



# Louisiana

## **fosdenopterin (Nulibry™)**

**Policy #** 00753

**Original Effective Date:** 09/13/2021

**Current Effective Date:** 09/13/2021

*Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.*

### **When Services May Be Eligible for Coverage**

*Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:*

- *Benefits are available in the member’s contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider fosdenopterin (Nulibry™)‡ for the reduction of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A to be **eligible for coverage.\*\***

#### Patient Selection Criteria

Coverage eligibility for fosdenopterin (Nulibry) will be considered when the following criteria are met:

##### **Initial/Temporary:**

- Patient has a diagnosis of molybdenum cofactor deficiency (MoCD) Type A confirmed via genetic testing which identifies a mutation in the *MOCS1* gene; AND  
*(Note: If this criterion is not met, but all other criteria are met on an initial request, a temporary 30 day approval will be granted to account for genetic testing turnaround time. If the confirmatory genetic testing is provided on the initial review OR if confirmatory genetic testing is provided after the temporary 30 day approval, a 1 year authorization will be granted.)*
- Patient is exhibiting at least one of the following:
  - Seizures; OR
  - Exaggerated startle response; OR
  - High-pitched cry; OR
  - Axial hypotonia; OR
  - Limb hypertonia; OR
  - Feeding difficulties; AND

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- Patient has elevated urinary sulfite and/or SSC (S-Sulfocysteine) levels; AND
- Dosing is as follows:
  - Patients less than 1 year of age:

Titration Schedule	Preterm Neonates (Gestational Age Less than 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 and thereafter	0.9 mg/kg once daily	0.9 mg/kg once daily

- Patients 1 year of age and older:
  - 0.9 mg/kg given once daily

### Re-authorization (for therapy beyond the first year of treatment):

- Patient received an initial authorization with confirmatory genetic testing; AND
- Patient's dose of the requested drug is 0.9 mg/kg once daily; AND
- Patient is responding to Nulibry as evidenced by an improvement in clinical presentation (e.g., decrease in seizure activity, improved feeding, decreased urinary sulfite or SSC levels, etc.)

*(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary\*\* if not met).*

### When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the continued use of fosdenopterin (Nulibry) when the patient is NOT responding to therapy to be **not medically necessary.\*\***

### When Services Are Considered Investigational

*Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.*

Based on review of available data, the Company considers the use of fosdenopterin (Nulibry) when the initial/temporary patient selection criteria are not met to be **investigational.\***

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## **Background/Overview**

Nulibry is cyclic pyranopterin monophosphate (cPMP) indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A. Nulibry is available as 9.5 mg of lyophilized drug in a single dose vial for reconstitution. The dosage varies based on age, however the maximum dosage is 0.9 mg/kg given once daily via intravenous infusion.

MoCD Type A is an autosomal recessive disorder caused by mutations in the molybdenum cofactor synthesis 1 gene (*MOCS1*). This mutation leads to an inability to synthesize cPMP. This results in decreased sulfite oxidase activity and a buildup of sulfite and secondary metabolites, such as S-Sulfocysteine, in the brain. This buildup can lead to irreversible neurological damage and is severely life-limiting. The most common presenting symptoms of this condition include seizures, feeding difficulties, and hypotonia. Nulibry provides an exogenous source of cPMP to counter the downstream impacts of the gene mutation. The incidence of MoCD Type A is unknown, however it is estimated to be 1 per 342,000 to 411,000 live births. Death often occurs soon after birth, but there was noted to be a median survival of 4 years observed in a cohort of 37 patients. Due to the impact of this condition, the FDA recommends that Nulibry be initiated if there is a presumptive diagnosis based on clinical symptoms while confirmatory genetic testing is taking place. Nulibry is currently the only medication approved by the FDA for this condition.

## **FDA or Other Governmental Regulatory Approval**

### **U.S. Food and Drug Administration (FDA)**

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

## **Rationale/Source**

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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The efficacy of Nulibry for the treatment of patients with MoCD Type A was established based on data from three clinical studies (Studies 1, 2, and 3) that were compared to data from a natural history study.

### Study 1

Study 1 was a prospective, open-label, single-arm, dose escalation study in patients with MoCD Type A who were receiving treatment with recombinant *E. coli* derived cyclic pyranopterin monophosphate (rcPMP) prior to treatment with Nulibry. Study 1 included 8 patients, 6 of whom previously participated in Study 3. 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

Study 2 was a prospective, open-label, single-arm, dose escalation study in one patient with MoCD Type A who had not been previously treated with rcPMP. 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).

### Study 3

Study 3 was 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.

### Efficacy Results

The efficacy of Nulibry and rcPMP were assessed in a combined analysis of the 13 patients with genetically confirmed MoCD Type A from Study 1 (n=8), Study 2 (n=1), and Study 3 (n=4) who received substrate replacement therapy with Nulibry or rcPMP. Overall Survival 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. In the Nulibry group, 15% of subjects died vs. 67% in the historical control. The 1 year mean survival probability was 92% in the Nulibry group vs. 67% in the historical control. The

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3 year survival probability was 84% in the Nulibry group vs. 55% in the historical control. Results were similar when comparing treated patients with all patients in the untreated natural history cohort with genetically confirmed MoCD Type A (n=37, includes the 18 genotype-matched untreated patients as well as 19 additional untreated patients who were not genotype-matched).

Treatment with Nulibry resulted in a reduction in urine concentrations of SSC in patients with MoCD Type A and the reduction was sustained with long-term treatment over 48 months. The baseline level of urinary S-Sulfocysteine (SSC) normalized to creatinine was characterized in one patient (Study 2) with a value of 89.8  $\mu\text{mol}/\text{mmol}$ . Following treatment with Nulibry in Studies 1 and 2 (n=9), the mean  $\pm$  SD levels of urinary SSC normalized to creatinine ranged from 11 ( $\pm 8.5$ ) to 7 ( $\pm 2.4$ )  $\mu\text{mol}/\text{mmol}$  from Month 3 to Month 48.

## References

1. Nulibry [package insert]. Origin Biosciences, Inc. Boston, Massachusetts. Updated February 2021.
2. Study of ORGN001 in Neonates, Infants, and Children with Molybdenum Cofactor Deficiency (MOCD) Type A. U.S. National Library of Medicine. NCT 02629393. [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Accessed July 2021.
3. Etiology and Prognosis of Neonatal Seizures. UpToDate. Accessed July 2021.
4. Molybdenum Cofactor Deficiency. MedlinePlus. U.S. National Library of Medicine. Accessed July 2021.

## Policy History

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08/05/2021 Medical Policy Committee review

08/11/2021 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 08/2022

## Coding

*The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2020*

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*by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J3490
ICD-10 Diagnosis	All related diagnoses

\*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

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whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
  2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
  3. Reference to federal regulations.

\*\*Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

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**NOTICE:** If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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**NOTICE:** Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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