Drug Monograph

Drug Name: **Nulibry™ (fosdenopterin hydrobromide) vial**
Drug Class: **Cyclic Pyranopterin Monophosphate (cPMP) Replacement Therapy**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Nulibry is available as a lyophilized powder or cake in a single-dose vial for reconstitution for intravenous administration containing 9.5 mg fosdenopterin
Manufacturer:	Distributed by: Origin Biosciences, Inc., Boston, MA 02116.
Summary of Findings:	The efficacy of Nulibry was established based on a combined analysis of three clinical studies that were compared to data from a natural history study. The first two studies were prospective, open-label, single-arm, dose-escalation studies, while the third was a retrospective, observational study. The combined analysis for efficacy of Nulibry in treating MoCD Type A resulted in a total of 13 treated patients from all the studies which was then compared to 18 genotype-matched, untreated patients in the natural history control group. The patients treated with Nulibry demonstrated improved overall survival probability of 92% at 1 year and 84% at 3 years vs 67% and 55% respectively for the untreated group. The patients treated with Nulibry also demonstrated an 82% reduction in the risk of death compared to the untreated group.
Status Recommendation:	☒ Clinical Edit ☐ PA Required ☐ Open Access ☐ PDL
Type of PA Criteria:	☒ Appropriate Indications ☐ Non-Preferred ☐ No PA Required ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1,2]

Molybdenum cofactor deficiency (MoCD) is an exceedingly rare genetic condition that is estimated to occur in 1 in 100,000 to 200,000 newborns worldwide. MoCD is characterized by brain dysfunction (encephalopathy) that worsens over time. Babies at birth may appear normal but within a week they have difficulty feeding and develop seizures that do not improve with treatment. It is thought that the condition is underdiagnosed due to the rapid decline and challenging diagnosis, but to date there have been 100 cases reported in the medical literature. MoCD is caused by mutations in the MOCS1, MOCS2, or GPHN gene, giving three forms of the disorder named types A, B, or C (i.e., MOCS1 gene mutations cause type A). The three forms of the disorder have the same signs and symptoms but are differentiated by their genetic cause or mutation. Each gene produces proteins that are involved with the formation of a molecule called molybdenum cofactor. Molybdenum cofactor is essential to the function of several enzymes that help metabolize different substances in the body. These substances can become toxic if not metabolized which in the case of MoCD leads to the buildup of sulfite, S-sulfocysteine (SSC), xanthine, and hypoxanthine. High levels of sulfite is thought to be mostly responsible for the encephalopathy, seizures, and other brain abnormalities that result in irreversible damage and severe developmental delays for the infant. A urine test to check for high levels of sulfite or S-sulfocysteine along with the child's symptoms are enough to diagnosis MoCD but a genetic test is the only way to confirm the diagnosis and determine which type or form of MoCD. Unfortunately, the prognosis is poor for all 3 forms of MoCD most children only surviving until 3-4 years of age and with greatly reduced quality of life.

Dosage Form [2]

Nulibry is available as a lyophilized powder or cake in a single-dose vial for reconstitution for intravenous administration containing 9.5mg fosdenopterin.

Manufacturer [2]

Distributed by: Origin Biosciences, Inc., Boston, MA 02116.

Indication(s) [2]

Nulibry is indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.

Clinical Efficacy [1,2,3] (mechanism of action/pharmacology, comparative efficacy)

Nulibry is a cyclic pyranopterin monophosphate that undergoes conversion to molybdopterin, which is further converted to molybdenum cofactor. Molybdenum cofactor is required for

molybdenum-dependent enzyme activation, including sulfite oxidase (SOX), which is an enzyme that reduces levels of neurotoxic sulfites.

Pharmacokinetics:

Absorption	Both C_{max} and $AUC_{0\text{-}inf}$ appear to increase proportionally with increasing doses
Metabolism	Nonenzymatic degradation processes to compound Z, an inactive oxidation product of endogenous cPMP
Excretion	Renal 40%
Half-life	$t_{1/2}$=1.2 to 1.7 hours

Clinical Trials Experience:

STUDY DESIGN **(NCT02047461)** **(NCT02629393)**	Combined analysis of 3 studies for a total of 13 treated patients. Study 1: a prospective, open-label, single-arm, dose escalation study in patients with MoCD Type A who were receiving treatment with recombinant cPMP (rcPMP) prior to treatment with Nulibry. Study 1 included 8 patients, 6 of whom previously participated in Study 3. Study 2: a prospective, open-label, single-arm, dose escalation study in one patient with MoCD Type A who had not been previously treated with rcPMP. Study 3: a retrospective, observational study that included 10 patients with a confirmed diagnosis of MoCD Type A, who received rcPMP. Six of these 10 patients were later enrolled in Study 1 to receive treatment with Nulibry.
INCLUSION CRITERIA	• Male or female patients with a genetically confirmed diagnosis of MoCD Type A (MOCS1 mutation) • Currently treated with rcPMP infusions
EXCLUSION CRITERIA	• Current or planned treatment with another investigational drug or device, with the exception rcPMP treatment through Day -1
TREATMENT REGIMEN	Study 1: The initial Nulibry dosage was matched to the patient's rcPMP dosage upon entering the study. The Nulibry dosage was then titrated over a period of 5 months to a maximum dosage of 0.9 mg/kg administered once daily as an intravenous infusion. Study 2: The initial dosage of Nulibry in Study 2 was based on the gestational age of the patient (i.e., 36 weeks). The initial dosage was then incrementally escalated up to a maximum dosage of 0.98 mg/kg administered once daily as an intravenous infusion (1.1 times the maximum approved recommended dosage)
RESULTS	Efficacy was assessed by comparing overall survival in pediatric patients treated with Nulibry or rcPMP (n=13) with an untreated natural history cohort of pediatric patients with genetically confirmed MoCD Type A who were genotype-matched to the treated patients (n=18). Patients treated with Nulibry or rcPMP had an improvement in overall survival compared to the untreated, genotype-matched, historical control group. At 1 year, the Kaplan Meier Survival Probability for the Nulibry (or rcPMP) group was 92% vs 67% for the untreated historical control group. At 3 years, the probability was found to be 84% in the treatment group vs 55% in the untreated historical control group. The patients treated with Nulibry also demonstrated an 82% reduction in the risk of death compared to the untreated group provided by a Hazard Ratio for Risk of Death 0.18 (95% CI: 0.04, 0.72).

	For a secondary endpoint in Studies 1 and 2 (n=9), treatment with Nulibry resulted in a reduction in baseline urine concentrations of SSC in patients with MoCD Type A and the reduction was sustained with long-term treatment over 48 months.
SAFETY	Discussed in the Adverse Effects section below.

Contraindications [(2)]

- None

Warnings and Precautions [(2)]

- Potential for Photosensitivity: Advise patients/caregivers to avoid patient exposure to sunlight, and to have the patient wear sunscreen, protective clothing, and sunglasses when exposed to the sun. If photosensitivity occurs, advise caregivers/patients to seek medical attention immediately and consider a dermatological evaluation.
- Pregnancy/Lactation: No studies have been performed.

Adverse Effects [(2)]

Most common, ≥ 25 %	**Nulibry Treated Patients (N= 9) n (%)**
Catheter-related complications	8 (89)
Pyrexia	7 (78)
Viral infection	5 (56)
Pneumonia	4 (44)
Otitis Media	4 (44)
Vomiting	4 (44)
Coughing/Sneezing	4 (44)
Upper viral respiratory infection	3 (33)
Gastroenteritis	3 (33)
Diarrhea	3 (33)
Bacteremia	3 (33)

Drug Interactions [(2)]

- No known significant drug interactions

Dosage and Administration [(2)]

- Start Nulibry if known or presumed MoCD Type A. Promptly discontinue if MoCD Type A is not confirmed by genetic testing.
- Reconstitute before use and complete infusion within 4 hours of reconstitution.
- Administer as an intravenous infusion once daily at a rate of 1.5 mL/minute with non-DEHP tubing with a 0.2 micron filter. Volumes below 2 mL may require syringe administration through slow intravenous push.

- Recommended Dosage in Patients One Year of Age or Older: 0.9 mg/kg given as an intravenous infusion once daily.
- See the table below for the recommended dosage in patients less than one year of age

Titration Schedule	Preterm Neonates (Gestational Age < 37 Weeks)	Term Neonates (Gestational Age 37 weeks and Above)
Initial Dosage	0.4 mg/kg once daily	0.55 mg/kg once daily
Month 1	0.7 mg/kg once daily	0.75 mg/kg once daily
Month 3	0.9 mg/kg once daily	0.9 mg/kg once daily

Cost [3]

Generic Name	Brand Name	Manufacturer	Dose	Cost**/Vial
Fosdenopterin	Nulibry™	Origin Biosciences	0.9mg/kg once daily	$1,369.86

** Wholesale Acquisition Cost

Conclusion

MoCD Type A is considered an ultra-rare disease with an estimated incidence of 1 per 342,000 to 411,000 live births. It is believed to be underdiagnosed due to the clinical presentation and challenging diagnosis. Nulibry is the first therapy approved by the FDA to reduce to risk of mortality in patients with MoCD Type A. Due to the low incidence of the rare disease, the approval was based on a very small patient population and the long-term outcomes of Nulibry therapy into adolescents remains unknown. The efficacy of Nulibry was established based on data combined from 3 clinical studies compared to data from a genotype-matched historical control. In the combined analysis, patients treated with Nulibry had a survival rate of 84% at 3 years compared to 55% for the untreated matched control patients. The most common adverse reactions (≥25%) were catheter-related complications, pyrexia, viral infection, pneumonia, otitis media, vomiting, cough/sneezing, viral upper respiratory infection, gastroenteritis, bacteremia and diarrhea. Prior to Nulibry, therapy for MoCD Type A was strictly supportive management of symptoms such as anticonvulsants for seizures. Therapy with Nulibry is a life-long therapy and will likely be at a cost of over $500,000 annually, based on patient's weight and gestational age. The manufacturer developed a patient support program to assist patients in accessing Nulibry and provide resources to their treatment.

Recommendation

The MO Healthnet Division recommends adding this drug to the Nulibry clinical edit.

References

1) National Institutes of Health. https://ghr.nlm.nih.gov/condition/molybdenum-cofactor-deficiency. Accessed July 2, 2021.
2) Nulibry (fosdenopterin) [prescribing information]. Boston, MA: Origin Biosciences Inc; February

2021.
3) IPD Analytics RxInsights: New Drug Approval Review: Nulibry for the Treatment of Molybdenum Cofactor Deficiency Type A. Accessed July 2, 2021.

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