BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

EVIDENCE-BASED CRITERIA	**ORIGINAL EFFECTIVE DATE: 08/17/23**
SECTION: SPECIALTY MEDICAL DRUGS	**LAST REVIEW DATE: 08/15/24**
	CURRENT EFFECTIVE DATE: 10/14/24
	LAST CRITERIA REVISION DATE: 08/15/24
NEXT ANNUAL REVIEW DATE: 3RD QTR 2025	**ARCHIVE DATE:**

NULIBRY™ (fosdenopterin)

Non-Discrimination Statement is located at the end of this document.

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Evidence-Based Criteria must be read in its entirety to determine coverage eligibility, if any.

This Evidence-Based Criteria provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Evidence-Based Criteria are subject to change as new information becomes available.

For purposes of this Evidence-Based Criteria, the terms "experimental" and "investigational" are considered to be interchangeable.

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Criteria:

Refer to FDA website for current indications and dosage.

- **Criteria for initial therapy:** Nulibry (fosdenopterin) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Prescriber is, or is in consultation with, a Neurologist, Geneticist, or physician specializing in the individual's diagnosis

  2. Individual has a confirmed diagnosis of **ONE** of the following:

     - Molybdenum cofactor deficiency (MoCD) Type A determined by genetic testing of mutations in the *MOCS1* gene
     - Presumptive diagnosis of MoCD confirmed by **ALL** of the following:

       a. Clinical signs and symptoms of MoCD (e.g., encephalopathy, intractable seizures, feeding difficulties, exaggerated startle reaction, microcephaly, coarse facial features)
       b. Documentation of lab abnormalities, such as: elevated urinary sulfite, elevated S-sulfocysteine (SSC), elevated xanthine and/or decreased uric acid in urine or blood.
       c. Individual is awaiting results of confirmatory genetic testing of *MOCS1* gene

  3. Individual does **NOT** have molybdenum cofactor deficiency Type B or C

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Nulibry (fosdenopterin) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

  1. Individual continues to be seen by a prescriber who is, or in consultation with, a Neurologist, Geneticist, or physician who specializes in the individual's diagnosis

  2. Individual has a confirmed diagnosis of Molybdenum cofactor deficiency Type A determined by genetic testing of mutations in the *MOCS1* gene

  3. Individual's condition has responded while on therapy with response defined as **ONE** of the following:

     - Decrease in urinary S-sulfocysteine (SSC)
     - Improvement in clinical signs and symptoms such as: decrease in seizure activity, improvement in feeding/alertness/responsiveness, improvement in gross motor function and/or growth

  4. Individual has been adherent with the medication

NULIBRY™ (fosdenopterin)

5. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use, such as severe phototoxicity

6. Individual does **NOT** have molybdenum cofactor deficiency Type B or C

Renewal duration: 12 months

- Nulibry (fosdenopterin) for all other indications not previously listed is considered ***experimental or investigational*** and will not be covered when any **ONE** or more of the following criteria are met:

1. Lack of final approval from the appropriate governmental regulatory bodies (e.g., Food and Drug Administration); or
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes; or
3. Insufficient evidence to support improvement of the net health outcome; or
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives; or
5. Insufficient evidence to support improvement outside the investigational setting.

These indications include, *but are not limited to:*

- Treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, or duration.

Description:

Nulibry (fosdenopterin) is a cyclic pyranopterin monophosphate (cPMP) indicated to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A. Individuals with MoCD Type A have mutations in the *MOCS1* gene. Replacement therapy with fosdenopterin provides cPMP which is converted to molybdopterin, which is further converted to molybdenum cofactor. Molybdenum cofactor is necessary for the activation of sulfite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulfites. Patients with MoCD Type A have increased urinary levels of a substance called S-sulfocysteine, leading to neonatal seizures and increased mortality.

Definitions:

MOCS1: Molybdenum cofactor biosynthesis protein 1

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Urinalysis Reference Table

Lab	0-3 years	4-6 years	7-12 yeas	13-18 years	>18 years
Hypoxanthine	≤65	≤30	≤30	≤30	≤30
Xanthine	≤54	≤21	≤35	≤15	≤20
Uric Acid	350-2500	350-2500	200-1400	150-700	70-700
S-Sulfocysteine	≤11	≤5	≤5	≤5	≤5

All results reported as mmol/mol creatinine
(Mayo Clinic Laboratories Extended Catalog, 2023 https://www.testcatalog.org/show/SSCTU)

Features of Early-Onset or Severe Molybdenum Cofactor Deficiency (within 1-50 days of life)

Feature	% Affected	Comment
Encephalopathy	100%	
Developmental/ Intellectual Delay	100%	
Neonatal Seizures	93%	Often refractory to anti-seizure medications
Feeding difficulties	66%	At onset of symptoms
Craniofacial dysmorphic features	61%	May include sinking of the eyeball into the orbital cavity, prominent cheeks, coarse features
Appendicular hypertonia	59%	Rigidity may be present early in disease course and progressively worsens
Acquired microcephaly	45%	
Axial hypotonia	41%	Presents early in disease course
Ectopia lentis	16%	Usually develops later in disease course

(Misko et al., 2021)

History:	**Date**:	**Activity**:
Pharmacy and Therapeutics Committee	08/15/24	Review with revisions: criteria (effective 10/14/24)
Pharmacy and Therapeutics Committee	08/17/23	Approved guideline
Clinical Pharmacist	07/28/23	Development

Coding:

HCPCS: C9399/J3490

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Resources:

Literature reviewed 08/15/24. We do not include marketing materials, poster boards and non-published literature in our review.

1. Johannes L, Fu CY, Schwarz G. Molybdenum cofactor deficiency in humans. *Molecules 2022;* 27:6896-6915.

2. Misko A, Mahtani K, Abbott J, et al. Molybdenum Cofactor Deficiency. 2021 Dec 2 [Updated 2023 Feb 2]. In: Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2023. Available from: https://www.ncbi.nlm.nih.gov/books/NBK575630/

3. Nulibry (fosdenopterin) product information, revised by Origin Biosciences, Inc. 10-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed May 30, 2024.

4. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. *Lancet 2015; 386:*1955-1963.

5. Shellhaas R. Etiology and prognosis of neonatal seizures. In: Nordli DR, Garcia-Prats JA, Dashe JF (Eds). UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated July 29, 2022. Accessed June 5, 2024.

6. Shellhaas R. Treatment of neonatal seizures. In: Nordli DR, Garcia-Prats JA, Dashe JF (Eds). UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Topic last updated March 12, 2024. Accessed June 5, 2024.

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Non-Discrimination Statement:

Blue Cross Blue Shield of Arizona (BCBSAZ) complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability or sex. BCBSAZ provides appropriate free aids and services, such as qualified interpreters and written information in other formats, to people with disabilities to communicate effectively with us. BCBSAZ also provides free language services to people whose primary language is not English, such as qualified interpreters and information written in other languages. If you need these services, call (602) 864-4884 for Spanish and (877) 475-4799 for all other languages and other aids and services.

If you believe that BCBSAZ has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability or sex, you can file a grievance with: BCBSAZ's Civil Rights Coordinator, Attn: Civil Rights Coordinator, Blue Cross Blue Shield of Arizona, P.O. Box 13466, Phoenix, AZ 85002-3466, (602) 864-2288, TTY/TDD (602) 864-4823, crc@azblue.com. You can file a grievance in person or by mail or email. If you need help filing a grievance BCBSAZ's Civil Rights Coordinator is available to help you. You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at: U.S. Department of Health and Human Services, 200 Independence Avenue SW., Room 509F, HHH Building, Washington, DC 20201, 1–800–368–1019, 800–537–7697 (TDD). Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html