dordaviprone (Modeyso™)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO336

Description

Dordaviprone (Modeyso) is an orally administered protease activator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
dordaviprone (Modeyso)	Diffuse midline glioma harboring an H3 K27M mutation with progressive disease following prior therapy	125 mg capsule	1 to <17 years old: see appendix*
			≥17 years old: 20 capsules/28 days

**Please note that for pediatric members the dose is based on body weight. Please see appendix for dosing limits.*

Initial Evaluation

I. **Dordaviprone (Modeyso)** may be considered medically necessary when the following criteria are met:
   A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   B. Not used in combination with any other oncology therapy; **AND**
   C. A diagnosis of **diffuse midline glioma (DMG)** when the following are met:
      1. Documentation the member has a biopsy confirmed H3 K27M mutation; **AND**
      2. ~~2.~~ Documentation the member does not have diffuse intrinsic pontine glioma (DIPG) or a primary spinal tumor; **AND**
      3. Documentation of a Karnofsky/Lansky performance score (KPS/LPS) of ≥60; **AND**
      4. The member has had disease progression following radiation therapy; **AND**
      5. Treatment with temozolomide has been ineffective, contraindicated, or not tolerated; **AND**
      6. Provider attestation that member is not a candidate for clinical trial participation; **AND**
      7. Member is one to 21 years of age; **AND**
         i. The tumor has been treated with reirradiation or documentation that reirradiation is not feasible; **OR**
      8. Member is 22 years of age or older; **AND**
         i. The member has had disease progression on one of the following unless not tolerated, contraindicated or ineffective:
            a. Re-treatment with temozolomide; **OR**
            b. Bevacizumab*; **OR**
            c. Lomustine or carmustine; **OR**

ii. Provider attestation the member is not a candidate for chemotherapy due to tolerability concerns or not in alignment with care goals

*Please note: medications notated with an asterisk may require additional review

II. Dordaviprone (Modeyso) is considered investigational when used for all other conditions, including but not limited to:
   A. Dordaviprone (Modeyso) used in combination with another oncology therapy
   B. Diffuse intrinsic pontine glioma (DIPG) and primary spinal tumors
   C. Refractory meningioma
   D. Maintenance therapy in acute myeloid leukemia and myelodysplastic syndrome after stem cell transplant
   E. Colorectal cancer

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The medication will not be used in combination with other oncology therapy; **AND**
IV. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
V. Documentation of member's body weight if member is one to <17 years of age.

Supporting Evidence

I. Dordaviprone (Modeyso) was FDA-approved based on the findings of an integrated analysis of five separate open label, single-arm studies consisting of Phase I/II trials and compassionate use/expanded access programs. Eligible patients were included in the integrated analysis as they enrolled in their corresponding trials until a total of 50 patients were reached based on prespecified inclusion and exclusion criteria. Included patients had recurrent and/or progressive H3 K27M mutant DMG that was measurable per Response Assessment in Neuro-Oncology-High Grade Glioma (RANO-HGG) criteria, ≥2 years of age, had a Karnofsky/Lansky performance score (KPS/LPS) of ≥60, and previously received RT with a 90-day washout. Patients were excluded if they had a diagnosis of diffuse intrinsic pontine glioma (DIPG) or a primary spinal tumor. The median age was 30, including four patients aged <18 years. Previous use of temozolomide was in 44 (88%), prior bevacizumab in 13 (26%), history of re-irradiation in 3 (6%), and 37 (74%) had their first recurrence. Overall response rate was 22% (95% CI; 22, 36), with a partial response of 8 (16%) and a minor response of 3 (6%). Duration of response (n=11) was 10.3 months (95% CI:

7.3, 15.2), with an observed DOR ≥6 months for 8 (73%) and ≥12 months for 3 (27%) of the 11 patients.

II. Confidence in the integrated analysis is low, particularly due to selection bias and the open-label, single-arm, early-phase trial designs which are considered observational, providing only a signal of potential clinical usefulness. Additionally, ORR is a surrogate endpoint which has not been established to correlate with overall survival and progression free survival. Limitations include heterogeneity across trials, underrepresentation of pediatric patients, and a narrow selection criteria that enriched for a less clinically severe cohort, which precludes extrapolation of data to the broader patient population with DMG. The results do not apply to patients with an unknown H3 K27M status, DIPG or spinal tumors and require validation in a confirmatory randomized clinical trial.

III. Diffuse intrinsic pontine glioma (DIPG) refers to tumors centered in the pons part of the brain and is considered a location-specific subtype of DMG. In contrast, DMG is a broader category encompassing tumors that arise in midline structures of the brain central nervous system, including the thalamus, hypothalamus, basal ganglia, brainstem [non-DIPG], cerebellum, cerebellar peduncle, midline cortex, corpus callosum, pineal region, optic tract, or optic chiasm. The World Health Organization (WHO) classifies H3 K27M-mutant glioma as a pediatric-type diffuse high-grade glioma, although, it is also diagnosed in adults. The National Comprehensive Cancer Network (NCCN) guidelines differentiate and have separate guidelines for both pediatrics and adults—pediatric aged 21 years and younger and adults 22 years and older. Both pediatric and adult NCCN guidelines prefer clinical trial participation following tumor progression/recurrence prior to opting for additional systemic treatments as a Category 2A recommendation. Of note, in regard to the adult treatment guidelines, “due to a lack of other effective therapies for H3-mutated high-grade gliomas, the current treatment recommendations are the same as options for glioblastoma,” hence the NCCN recommendations for adults will be viewed under glioblastoma as of this writing. Histone-driven gliomas are no longer classified as glioblastomas, and it is possible that future NCCN guidelines will reflect this reclassification.

IV. Patients with DIPG and primary spinal tumors were excluded from the integrated analysis supporting FDA approval of dordaviprone (Modeyso) due to challenges in reliably assessing imaging and determining treatment response in these populations. As a result, there is insufficient evidence to support efficacy or safety in these tumor types. Coverage is therefore limited to avoid extrapolation beyond the studied disease population and maintain alignment with currently available clinical evidence.

V. Provider attestation is required to confirm that the member is not a candidate for continued chemotherapy or participation in a clinical trial. Per NCCN guidelines, all patients with DMG should be encouraged to enroll in clinical trials at any stage of their diagnosis and treatment journey, as these trials may currently offer the most appropriate treatment options for this rare and complex cancer.

VI. Documentation is required for reirradiation feasibility to ensure alignment with the NCCN guidelines as a 2A recommendation. Radiation therapy (RT) and reirradiation are highly effective for symptom management although its effects are temporary and symptoms reoccur. The NCCN guidelines note that majority of studies for reirradiation were conducted in adults with

recurrent glioblastoma multiforme (GBM) and have suggested improvements in progression free survival (PFS) and quality of life measurements but fall short of overall survival benefits.

VII. Provider attestation is required to assess for member candidacy of other NCCN guideline recommended systemic therapies, (e.g., retreatment with temozolomide, or bevacizumab, or lomustine). Although these systemic agents hold a Category 2A recommendation per NCCN, their evidence is largely extrapolated to patients with this specific form and genetic variant of DMG. Uniquely, dordaviprone (Modeyso) is the first FDA-approved treatment for H3 K27M-mutant DMG and an attestation allows for provider clinical discretion when balancing potential toxicities and patient specific treatment goals against best available evidence-based practices.

VIII. Retreatment with temozolomide is recommended for members aged 22 years and older, unless significant toxicity concerns exist or the tumor is MGMT-unmethylated. This approach is supported by the NCCN guidelines as a preferred regimen with a Category 2A recommendation. Evidence includes a retrospective review, demonstrating a 57% progression-free survival (PFS) at 6 months with adjuvant temozolomide (Perry JR, et al) and an open-label, randomized study with temozolomide + radiotherapy (RT) followed by adjuvant temozolomide showing overall survival (OS) of 9–10 months. Patients with MGMT-methylated tumors had better outcomes—6 -month PFS: 39.7% vs. 6.9% for unmethylated tumors (Weller M, et al). National Comprehensive Cancer Network guidelines also advise avoiding temozolomide in patients with MGMT-unmethylated tumors.

IX. For members aged 22 years and older, bevacizumab may be appropriate for symptom management such as peritumor edema due to its steroid-sparing effects. Bevacizumab may also be continued for members who have evidence of radiographic progression in effort to prevent rapid neurologic deterioration. This approach is supported by NCCN guidelines as a preferred regimen with a Category 2A recommendation. Evidence includes a randomized, non-comparative, Phase II trial that assessed bevacizumab monotherapy or in combination with irinotecan demonstrating a median OS of 9-10 months for both groups with significantly less adverse events/toxicities in the bevacizumab only group (Cloughesy T, et al).

X. Lomustine and carmustine may be appropriate for members aged 22 years and older unless toxicity concerns are present. This approach is supported by NCCN guidelines as a preferred regimen with a Category 2A recommendation for both agents. Evidence to support this approach for lomustine includes an open-label, randomized, Phase III trial that compared lomustine vs enzastaurin for the treatment of recurrent intracranial glioblastoma which demonstrated an OS of about 7 months for both groups; however, significantly more adverse effects/toxicities and deaths were noted in the enzastaurin group (Wick W, et al). Evidence to support this approach for carmustine includes a Phase II trial of 40 patients that assessed carmustine 80 mg/m2 on days 1-3, every 8 weeks, for a maximum of 6 cycles which demonstrated a median time-to-progression of 13.3 weeks and 6-month PFS of 17.5%; authors noted significant major side effects (hematologic, hepatic and pulmonary toxicities) and slow recovery (Brandes AA, et al).

XI. A confirmatory Phase 3 trial, ACTION, is currently being investigated assessing dordaviprone (Modeyso) in H3 K27M-mutant DMG following RT, in the first-line setting for systemic therapy.

Investigational or Not Medically Necessary Uses

I. Dordaviprone (Modeyso) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Dordaviprone (Modeyso) used in combination with another oncology therapy
   B. Diffuse intrinsic pontine glioma (DIPG) and primary spinal tumors
   C. Refractory meningioma
      i. A Phase 2 trial for the treatment of refractory meningioma is currently suspended pending protocol rewrite, scientific review committee approval and institutional review board approval (NCT06012929). Estimated study completion date is April 2027. Requests for this indication are considered experimental and investigational at this time.
   D. Maintenance therapy in acute myeloid leukemia and myelodysplastic syndrome after stem cell transplant
      i. Dordaviprone (Modeyso) was studied in a Phase 1 trial single-center pilot study of 20 patients with AML/MDS status-post allogeneic hematopoietic stem cell transplant to determine safety and preliminary efficacy as maintenance therapy (NCT03932643). Study completion date was March 27, 2025; however, results are not available at this time. Requests for this indication are considered experimental and investigational at this time.
   E. Colorectal cancer
      i. Dordaviprone (Modeyso) is currently being investigated in a Phase 1 trial to determine safety, side effects and appropriate dose in preventing colorectal cancer in patients with familial adenomatous polyposis (FAP) or a history of multiple polyps (NCT05630794). Primary completion is estimated in March 2026. Requests for this indication are considered experimental and investigational at this time.

Appendix

Table 1: Recommended Body Weight-Based Dosage for Pediatric Members

Body Weight	Recommended Dosage	Quantity Limit (per 28 days)
10 kg to < 12.5 kg	125 mg Once Weekly	4 capsules
12.5 kg to < 27.5 kg	250 mg Once Weekly	8 capsules
27.5 kg to < 42.5 kg	375 mg Once Weekly	12 capsules
42.5 kg to < 52.5 kg	500 mg Once Weekly	16 capsules
> 52.5 kg	625 mg Once Weekly	20 capsules

References

1. National Comprehensive Cancer Network. Pediatric Central Nervous System Cancers. (Version 3.2025). NCCN. September 2, 2025. Accessed November 10, 2025. https://www.nccn.org/professionals/physician_gls/pdf/ped_cns.pdf

2. National Comprehensive Cancer Network. Central Nervous System Cancers. (Version 2.2025). NCCN. August 28, 2025. Accessed November 10, 2025. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
3. National Cancer Institute. Diffuse midline glioma: diagnosis and treatment. *National Cancer Institute*. Accessed November 10, 2025. https://www.cancer.gov/rare-brain-spine-tumor/tumors/diffuse-midline-gliomas.
4. Argersinger DP, Rivas SR, Shah AH, Jackson S, Heiss JD. New Developments in the Pathogenesis, Therapeutic Targeting, and Treatment of H3K27M-Mutant Diffuse Midline Glioma. Cancers (Basel). 2021;13(21):5280. Published 2021 Oct 21.
5. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251.
6. Zhou H, Liu Y, Zhang Y, et al. Targeting H3K27M-mutant diffuse midline glioma with a novel epigenetic therapy. *Int J Radiat Oncol Biol Phys*. 2024;119(5):1123-1134.
7. Modeyso. Package insert. Jazz Pharmaceuticals, Inc; 2025.
8. Perry JR, Rizek P, Cashman R, et al. Temozolomide rechallenge in recurrent malignant glioma by using a continuous temozolomide schedule: the "rescue" approach. Cancer. 2008;113(8):2152-2157.
9. Cloughesy T, Prados MD, Mikkelsen T, et al. A phase 2 randomized non-comparative clinical trial of the effect of bevacizumab alone or in combination with irinotecan on 6-month progression-free survival in recurrent refractory glioblastoma [abstract]. J Clin Oncol. 2008;26(suppl):Abstract 2010b.
10. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. J Clin Oncol. 2010;28(7):1168-1174.
11. Weller M, Tabatabai G, Kastner B, et al. MGMT promoter methylation is a strong prognostic biomarker for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: the DIRECTOR trial. Clin Cancer Res 2015;21:2057-2064.
12. Nabors B, Portnow J, Hattangadi-Gluth J, et al. NCCN CNS tumor guidelines update for 2023. *Neuro Oncol*. 2023;25(12):2114-2116.
13. Brandes AA, Tosoni A, Amista P, et al. How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. Neurology 2004;63:1281-1284.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2026