New Drug Fact Blast

Clinical Services

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<tr><td>Drug/Manufacturer:</td><td>Nulibry™ (fosdenopterin) [BridgeBio Pharma, Inc. and affiliate Origin Biosciences, Inc.]</td></tr>
<tr><td>Dosage Formulations:</td><td>9.5 mg fosdenopterin as a lyophilized powder/cake per single-dose glass vial for reconstitution and injection</td></tr>
<tr><td>FDA Approval Date:
FDB File Date:</td><td>FDA: February 26, 2021
FDB: March 6, 2021</td></tr>
<tr><td>Indication:</td><td>To reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A.</td></tr>
<tr><td>Mechanism of Action:</td><td>Nulibry functions as substrate replacement therapy by providing an exogenous source of cyclic pyranopterin monophosphate (cPMP).</td></tr>
<tr><td>Dose/ Administration:</td><td>

Patients ≥ 1 year of age: 0.9 mg/kg administered as a once daily intravenous (IV) infusion at a rate of 1.5 mL/minute. Volumes below 2 mL may require syringe administration through slow IV push.
Patients < 1 year of age:

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<tr><th>Titration Schedule</th><th>Preterm Neonates (Gestational Age < 37 Weeks)</th><th>Term Neonates (Gestational Age ≥ 37 Weeks)</th></tr>
<tr><td>Initial Dosage</td><td>0.4 mg/kg once daily</td><td>0.55 mg/kg once daily</td></tr>
<tr><td>Month 1</td><td>0.7 mg/kg once daily</td><td>0.75 mg/kg once daily</td></tr>
<tr><td>Month 3</td><td>0.9 mg/kg once daily</td><td>0.9 mg/kg once daily</td></tr>
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To be initiated if known or presumed MoCD Type A and promptly discontinued if condition is not confirmed by genetic testing.
Prior to use, vials are stored frozen (between -13°F and 14°F) and must come to room temperature prior to reconstitution with 5 mL Sterile Water for Injection, USP.
Infusion must be completed within 4 hours of reconstitution.
Nulibry is to be administered by a healthcare provider but may be administered at home by a caregiver if deemed appropriate.

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<tr><td>Disease State Clinical Highlights:</td><td>

MoCD is a rare condition that is estimated to occur in 1 in 100,000-200,000 newborns worldwide. Less than 150 patients have been identified worldwide.
MoCD is typically identified within days to 1 week after birth and is associated with encephalopathy, intractable seizures, dislocated ocular lenses and feeding difficulties. Developmental delays, excessive startle reaction (hyperekplexia), abnormal muscle tone, microcephaly and other dysmorphic features are also characteristic of the condition.
Two forms of MoCD have been described: classical severe and late onset. Classical severe is characterized as above, while the clinical course of late onset may appear as a milder course of disease, but onset is typically within the first 2 years of life. Only 13 cases of late onset have been identified in the literature. Mild intellectual disability has been reported in these patients and seizures are not as common and are often controlled by anticonvulsants.
The median survival age of patients with MoCD is 4 years. Despite having a characteristic biochemical profile, MoCD is often misdiagnosed as hypoxic-ischemic encephalopathy (HIE) secondary to perinatal asphyxia.
There are three types of MoCD (Types A, B, and C), with Type A being the most common. MoCD Type A is an autosomal recessive condition caused by a mutation in the molybdenum cofactor synthesis 1 (MOCS1) gene which leads to deficient synthesis of cPMP, an intermediate substrate, which is then converted to molybdopterin. Molybdopterin is converted to molybdenum cofactor which is needed for the activation

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of molybdenum-dependent enzymes, including sulfite oxidase (SOX) and xanthine oxidase. The SOX enzyme reduces levels of neurotoxic sulfites such as S-sulfocysteine (SSC), while xanthine oxidase is involved in the conversion of xanthine and hypoxanthine to uric acid. The lack of molybdenum-dependent enzyme activity leads to the buildup of sulfites and secondary metabolites which evokes rapid and irreversible neurological damage. In addition, serum uric acid is consistently markedly reduced in patients with MoCD.

Drug Clinical Highlights:

- First-in-class. Received Orphan Drug Designation, Breakthrough Therapy Designation, and Rare Pediatric Disease Designation.
- Efficacy was based on combined analysis from three clinical studies (n=13) which were compared to data from a natural history study (n=18).
  - All 13 patients in the clinical studies had genetically confirmed MoCD Type A.
  - Patients received either Nulibry or recombinant *Escherichia coli*-derived cPMP (rcPMP); rcPMP is the same active moiety and has the same biologic activity as Nulibry.
  - The age at first dose was ≤ 14 days for 10 patients (Day 1 for 5 patients) and 32-69 days for the remaining 3 patients.
- Results

	Nulibry (or rcPMP) (n=13)	Untreated Genotype-Matched Historical Control (n=18)
Number of Deaths (%)	2 (15%)	12 (67%)
50th Percentile (Median) Survival Time in Months (95% CI)	NE (16, NE) months	48 (10, 99) months
Kaplan Meier Survival Probability (95% CI) 1 year 3 years	 92% (57%, 99%) 84% (49%, 96%)	 67% (40%, 83%) 55% (30%, 74%)
Mean Survival Time (Months) At 1 year (95% CI) At 3 years (95% CI)	 11 (9, 13) months 32 (26, 37) months)	 10 (8, 12) months 24 (17, 31) months

NE = not estimable

- Biomarker Results: treatment with Nulibry resulted in a reduction in SSC urine concentrations which was sustained with long-term treatment over 48 months. This was categorized in one patient whose baseline level of urinary SSC normalized to creatinine was 89.8 umol/mmol and following treatment with Nulibrily the mean ± SD levels ranged from 11 (±8.5) to 7 (±2.4) umol/mmol from Month 3 to Month 48.
- Contraindications: none
- Warnings/Precautions: potential for photosensitivity. Direct sunlight and artificial UV light exposure should be avoided/minimized.
- Adverse reactions:

Adverse Reaction (>22%)	Nulibry n (%)	Adverse Reaction (≤ 22%)	Nulibry n (%)
Catheter-related complications	8 (89%)	Abdominal pain	2 (22%)
Pyrexia	7 (78%)	Influenza	2 (22%)
Viral infection	5 (56%)	Lower respiratory tract infection	2 (22%)
Pneumonia	4 (44%)	Viral tonsillitis	2 (22%)
Otitis Media	4 (44%)	Oropharyngeal pain	2 (22%)
Vomiting	4 (44%)	Rash maculo-papular	2 (22%)
Cough/Sneezing	4 (44%)	Anemia	2 (22%)
Upper viral respiratory infection	3 (33%)	Eye swelling	2 (22%)
Gastroenteritis	3 (33%)	Seizure	2 (22%)
Diarrhea	3 (33%)	Agitation	2 (22%)
Bacteremia	3 (33%)		

- Effect of renal/hepatic impairment on Nulibry are unknown.

	• Forging Bridges – NULIBRY Access and Support
	  ○ Origin Biosciences, Inc. program to assist hospitals/healthcare organizations in obtaining product (can only be requested by neonatologist, pediatrician, pediatric neurologist, neonatal neurologist, or geneticist) as well as provides support and education to participants and their caregivers.
	  ○ One component of the program is the NULIBRY Sample Program which provides up to a 28-day supply of Nulibry at no cost: "designed to provide HCPs with free product samples of NULIBRY to dispense so that the HCPs and Patient caregivers can evaluate the efficacy and tolerability of NULIBRY for the Patients."

Price Per Unit (WAC):	• $1,369.86 per vial (WAC) • Dose and number of vials necessary is based on weight and gestational age.
Therapeutic Alternatives:	• No therapeutic alternatives exist for the treatment of MoCD, only supportive therapies such as anticonvulsants for management of seizures. • Low sulfur diets plus sulfate supplementation have been utilized but have not shown an effect in preventing/slowing long-term neurological damage.
Prior Authorization Approval Criteria:	**Must meet the following criteria:** <u>Initial Therapy:</u> • Prescribed by or in consultation with neonatologists or other specialist in the treated disease state • Confirmed or suspected molybdenum cofactor deficiency (MoCD) Type A (ICD10 E61.5) • Genetic testing to confirm pathogenic variant of *MOCS1* gene • Maximum dosage limitation of 0.9 mg/kg per day • Initial approval of prior authorization: 12 months <u>Continuation of Therapy:</u> • Documentation of clinical benefit of therapy (less than expected decline in functional ability and/or symptoms of disease) **Additional Provider Diagnostic/Monitoring Criteria, if desired:** • Nulibry must be discontinued if genetic testing does not confirm MoCD • Biomarkers (SSC, xanthine, hypoxanthine, uric acid), neurological function, gross motor function, developmental milestones
Implication to State Medicaid Program:	Loss of Exclusivity: TBD Claims are likely to be seen in the outpatient setting but may be seen in the inpatient hospital setting if patient with the condition is admitted.

	≤ 23.5 lb (10.68 kg)	23.6-46 lb (10.73-20.91 kg)
Vials per dose	1	2
Cost per dose*	$1,369.86	$2,739.72
30-day supply*	$41,095.80	$82,191.60
1-year supply*	$493,150	$986,300

*Cost based on WAC

<u>References:</u>

1. NULIBRY™ (fosdenopterin) [package insert]. Boston, MA: Origin Biosciences, Inc. February 2021.
2. Nagappa, M., Bindu, P.S., Taly, A.B. Child Neurology: Molybdenum cofactor deficiency. American Journal of Neurology. December 8, 2015; 85(23). https://n.neurology.org/content/85/23/e175. Accessed 12 March 2021.
3. IPD Analytics. New Drug Review: Nulibry (fosdenopterin). March 2021.
4. IPD Analytics. NOC Code Guide: Nulibry (fosdenopterin) Injection, for Intravenous use. March 2021.
5. BridgeBio Pharma's Origin Biosciences Presents New Data On The Natural History Of Molybdenum Cofactor Deficiency (MoCD) Type A At The Society Of The Study Of Inborn Errors Of Metabolism (SSIEM) Conference. September 5, 2019.

https://bridgebio.com/news/bridgebio-pharmas-origin-biosciences-presents-new-data-on-the-natural-history-of-molybdenum-cofactor-deficiency-mocd-type-a-at-the-society-of-the-study-of-inborn-errors-of-metabolism-ssiem. Accessed 12 March 2021.

6. FDA News Release. FDA Approves First Treatment for Molybdenum Cofactor Deficiency Type A. February 26, 2021. Accessed 12 March 2021.
7. ForgingBrides | NULIBRY Access and Support. https://www.nulibry.com/forging-bridges-overview. Accessed 17 March 2021.
8. Scelsa, B., Gasperini, S., Righini A., et. Al. Mild phenotype in Molybdenum cofactor deficiency: A new patient and review of the literature. Molecular Genetics & Genomic Medicine. 2019 June; 7)6): e657. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6565584/. Accessed 17 March 2021.