CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214018Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214108
PDUFA Goal Date	February 26, 2021
OSE RCM #	2020-401
Reviewer Name	Mona Patel, PharmD, RAC
Team Leader	Laura Zendel, PharmD
Deputy Director	Cynthia LaCivita, PharmD
Review Completion Date	February 25, 2021
Subject	Evaluation of Need for a REMS
Established Name	fosdenopterin
Trade Name	Nulibry
Name of Applicant	Origin Biosciences, Inc.
Therapeutic Class	cyclic pyranopterin monophosphate (cPMP) analog
Formulation	Intravenous Infusion
Dosing Regimen	

Titration Schedule- Pediatric Patients less than 12 months	Gestational Age ≥ 37 weeks mg/kg	Gestational Age < 37 weeks mg/kg
Initial Dose	0.55 mg	0.40 mg
Month 1	0.75 mg	0.70 mg
Month 3	0.90 mg	0.90 mg

For patients 1 year and older, the recommended dose is 0.9 mg/kg daily

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Executive Summary

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Nulibry (fosdenopterin) for injection is necessary to ensure the benefits outweigh its risks. Origin Biosciences, Inc. submitted a New Drug Application (NDA) 214108 for fosdenopterin with the proposed indication for the treatment of molybdenum cofactor deficiency (MoCD) Type A. The risk associated with the use of fosdenopterin includes potential for photosensitivity based on animal studies. During the review of the application, the indication was revised to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A. The applicant did not submit a proposed REMS but did submit an enhanced Pharmacovigilance plan for phototoxicity.

The Division of Risk Management (DRM) has determined that a REMS is not needed to ensure the benefits of fosdenopterin outweigh its risks. Fosdenopterin has proven to treat MoCD by providing an exogenous source of cyclic pyranopterin monophosphate (cPMP) which is necessary in molybdenum cofactor (MoCo) biosynthesis. Based on the clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required to ensure the benefits outweigh the risks. Photosensitivity was not serious or severe and did not require drug discontinuation. In general, geneticists, developmental specialists, and neurologists should instruct patients/caregivers to use sunblock and wear clothing and sunglasses that protect against sun exposure and report symptoms of photosensitivity reactions.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Nulibry (fosdenopterin) is necessary to ensure the benefits outweigh its risks. Origin Biosciences, Inc submitted a New Drug Application (NDA) 214108 for fosdenopterin with the proposed indication for the treatment of molybdenum cofactor deficiency (MoCD) Type A. This application is under review in the Division of Rare Diseases and Medical Genetics (DRDMG). The applicant did not submit a proposed REMS, but did submit an enhanced PV plan for phototoxicity.

2 Background

2.1 Product Information

Fosdenopterin, a new molecular entity, is a synthetic form of endogenous cyclic pyranopterin monophosphate (cPMP) analog proposed for the treatment of MoCD Type A.[a] During the review of the application the indication was revised to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A. Fosdonopterin replaces the cPMP substrate and permits the remaining molybdenum cofactor deficiency (MoCD) Type A synthesis steps to proceed, enabling activation of the MoCo-dependent enzymes and elimination of sulfites.[1]

Fosdenopterin is proposed to be available in a single-dose vial containing 9.5 mg of fosdenopterin as a lyophilized powder to be administered via intravenous infusion by a healthcare professional. The dosing

[a] FDAAA factor (F): whether the drug is a new molecular entity

regimen is determined by the patient's age and weight. The recommended starting dosage for patients less than 1 year of age who were term neonates is 0.55 mg/kg and for preterm neonates, 0.4 mg/kg, infused intravenously at a rate of 1.5 mL/min and then titrated to the target dose of 0.9 mg/kg over a period of 3 months. For patients greater than 1 year of age, the recommended dosage of fosdenopterin is 0.9 mg/kg/day infused intravenously at a rate of 1.5 mL/min for longterm use. [b] Fosdenopterin may be administered at home by the patient's caregiver if a healthcare provider determines that it is appropriate. Fosdenopterin was granted orphan designation on November 5, 2009, breakthrough therapy designation on October 23, 2013, and rare pediatric disease designation on June 15, 2017 . Fosdenopterin has not been approved or marketed in any country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214108 relevant to this review:

- 10/16/2013: Breakthrough therapy designation granted for fosdenopterin to treat MoCD (Type A).
- 06/15/2017: Rare pediatric disease designation granted for MoCD.
- 11/15/2017: Guidance meeting to discuss the clinical status of the development program and obtain feedback on adequacy of clinical data to support an NDA.
- 11/15/2019: Rolling review granted.
- 11/27/2019: Part 1 of 3 of rolling New Drug Application 214108 for fosdenopterin to treat MoCD Type A received consisting of the nonclinical section of the NDA.
- 12/18/2019: Pre-NDA meeting held during which applicant was informed that a REMS will likely not be needed for fosdenopterin.
- 5/5/2020: Part 2 of 3 of rolling New Drug Application 214108 for fosdenopterin to treat MoCD Type A received consisting of the clinical section of the NDA.
- 6/29/2020: Part 3 of 3 of rolling New Drug Application 214108 for fosdenopterin to treat MoCD Type A received consisting of the Chemistry, Manufacturing and Controls (CMC) section of the NDA.
- 8/6/2020: FDA sent information request (IR) to Origin requesting a risk assessment of the proposed administration of the drug by a patient's caregiver and to provide risk mitigation strategies that should be employed to reduce risks.
- 8/14/2020: FDA received an amendment containing a response to 8/6/2020 IR concluding that risk assessment combined with planned mitigation measures support that use of fosdenopterin in the home setting is appropriate.
- 10/5/2020: FDA communicated the following IRs during the Mid-Cycle Communications Meeting

[b] FDAAA factor (D): The expected or actual duration of treatment with the drug

- (A) Provide additional information on the reasons for treatment discontinuation for patients who received treatment with fosdenopterin under named-patient use (e.g. expanded access individual patient INDs outside US).

- (B) Provide a proposal for a postmarketing phototoxicity pharmacovigilance plan.

- 10/14/2020: FDA sent follow-up IR in response to 8/14/2020 amendment requesting justification for inclusion of statement in the Prescribing Information that fosdenopterin may be administered at home by the patient's caregiver if a healthcare provider determines that it is appropriate.
- 10/19/2020: FDA received an amendment containing a response to part A of the 10/5/2020 IR.
- 10/22/2020: FDA sent IR to Origin requesting an enhanced pharmacovigilance (EPV) plan to include an assessment and analysis of reports of photosensitivity in patients treated with fosdenopterin.
- 10/30/2020: FDA received an amendment containing a response to the 10/14/2020 IR.
- 11/9/2020: FDA received an amendment containing a response to part B of the 10/5/2020 IR. The submission included an enhanced PV plan and photosensitivity adverse event follow-up questionnaire to assess the potential for photosensitivity as requested in the 10/21/2020 IR.
- 11/18/2020: FDA sent IR to Origin pertaining to the reasons for discontinuation in patients treated within and outside of the clinical program.
- 11/25/2020: FDA received an amendment containing a response to the 11/18/2020 IR.
- 1/19/2021: FDA provided recommendations to Origin on proposed PV plan.
- 2/2/2021: FDA sent IR to Origin pertaining to fosdenopterin infusion information from studies ALXN1101-MCD-201 & ALXN1101-MCD-202.
- 2/5/2021: FDA received an amendment containing a response to the 2/2/2021 IR
- 2/16/2021: FDA sent IR to Origin pertaining to infusion administration and precautions for caregiver administration of the drug.
- 2/17/2021: FDA received an amendment containing a response to the 1/19/2021 comments.
- 2/18/2021: FDA received an amendment containing a response to the 2/16/2021 IR
- 2/22/2021: FDA sent edits to the latest draft labeling which included revising the indication to *"reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A."*
- 2/23/2021: FDA received a request from Origin for a telecon to discuss revisions to the indication statement.
- 2/23/2021: FDA sent to Origin that the indication should continue to be revised as *"to reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A."*

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

MoCD Type A is a rare, fatal, autosomal recessive disease. Mutations in the Molybdenum cofactor biosynthesis protein 1 *(MOCS1)* gene lead to deficient molybdenum cofactor synthesis. Without this cofactor, molybdenum-dependent enzyme activity is deficient. Deficiency in the molybdenum-dependent enzyme, sulfite oxidase (SOX), results in the accumulation of neurotoxic sulfites, primarily S-sulfocysteine (SSC). Elevated levels of urinary sulfite and SSC also are a characteristic finding. Elevated levels of sulfites in the central nervous system (CNS) leads to the largely irreversible neuronal injury seen in patients with this disease. MoCD Type A typically presents in the neonatal period or early infancy with intractable seizures, feeding difficulties, axial hypotonia with limb hypertonia, impairment of growth, and significantly delayed cognitive and motor skills.[1] The metabolic derangements lead to rapidly progressive neurologic decline and patients usually die in the first years of life (Mechler et al. 2015). [c] The incidence of MoCD type A is approximately 1 in 340,000 to 400,000 live births. The estimated prevalence of MoCD type A in the US is 45 to 54 patients, all under 10 years of age.[d,2]

3.2 Description of Current Treatment Options

There are no FDA-approved therapies for the treatment of MoCD Type A. Current treatment options for patients with MoCD Type A are symptom driven to provide relief from clinical manifestations of the disease (e.g., antiepileptic drugs for seizures) and supportive care, such as placement of a feeding tube. There is an unmet medical need for treatment for MoCD Type A.

4 Benefit Assessment

The efficacy and safety of fosdenopterin to treat MoCD Type A in patients was assessed by analysis of data from two open label studies, Study ALXN1101-MCD-201 (NCT02047461), Study ALXN1101-MCD-202 (NCT02629393), and a retrospective study, Study ALX-MCD-501 (NCT01640717) .

Study MCD-201 is an ongoing prospective, multicenter, multinational, open label, study designed to evaluate the efficacy and safety of the drug administered to infants and children with MoCD Type A who were being treated with recombinant cyclic pyranopterin monophosphate (rcPMP), an *E. coli* derived form of cyclic pyranopterin monophosphate (cPMP).

The initial dose of fosdenopterin was matched to the patient's dose of rcPMP upon entering the study. Once treatment with fosdenopterin was started, no further rcPMP was administered. After the first 2 months of treatment, the dose was increased every month by no more than 240 ug/kg/day for 5 months to a maximum of 1200 mcg/kg/day if the patient's clinical, pharmacokinetic, and safety assessments permitted, including the absence of signs and symptoms of drug-related toxicity.[3] Efficacy endpoints included changes in urine SSC (normalized to creatinine and uncorrected) and blood SSC levels, growth

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

parameters (body weight, body length, head circumference), feeding patterns, motor and cognitive assessment results, and clinical findings from seizures, neurologic examination and neuroimaging.

Seven pediatric patients were enrolled and have completed at least 48 months of treatment. There is no primary efficacy endpoint specified in this study. At 6 months, median urine SSC normalized to creatinine was 5.5 umol/mmol, representing a median percent change in urinary SSC normalized to creatinine of -67.7% indicating improvement from baseline in all seven patients. During the study, there was an increase in growth parameters which is positive since the disease is characterized by an impairment of growth. There are no changes noted in feeding patterns, gross motor function, or number of patients experiencing seizures. Clinical findings were also stable during the study.

Study MCD-202 is an ongoing Phase 2/3, multicenter, multinational, open label, study designed to evaluate the efficacy and safety of daily IV administration of fosdenopterin to neonates diagnosed with MoCD Type A who had not been previously treated with cyclic pyranopterin monophosphate (cPMP). Similar to Study MCD-201, Study MCD-202 applied a dose titration scheme based on gestational age. For term neonates, the initial dose was 700 µg/kg/day and for preterm neonates, 525 µg/kg/day.[3] Thereafter, the dose is escalated on Day 28 and at months 3,6 and 9 up to 1300 µg/kg/day if the patient's clinical, pharmacokinetic, pharmacodynamic, and safety assessments permitted, including the absence of signs and symptoms of drug-related toxicity. Efficacy endpoints included assessments of growth parameters (body weight, body length, head circumference), feeding patterns, motor and cognitive assessment results, and clinical findings from seizures, neurologic examination and neuroimaging.

Two neonates were enrolled. At the time of data cutoff, data were available for one neonate with a confirmed diagnosis of MoCD Type A who had been treated with fosdenopterin for 36 months and was ongoing on treatment at that time. There is no primary efficacy endpoint specified in this study. Developmentally, the patient demonstrated progress in cognitive function and fine and gross motor skills. Based on the Bayley assessment at (b) (6) months of age, the patient had age-equivalent scores of 13 months on the Cognitive Scale, 15 months on the Fine Motor subtest, and 7 months on the Gross Motor subtest.[2] The patient had near-normal development in growth, including weight, length, and head circumference. By month 36, the patient's weight corresponded to the 37th age percentile, length to 7th age percentile, and head circumference to 96th age percentile.

Study MCD-501 is a noninterventional, observational, retrospective, multinational, multicenter study to collect data on pediatric patients with MoCD who received rcPMP as substrate replacement therapy for treatment of MoCD. The study neither provided treatment with rcPMP nor altered any ongoing treatment schedules. Efficacy endpoints included assessments of MoCD-associated biomarkers, growth parameters (body weight, body length, head circumference), feeding patterns, neurologic examination and neuroimaging and developmental assessments.

Fifteen patients were included in this study, including 10 patients with a confirmed diagnosis of MoCD Type A. Six of the 10 patients were subsequently enrolled and transitioned to treatment with fosdenopterin in the prospective Study MCD-201. Four were no longer receiving rcPMP treatment at the end of study, including two patients who died and two patients who were alive but had discontinued treatment with rcPMP. Efficacy was assessed by review of MoCD-associated biomarkers, neurological

examinations, growth, feeding patterns, neuroimaging and developmental assessments. Median concentrations of normalized urinary SSC were 51.5, 28.9, and 16.3 umol/mmol at Days 2, 7, and Month 12 of rcPMP treatment reflecting a median percentage decrease of 34.8%, 80.5%, 91.2% respectively.[3] During the study, there was an in increase in growth parameters. Between months 3 and 30, the median changes from baseline in head circumference ranged from 5.1 to 14.8 cm and the median z-scores ranged from -2.93 to 2.86. Between months 3 and 30, the median changes from baseline in height ranged from 13.74 to 46.0 cm and the median z-score ranged from -2.20 to 1.18. Between months 3 and 30, the median changes from baseline in weight ranged from 2.5 to 12.2 kg and the median z-score ranged from 0.02 to 2.35. There were no changes in feeding patterns, gross motor function, or number of patients experiencing seizures.

Efficacy was assessed by comparing overall survival in patients treated with fosdenopterin with an untreated natural history cohort and the overall survival results. According to the clinical reviewer, despite the limitations resulting from the lack of randomization, the use of an external non-contemporaneous control group, and the use of retrospective observational data in the treatment cohort, the efficacy data support a conclusion that Nulibry provides a survival benefit in patients with MoCD Type A.[e, 3]

5 Risk Assessment & Safe-Use Conditions

The safety assessment of fosdenopterin was primarily based on patients from Studies MCD-501, MCD-201, and MCD-202. The studies included a total of 19 patients with MoCD Type A.

An overall summary of treatment-emergent adverse events (TEAEs) across the three studies is presented below in Table 1:

Table 1. Overview of Treatment-Emergent Adverse Events by Study

Event	MCD-501 N=10 n (%)	MCD-201 N=8 n (%)	MCD-202 N=1 n (%)
Any treatment-emergent AE[1]	10(100%)	8 (100%)	1(100%)
Moderate or severe AEs (grades 3-5)[2]	6 (60%)	8 (100%)	1(100%)
SAEs	8 (80%)	7(88%)	1(100%)
SAEs with a fatal outcome	2 (20%)	0	0
AEs leading to discontinuation of study drug	0	0	0
AEs leading to dosage modification of study drug	0	0	0
AEs leading to interruption of study drug	0	0	0
AEs leading to reduction of study drug	0	0	0
AEs leading to dosage delay of study drug	0	0	0

Source: Clinical Reviewer generated February 5, 2021 (ongoing)
[1] Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with at least one event

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

All patients in the three studies experienced at least one TEAE. The majority of TEAEs were related either to infections or device (i.e., central venous catheter) related. The device related adverse events reported in more than one patient in Study MCD-501 include device-related infection (three patients), device dislocation, medical device complication, device leakage, sepsis and device-related sepsis (two patients each).[3] Among the nine patients who were treated in Studies MCD-201 and MCD-202, eight experienced at least one device-related TEAE. The device related events reported in more than one patient include complication associated with device (six patients), device dislocation and catheter site infection (three patients) and catheter site extravasation, catheter site pain, catheter site discharge and vascular device infection (two patients each). Infections (unrelated to device) were the other category with frequent TEAEs seen in the studies. See Table 3 for a list of TEAEs seen in more than one patient in any study.

Device-related TEAEs are unrelated to fosdenopterin and related to the administration method of the drug. According to the clinical reviewer, the benefit of prolonged survival outweighs the risks of device related complications associated with the delivery of the drug and aside from the infections related to the device, infections overall are likely not drug-related due to the high prevalence of infections in children and in particular children with neurologic impairment.[3]

Table 3. Treatment-Emergent Adverse Events[1] Occurring in >1 Patient in Studies MCD-501, -201, and -202

Preferred Term[2]	MCD-501 N=10 (%)	MCD-201 N=8(%)	MCD-202 N=1 (%)
Infection Related			
Pyrexia	3 (30%)	6 (75%)	1 (100%)
Complication associated with device	0	6 (75%)	1 (100%)
Device-related infection	3 (30%)	1 (13%)	0
Pneumonia	3 (30%)	3 (38%)	1 (100%)
Viral infection	0	4 (50%)	1 (100%)
Device-related sepsis	2 (20%)	0	0
Vascular device infection	0	2 (25%)	0
Bacteremia	0	1 (13%)	1 (100%)
Sepsis	2 (20%)	1 (13%)	0
Catheter site discharge	0	2 (25%)	0
Catheter site infection	0	2 (25%)	1 (100%)
Otitis media	2 (20%)	3 (38%)	0
Ear infection	0	2 (25%)	0
Gastroenteritis	1 (10%)	1 (13%)	1 (100%)
Upper respiratory infection	3 (30%)	2 (25%)	0
Oral candidiasis	3 (30%)	1 (13%)	0
Varicella	2 (20%)	1 (13%)	0
Viral upper respiratory infection	0	2 (25%)	0
Respiratory tract infection	1 (10%)	1 (13%)	0
Urinary tract infection	1 (10%)	1 (13%)	0
Bronchitis	1 (10%)	1 (13%)	0
Fungal skin infection	2 (20%)	0	0
Viral tonsillitis	0	1 (13%)	1 (100%)

Preferred Term[2]	MCD-501 N=10 (%)	MCD-201 N=8(%)	MCD-202 N=1 (%)
Device Related			
Catheter site extravasation	0	2 (25%)	0
Catheter site pain	0	2 (25%)	0
Device dislocation	2 (20%)	3 (38%)	1 (100%)
Device leakage	0	2 (25%)	0
Medical device complication	2 (20%)	0	0
Catheter site inflammation	1 (10%)	1 (13%)	0
Skin			
Dermatitis	1 (10%)	0	1 (100%)
Eczema	2 (20%)	0	0
Rash maculopapular	0	2 (25%)	0
Skin disorder	0	2 (25%)	0
Other			
Vomiting	0	3 (38%)	1 (100%)
Diarrhea	0	2 (25%)	1 (100%)
Abdominal pain	0	2 (25%)	0
Constipation	1 (10%)	1 (13%)	0
Seizure	0	2 (25%)	0
Irritability	1 (10%)	1 (13%)	0
Anemia	2 (20%)	1 (13%)	1 (100%)
Eye swelling	0	2 (25%)	0
Conjunctival hemorrhage	1 (10%)	0	1 (100%)
Oropharyngeal pain	0	2 (25%)	0
Cough	1 (10%)	4 (50%)	0
Sneezing	1 (10%)	2 (25%)	0
Asthma	1 (10%)	1 (13%)	0
Rhinorrhea	1 (10%)	0	1 (100%)
Strabismus	1 (10%)	1 (13%)	0

No deaths were reported during treatment with fosdenopterin in Studies MCD-201 and MCD-202; all eight patients in these studies were ongoing on treatment as of the data cutoff. Two patients died during Study MCD-501.[3] One patient died due to RSV pneumonia, which was not considered to be treatment-related, and another patient died due to necrotizing enterocolitis, which was considered by the Investigator to be possibly treatment-related.

5.1 POTENTIAL RISK OF PHOTOTOXICITY

A significant safety concern for phototoxicity with fosdenopterin was identified at doses ≥4.4× the maximum recommended human dose of 0.9 mg/kg/day (based on the human equivalent dose [HED]) in a standalone phototoxicity study in rats.[3] This was evidenced by cutaneous skin reactions and ophthalmic and histopathological findings indicative of phototoxicity. Photosensitivity was not serious or severe, and did not lead to study drug discontinuation or withdrawal from study. Based on the clinical reviewer, photosensitivity reactions can be managed with labeling and an enhanced PV plan to mitigate

the risks and preserve benefits in the treatment of MoCD Type A. No additional risk minimization measures are considered necessary.

5.2 Administration by a Caregiver

Caregiver administration of Nulibry occurred in the clinical studies (when deemed appropriate as specified in the study protocols). All but one of the patients currently enrolled in Studies MCD-201 and MCD-202 received Nulibry via caregiver administration, and the transition to caregiver administration occurred soon after treatment initiation for most of these patients. An analysis comparing AEs recorded as device complications or infections associated with devices in Studies MCD-201 and MCD-202 demonstrated similar incidences of these AEs reported with healthcare provider administration and caretaker administration. Of these 49 AEs, 22 (45%) occurred during healthcare provider administration and 27 (55%) occurred during caregiver administration.[3] Notably, the majority of Nulibry dosing occurred during periods of caregiver administration (83% of all administered doses) rather than healthcare provider administration (17% of all administered doses). Therefore, the similar numbers of events reported during healthcare provider and caregiver administration despite the overall greater exposure with caregiver administration provide reassurance that caregiver administration does not increase the risk of these events. Labeling will reflect that caregiver administration is only permitted if deemed appropriate by the patient's healthcare provider.

6 Expected Postmarket Use

Although treatment with fosdenopterin is anticipated to be initiated in the hospital setting, the anticipated long-term daily use will necessitate the use of fosdenopterin in the out-patient setting. The likely prescribers will be geneticists, developmental specialists, and neurologists in the outpatient or inpatient settings. In the studies, photosensitivity was not serious or severe, and this risk will be included in labeling in section 5 Warnings & Precautions. Prescribers should instruct patients/caregivers to minimize or avoid exposure to sunlight. Patients should use sunblock and wear clothing and sunglasses that protect against sun exposure.

7 Risk Management Activities Proposed by the Applicant

The Applicant proposes risk management activities for fosdenopterin that include an enhanced PV plan for photosensitivity. The PV plan will include expedited reporting, an adverse event follow-up questionnaire, and analyses in periodic safety reports.[4] The Applicant stated that the proposed labeling and enhanced PV plan are sufficient to mitigate the risks and preserve benefits in the treatment of MoCD Type A. Origins does not propose a Boxed Warning in the labeling. They do propose an Instructions For Use for preparing and administering fosdenopterin to support use in the home setting.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Nulibry on the basis of the efficacy and safety information currently available.

Molybdenum cofactor deficiency (MoCD) Type A leads to elevated levels of urinary sulfite and S-sulfocysteine in the central nervous system (CNS) which causes largely irreversible neuronal injury seen

in patients with this disease. Patients with this disease experience intractable seizures, feeding difficulties, axial hypotonia with limb hypertonia, impairment of growth, and significantly delayed cognitive and motor skills. There are no FDA-approved therapies for the treatment of (MoCD) Type A. Current treatment options for patients with MoCD Type A are symptom driven to provide relief from clinical manifestations of the disease.

Two open label studies and a retrospective study demonstrate effectiveness of fosdenopterin to be administered intravenously for the treatment of (MoCD) Type A. The efficacy data support a conclusion that fosdenopterin provides a survival benefit in patients with MoCD Type A. The strength of these data, including the use of a reliable and objective endpoint of mortality and the demonstration of a large treatment effect size, outweigh the limitations.

In the clinical development program thus far, two safety issues were identified; the potential for photosensitivity with the drug and caregiver administration of fosdenopterin. Photosensitivity was not serious or severe, and this reviewer has determined that the proposed labeling and enhanced PV plan are sufficient to mitigate the risks of photosensitivity. Caregiver administration of fosdenopterin did not show significant differences in the number of adverse events compared to healthcare provider administration. Labeling will reflect that caregiver administration is only permitted if deemed appropriate by the patient's healthcare provider. This reviewer is not recommending a REMS to address either of these risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with fosdenopterin will be addressed in labeling. In general, geneticists, developmental specialists and neurologists who prescribe fosdenopterin should be capable with how to manage the potential risk of photosensitivity reactions that are associated with fosdenopterin by instructing patients/caregivers on how to mitigate the risk with sunscreen, staying in the shade, and using long sleeves, etc. Should Division of Rare Diseases and Medical Genetics have any concerns or questions or if new safety information becomes available, please send a consult to the Division of Risk Management.

10 Appendices

10.1 References

1. Farrell, Sheila. DRDMG. Integrated Review for Nulibry (fosdenopterin), February 3, 2020.
2. Origin Biosciences. Clinical Overview for Nulibry (fosdenopterin), May 5, 2020
3. Origin Biosciences. Summary of Clinical Safety for Nulibry (fosdenopterin), May 5, 2020
4. Ryan, Debra. DRDMG. Pharmacovigilance Plan for Nulibry (fosdenopterin), January 7, 2021

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/s/

MONA G PATEL
02/25/2021 02:54:53 PM

LAURA A ZENDEL
02/25/2021 02:57:01 PM

CYNTHIA L LACIVITA
02/25/2021 09:07:06 PM