NEW DRUG APPROVAL

Brand Name	Nulibry™
Generic Name	fosdenopterin
Drug Manufacturer	Origin Biosciences, Inc.

New Drug Approval

FDA Approval Date: February 26, 2021

Review Designation: Priority; Orphan

Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214018

Dispensing Restriction: None

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Molybdenum cofactor deficiency (MoCD) is an ultra-rare autosomal recessive disorder most often presenting with severe neonatal seizures. It should be suspected in any infant with progressive neurologic decline in which asphyxia is suspected but there is no clear documentation of a hypoxic-ischemic event. The neonatal seizures are difficult to treat with standard anticonvulsants. The neurologic decline may present as initial worsening hypotonia with neonatal myoclonic or other exaggerated responses to stimuli. MoCD deficiency is often fatal and most infants who survive demonstrates severe developmental delay.

MoCD Type A is an inborn error of metabolism caused by mutations in the molybdenum cofactor synthesis 1 gene (MOCS1) and characterized by a deficiency in molybdenum cofactor (MoCo) production, leading to a lack of molybdenum-dependent enzyme activity. The lack of activity leads to decreased sulfite oxidase activity with build-up of sulfite and secondary metabolites (such as S-sulfocysteine (SSC)) in the brain, which causes irreversible neurological damage. There are 3 different types of MoCD: A, B, and C, with Type A being the most common.

The incidence and prevalence of MoCD Type A in the United States are not known, but the estimated incidence is 1 per 342,000 to 411,000 live births (0.24 and 0.29 per 100,000). Based on these estimates, MoCD Type A is likely to be underdiagnosed, with an estimated 22 to 26 missed diagnoses per year in the United States and European Union.

Efficacy

The efficacy was 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. Patients treated with Nulibry™ or investigational rcPMP had an improvement in overall survival compared to the untreated, genotype-matched, historical control group (See Table 1).

Treatment with Nulibry™ also resulted in a reduction of urine concentrations of SSC and the reduction was sustained with long-term treatment over 48 months.

Table 1. Nulibry™ Clinical Studies	
Study Population	**Study 1**: Ongoing, prospective, Phase 2, open-label, single-arm, dose escalation study (n=8)

	• Male or female patients with a genetically confirmed diagnosis of MoCD Type A (MOCS1 mutation) • Currently treated with investigational recombinant Escherichia coli-derived cyclic pyranopterin monophosphate (rcPMP) [same active moiety and biologic activity as Nulibry™] • Exclusion criteria: Current or planned treatment with another investigational drug or device, with the exception of rcPMP treatment through Day -1 **Study 2**: Ongoing, prospective, Phase 2/3, open-label, single-arm dose escalation study (n=1) who had not been previously treated with rcPMP • Male or female neonatal, infant, or child with confirmed diagnosis of MoCD Type A • Exclusion criteria: Condition that is considered by treating physician to be a contradiction to therapy, clinically significant brain abnormalities on brain imaging, modified Glasgow Coma Scale for Infants and Children of <7 for more than 24 hrs **Study 3**: Retrospective, observational study in patients with a confirmed diagnosis of MoCD Type A who received rcPMP (n=10); 6 patients were later enrolled in Study 1 • 13 patients included in the combined analysis: 54% male, 77% white, 23% Asian o Median gestational age was 39 weeks (35 to 41 weeks) o Age at first dose: ≤ 14 days for 10 patients; and ≥ 32 days and < 69 days for the remaining 3 patients
Interventions	**Study 1:** Daily IV infusions of Nulibry™ starting on Day 1. Initial dosage was matched to the patient's rcPMP dosage upon entering the study and then the dose was titrated to a maximum of 0.9 mg/kg. **Study 2**: The initial dosage was based on the gestational age of the patient. The initial dosage was then incrementally escalated up to a maximum dosage of 0.98 mg/kg administered once daily as an intravenous infusion.
Endpoints	**Study 1:** Primary endpoint: Safety of fosdenopterin within the first 6 months of treatment Secondary Endpoints: Pharmacokinetic parameters, urine and blood biomarkers, neurologic function, long-term safety (72 months), cognitive function **Study 2:** Primary endpoint: Overall survival Secondary endpoints: Bayley Scales of infant development, gross motor function, feeding pattern, head circumference, length and weight, BMI • The efficacy was 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. • 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).

Table 2. Overall Survival in Patients with MoCD Type A Treated with Nulibry™ or rcPMP Versus Genotype-Matched Historical Control

	Nulibry™ (or rcPMP) (n=13)	Untreated Genotype-Matched Historical Control (n=18)	Treatment Difference (95% CI)
Number of Deaths (%)	2 (15%)	12 (67%)	
50th Percentile (Median) Survival Time in Months (95% CI)[a]	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[b]** **At 3 years[c]**	11 (9, 13) months 32 (26, 37) months	10 (8, 12) months 24 (17, 31) months	1 (-1, 4) months 8 (-1, 16) months
Hazard Ratio for Risk of Death (95% CI)[d]	0.18 (0.04, 0.72)		

[a] Quartile estimates from product-limit (Kaplan-Meier) method, with associated log-log confidence intervals.
[b] Based on the area under the survival curves up to 1 year of follow-up.
[c] Based on the area under the survival curves up to 3 years of follow-up.
[d] Based on Cox proportional hazards model regressing survival status on an indicator variable denoting treatment status.
The 95% CIs are based on the modified score test statistic under the Cox model. The hazard ratio represents the risk of death in the treated patients compared to the untreated historical control patients.

Safety

ADVERSE EVENTS

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.

WARNINGS & PRECAUTIONS

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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Patients with MoCD Type A have mutations in the MOCS1 gene leading to deficient MOCS1A/B dependent synthesis of the intermediate substrate, cPMP. Substrate replacement therapy with Nulibry™ provides an exogenous source of cPMP, which is converted to molybdopterin. Molybdopterin is then converted to molybdenum cofactor, which is needed for the activation of molybdenum-dependent enzymes, including sulfite oxidase (SOX), an enzyme that reduces levels of neurotoxic sulfites.

Dose & Administration

ADULTS

Recommended: 0.9 mg/kg IV once daily (using actual body weight)

PEDIATRICS

- See the table below for the recommended dosage in patients less than one 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
Dosage at Month 1	0.7 mg/kg once daily	0.75 mg/kg once daily
Dosage at Month 3	0.9 mg/kg once daily	0.9 mg/kg once daily

- For patients one year of age or older, the recommended dosage of Nulibry™ is 0.9 mg/kg (based on actual body weight) administered as an intravenous infusion once daily.
- If a Nulibry™ dose is missed, administer the missed dose as soon as possible. Administer the next scheduled dose at least 6 hours after the administration of the missed dose.

GERIATRICS

MoCD Type A is largely a disease of pediatric patients. Clinical studies of Nulibry™ did not include patients 65 years of age and older.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

N/A

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

For injection: 9.5 mg of fosdenopterin as a lyophilized powder or cake in a single-dose vial for reconstitution.