IOWA | Health and Human Services

Iowa PDL New Drug Review

Proprietary Name: Modeyso®
Common Name: dordaviprone
PDL Category: Antineoplastic Agents

Pharmacology/Usage: Dordaviprone, the active ingredient of Modeyso®, is a protease activator of the mitochondrial caseinolytic protease P (ClpP). Dordaviprone also inhibits the dopamine D2 receptor. Dordaviprone exhibited antitumor activity in cell-based assays and in vivo models of H3 K27M-mutant diffuse glioma.

Indication: 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. This indication is approved under accelerated approval based on overall 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).

There is no pregnancy category for this medication; however, the risk summary indicates that based on findings from animal studies and its mechanism of action, Modeyso® can cause fetal harm when administered to a pregnant woman. There are no available data with use in pregnant women to inform a drug-associated risk. Verify pregnancy status of females of reproductive potential prior to starting Modeyso®. In addition, advise females of reproductive potential and male patients with female partners of reproductive potential to use effective contraception during Modeyso® treatment and for 1 month after the last dose. The safety and efficacy of use in the pediatric population less than 1 year of age have not been established.

Dosage Form: Capsules: 125mg.

Recommended Dosage: Select patients for treatment with Modeyso® based on the presence of an H3 K27M mutation from tumor specimens. An FDA-approved test for the detection of this mutation is not currently available.

Monitor electrocardiograms (ECG) and electrolytes before starting Modeyso® and periodically during treatment as clinically indicated.

Take on an empty stomach (at least 1 hour before or 3 hours after food intake). The recommended dosage for adults is 625mg PO once weekly. The recommended dosage in pediatric patients aged 1 to less than 17 years who weigh at least 10kg is based on body weight. A recommended dosage has not been established in pediatric patients who weigh less than 10kg. Refer to the table below, which was adapted from the prescribing information.

Body Weight (kg)	Recommended Dosage
10kg to <12.5kg	125mg once weekly
12.5kg to <27.5kg	250mg once weekly
27.5kg to <42.5kg	375mg once weekly

Body Weight (kg)	Recommended Dosage
42.5kg to <52.5kg	500mg once weekly
≥52.5kg	625mg once weekly

Continue Modeyso® until disease progression or unacceptable toxicity.

Swallow capsules whole. For patients unable to swallow capsules whole, open each capsule, mix contents with about 15 to 30ml of liquid (sports drink, apple juice, lemonade, or water) before administration and administer orally as a liquid. Once mixed, administer within 2 hours of preparation or discard and mix a new dose.

If vomiting occurs after taking a dose, do not take an additional dose and take the next dose at the regularly scheduled time. If a dose is missed within 2 days, take the missed dose as soon as possible. If a dose is missed by more than 2 days, skip the missed dose and take the next dose at the scheduled time.

There are recommended dosage reductions for adverse reactions, such as hypersensitivity, QTc interval prolongation, and other adverse reactions. Refer to the prescribing information for additional information.

Drug Interactions: Dordaviprone is a CYP3A4 substrate. Avoid concomitant use of strong and moderate CYP3A4 inhibitors with Modeyso®. If concomitant use cannot be avoided for adults and pediatric patients who weigh at least 52.5kg, reduce the Modeyso® dose as recommended per the prescribing information.

Avoid concomitant use of strong and moderate CYP3A4 inducers with Modeyso®.

Modeyso® causes concentration dependent QTc interval prolongation. Avoid concomitant use of Modeyso® with products known to prolong the QTc interval. If concomitant use cannot be avoided, separate administration of Modeyso® and the QT-prolonging product.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Modeyso®) for all grades. There was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included fatigue (34%), gait disturbance (16%), headache (32%), cranial nerve disorders (16%), hemiparesis (15%), dysarthria (13%), dizziness (13%), ataxia (10%), vomiting (24%), nausea (24%), dysphagia (13%), constipation (11%), musculoskeletal pain (20%), muscular weakness (13%), hyperglycemia (12%), and rash (11%).

Laboratory abnormalities for all grades included alanine aminotransferase increased (28%), aspartate aminotransferase increased (22%), calcium decreased (20%), sodium decreased (14%), potassium decreased (13%), glucose decreased (11%), alkaline phosphatase increased (11%), hemoglobin decreased (25%), neutrophils decreased (24%), and lymphocytes decreased (19%).

Modeyso® can cause severe hypersensitivity reactions. Inform patients about the signs and symptoms of hypersensitivity reactions and instruct them to seek immediate medical attention if symptoms occur. If clinically significant hypersensitivity or anaphylaxis occur, interrupt Modeyso® and start appropriate medical treatment and supportive care. Based on the severity of the adverse reaction, temporarily interrupt or permanently discontinue Modeyso®.

Modeyso® causes a concentration-dependent QTc interval prolongation, which can increase the risk for ventricular tachyarrhythmias (e.g., torsade de pointes) or sudden death. Monitor ECGs and electrolytes prior to starting treatment and then periodically during treatment as clinically indicated. Significant prolongation of the QT interval may occur when Modeyso® is taken concomitantly with other products that have a known potential to prolong the QT interval. Avoid concomitant use of Modeyso® with products known to prolong the QT interval. If concomitant

use cannot be avoided, separate administration of Modeyso® and the QT-prolonging product. Increase the frequency of monitoring when administering Modeyso® 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. Interrupt or reduce the dose of Modeyso® in patients who develop QT prolongation, and permanently discontinue Modeyso® in patients with signs of life-threatening arrhythmias.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Jazz Pharmaceuticals, Inc.

Analysis: The efficacy of Modeyso® was assessed in adult and pediatric patients with glioma across 5 open-label, non-randomized clinical trials conducted in the US. Pre-specified criteria were defined to establish an integrated efficacy population; eligible patients were required to have received single-agent Modeyso®, 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. Patients received weight-based dosing of Modeyso® until disease progression or unacceptable toxicity.

The integrated efficacy population included patients (N=50) who met these criteria. Baseline demographics of included patients were a median age of 31 years (range 9 to 70), with 6% younger than 17 years of age, while 46% were female, 80% were White, and 72% had KPS/LPS 80 to 100. Relevant disease characteristics included 72% treated at first recurrence, 28% had 2 or more recurrences, primary tumor location was thalamic in 52% of patients and non-thalamic midline region in 48% of patients, 88% had received prior temozolomide, 62% were receiving corticosteroids at baseline, and the median time from end of prior radiation was 7.4 months.

The main efficacy outcome measure was overall response rate (ORR) as assessed by blinded independent central review (BICR) per RANO 2.0 criteria. Additional efficacy outcome measures were BICR-assessed ORR per RANO-HGG criteria and Response Assessment in Neuro-Oncology-Low Grade Glioma (RANO-LGG) criteria, duration of response, and time to response. Efficacy results are presented in the table below, which was adapted from the prescribing information.

Efficacy Parameter	Modeyso® (N=50)
Overall Response Rate (ORR)	22%
Partial Response	16%
Minor Response	6%
Duration of Response (DOR)	N=11
Median, months	10.3
% with observed DOR ≥6 months	73%
% with observed DOR ≥12 months	27%

Among the responders, the median time to response was 3.6 months (range 1.6, 15.6).

Using BICR-assessed RANO 2.0 criteria, there was one additional responder based on the integrated response assessment, which takes into account corticosteroid use and performance status. Based on BICR-assessed RANO-

HGG criteria (N=50), the ORR was 20%, with 1 complete and 9 partial responses. Based on BICR-assessed RANO-LGG criteria (N=50), the ORR was 20%, with 5 partial and 5 minor responses.

Place in Therapy: Modeyso® is a protease activator indicated 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. This indication is 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). Select patients for Modeyso® treatment based on the presence of an H3 K27M mutation from tumor specimens. Monitor ECG and electrolytes before starting treatment and periodically during treatment as clinically indicated. The efficacy of Modeyso® was assessed in adult and pediatric patients with glioma across 5 open-label, non-randomized clinical trials. The main efficacy outcome measure was overall response rate (ORR) assessed by BICR per RANO 2.0 criteria, and the ORR was 22%.

Summary

It is recommended that Modeyso® should be non-recommended with conditions in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:
- ☐ **Recommended**
- ☒ **Non-Recommended with Conditions**

References

[1] Modeyso [package insert]. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2025.