 4). The annual incidence of H3 K27M-mutant diffuse midline glioma in the United States is approximately 0.06 per 100,000 population.[3,d] H3 K27M-mutant diffuse midline gliomas are diagnosed in both adult and pediatric patients. Patients with high-grade gliomas frequently experience progressive neurological impairments such as cognitive decline, seizures, aphasia, personality changes, and decreased levels of consciousness.[4] The median overall survival is 10 to 15 months from diagnosis.[e]

3.2. Description of Current Treatment Options

The standard of care treatment of H3 K27M-mutant diffuse midline glioma includes surgery and radiation.[2] Gross total resections are typically infeasible due to the midline location. After radiation, most patients are enrolled on clinical trials or elect to pursue palliative/best supportive care. There are no specific therapies approved by the FDA for the treatment of H3 K27M-mutant diffuse midline glioma.

4. Benefit Assessment

The trials supporting this application for efficacy of dordaviprone consisted of five open label, non-randomized clinical studies conducted in the United States.[1,2] These studies included the Phase 2 ONC006 study (NCT 02525692), Phase 2 ONC013 study (NCT 03295396), Phase 1 ONC014 (NCT 03416530), compassionate use ONC016 study (NCT 05392374), and expanded access ONC018 study (NCT 03134131). An integrated efficacy population (N=50) was established using pre-specified criteria including patients who received single-agent dordaviprone, have diffuse midline glioma harboring an H3 K27M mutation with progressive and measurable disease per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, be ≥ 90 days post radiation therapy, have adequate washout from prior anticancer therapies, have a Karnofsky Performance Status/Lansky Performance Status (KPS/LPS) score ≥ 60, and have stable or decreasing corticosteroid use.

The major efficacy outcome measure was overall response rate (ORR) assessed by blinded independent central review (BICR) according to Response Assessment in Neuro-Oncology (RANO) 2.0 criteria. Additional efficacy outcome measures included BICR-assessed ORR according to RANO-HGG criteria and

[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.*

[e] 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.*

Response Assessment in Neuro-Oncology-Low Grade Glioma (RANO-LGG) criteria, duration of response (DOR), and time to response. The dordaviprone treatment group had an ORR assessed by BICR according to RANO 2.0 criteria of 22% (95% CI 12% to 36%). The median DOR was 10.3 months in the dordaviprone group (95% CI 7.3 to 15.2). Among responders, the median time to response was 3.6 months (range 1.6 to 15.6). The dordaviprone treatment group had an ORR, based on BICR-assessed RANO-HGG criteria, of 20% (95% CI 10% to 34%). In addition, the dordaviprone treatment group had an ORR, based on BICR-assessed RANO-LGG criteria, of 20% (95% CI 10% to 34%). The clinical reviewer recommended accelerated approval based on the currently available data.[f] Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial. The clinical reviewer stated the observed ORR, along with the observed duration of responses, is clinically meaningful in the setting of a genetically based biologic rationale and the lack of available therapies in this disease with poor prognosis.

5. Risk Assessment & Safe-Use Conditions

The safety of dordaviprone was evaluated in studies ONC006, ONC013, ONC014, and ONC018.[1,2,g] In the pooled safety population, which reflects exposure to dordaviprone at the recommended weight-based dose taken until disease progression or unacceptable toxicity, 376 patients received dordaviprone. Discontinuation due to an adverse reaction occurred in 2.1% of patients exposed to dordaviprone. Common adverse reactions reported with dordaviprone included fatigue, headache, vomiting, nausea, and musculoskeletal pain. The most common Grade 3 or 4 laboratory abnormalities included decreased lymphocytes, decreased calcium, and increased alanine aminotransferase.

In the pooled safety population, there were 33 deaths due to a treatment emergent adverse event within 30 days of the last dose of dordaviprone and before the initiation of additional anticancer therapies and 11 deaths due to a treatment emergent adverse event after the initiation of additional anticancer therapy.[2] Twenty-six deaths were due to disease progression. Eighteen deaths were due to other Grade 5 adverse events including death (n=3), respiratory failure (n=3), respiratory distress (n=2), dyspnea (n=2), aspiration (n=2), cardiac arrest (n=2), encephalopathy (n=1), sepsis (n=1), intracranial hemorrhage (n=1), and hydrocephalus (n=1). Per the clinical reviewer's assessment of the deaths, the cause of death due encephalopathy, cardiac arrest (n=2), and intracranial hemorrhage was likely disease-related, but it was challenging to rule out contribution of dordaviprone to the adverse event. The other causes of death were unlikely related to dordaviprone.

[f] 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.*

[g] 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 serious risks[h] associated with dordaviprone which include hypersensitivity, QTc interval prolongation, and embryo-fetal toxicity are summarized in the sections below**.**

5.1. Hypersensitivity

Dordaviprone can cause severe hypersensitivity reactions. An adverse reaction of Grade 3 hypersensitivity reactions occurred in 0.3% of patients receiving dordaviprone. The proposed label states to inform patients about the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical attention if symptoms occur. It recommends if clinically significant hypersensitivity or anaphylaxis occur to immediately interrupt dordaviprone and initiate appropriate medical treatment and supportive care. Based on the severity of the adverse reaction, temporarily interrupt or permanently discontinue dordaviprone. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2. QTc Interval Prolongation

Section 5 the draft labeling indicates that dordaviprone can cause a concentration dependent QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsades de pointes) or sudden death. At 1.2 times the maximum recommended dose, the estimated mean QTcF change was 11.8 msec. In the pooled safety population, in 82 patients who underwent at least one post-baseline ECG assessment, a QTc increase compared to baseline greater than 60 msec occurred in 6% of patients receiving dordaviprone, with a QTc greater than 500 msec was reported in 1.2% of patients.

The proposed label states to monitor ECGs and electrolytes prior to starting dordaviprone and then periodically during treatment as clinically indicated. The proposed label also states significant prolongation of the QT interval may occur when dordaviprone is taken concomitantly with other products that have a known potential to prolong the QT interval. The proposed label recommends avoiding concomitant use of dordaviprone with products known to prolong the QT interval and if concomitant use cannot be avoided, separate administration of dordaviprone and the QT-prolonging product.

The proposed label recommends increasing the frequency of monitoring when administering dordaviprone to patients taking other products that have a known potential to prolong the QT interval and in patients with congenital long QT syndrome, existing QTc prolongation, a history of ventricular arrhythmias, electrolyte abnormalities, heart failure, or who are taking strong or moderate CYP3A4 inhibitors. It recommends to interrupt or reduce the dose of dordaviprone in patients who develop QT

[h] 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.

prolongation, and permanently discontinue dordaviprone in patients with signs of life-threatening arrhythmias. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3. Embryo-fetal Toxicity

Dordaviprone may cause fetal harm based on the mechanism of action of the drug and animal studies. Dordaviprone orally administered to pregnant rats and rabbits during organogenesis caused embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures below the human exposure at the highest recommended dose. No clinical data is available with dordaviprone in pregnancy in humans. The proposed label states to advise pregnant women and females of reproductive potential of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting dordaviprone and to use effective contraception during treatment with dordaviprone and for 1 month after the last dose. In addition, in males with female partners of reproductive potential it is recommended to use effective contraception during treatment with dordaviprone and for 1 month after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

If approved, dordaviprone will primarily be used in both inpatient and outpatient settings. The likely prescribers will be oncologists who specialize in this type of CNS tumor**.** Pediatric patient's caregivers will be involved in treatment including monitoring for adverse effects.

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of dordaviprone on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). Dordaviprone is a protease activator and will be the first approved systemic therapy for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy. The efficacy of dordaviprone was supported by an integrated efficacy population from studies ONC006, ONC013, ONC014, ONC016, and ONC018, in which

the dordaviprone group had an ORR assessed by BICR according to RANO 2.0 criteria of 22%. The serious risks associated with dordaviprone of hypersensitivity, QTc interval prolongation, and embryo-fetal will be communicated in the warnings and precautions section of the label.

Diffuse midline glioma harboring an H3 K27M mutation is a rare brain tumor subtype, defined by somatic mutations in genes encoding the histone H3 protein. The annual incidence of H3 K27M-mutant diffuse midline glioma in the United States is approximately 0.06 per 100,000 population. H3 K27M-mutant diffuse midline gliomas are diagnosed in both adult and pediatric patients. The median overall survival is 10 to 15 months from diagnosis. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with dordaviprone. The clinical reviewer stated although dordaviprone can cause serious toxicities, these safety concerns are adequately addressed by information in the product labeling. If approved, based on the efficacy and risks associated with dordaviprone for the treatment of adult and pediatric patients 1 year of age and older with diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy, the DRM and DO2 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable in the context of the treatment of a life-threatening disease, therefore, a REMS is not necessary for dordaviprone 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. Appendices

10.1. References

[1] Proposed prescribing information for dordaviprone as currently edited by FDA, last accessed July 25, 2025.

[2] Dordaviprone NDA 219876 multi-disciplinary review and evaluation. Last accessed July 25, 2025.

[3] Price M, Ballard C, Benedetti J, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2017-2021. *Neuro Oncol*. 2024;26(Supplement_6):vi1-vi85.

[4] Chimerix, Inc. Dordaviprone. Module 2.5. clinical overview. December 18, 2024.

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/s/

BRAD T MORIYAMA
08/04/2025 01:06:45 PM

NAOMI S BOSTON
08/04/2025 01:15:02 PM

LAURA A ZENDEL
08/04/2025 04:04:52 PM