CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214018Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **February 15, 2021**

From: **Hitesh Shroff, Ph.D.**
Application Technical Lead, Branch IV
Division of New Drug Products II
Office of New Drug Products

Through: **Wendy Wilson, Ph.D.**
Division Director
Division of New Drug Products II
Office of New Drug Products

To: **CMC Review #1 of NDA**

Subject: **Recommendation for NDA 214018**

At the time when the CMC Review #1 was completed on November 27, 2020 it had noted the following pending issues:

- The label/labeling has ***not*** been finalized.

Because of these deficiencies, the NDA was not recommended for approval from the OPQ perspective.

The applicant submitted the revised the Prescribing Information (PI), IFU, immediate container and carton labels in the submissions listed below.

Document Reviewed (eCTD #)	Date Received
eCTD-0030 (SDN-30) Carton and Container Labels, PI and IFU	10/23/2020
eCTD-0040 (SDN-40) Carton and Container Labels	12/11/2020
eCTD-0042 (SDN-42) PI	12/28/2020
eCTD-0047 (SDN-47) PI and IFU	02/10/2021

The resubmitted CMC sections of the labeling/labels are acceptable. **(See the Attachment 1)**

Recommendation:
This NDA is now recommended for **Approval** from the OPQ perspective.

Application Technical Lead's Assessment and Signature

This NDA is recommended for **Approval** from the quality perspective.

Hitesh Shroff, Ph.D.
Application Technical Lead,
Branch IV Division of New Drug Products II
February 15, 2021

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2021.02.15 16:11:07 -05'00'

U.S. FOOD & DRUG ADMINISTRATION

Attachment 1

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 11, 2021

TO: Assessment #1 of NDA 214018 Quality Assessments – Labeling and Drug Product

FROM: Jane Chang, Ph.D.
Master Chemistry Reviewer, OPQ/ONDP/DNDP II

THROUGH Wendy Wilson, Ph.D.
Division Director (Acting Chief, Branch 4), OPQ/ONDP/DNDP II

SUBJECT: **Final Recommendation on Labeling/Labels**

SUMMARY

The previous Quality Assessment – Labeling, Assessment Cycle #1 dated 02-Oct-2020, made a recommendation of not ready for approval for NDA 214018 because of labeling deficiencies (see N214018 Labeling R01, Section 4.0). These labeling issues have been satisfactorily resolved based on the revisions made in eCTD-0040 and eCTD-0047.

RECOMMENDATION:

This application is now recommended for **Approval** from the CMC labeling/label perspective.

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0030 (SDN-30) Carton and Container Labels, PI and IFU	10/23/2020
eCTD-0040 (SDN-40) Carton and Container Labels	12/11/2020
eCTD-0042 (SDN-42) PI	12/28/2020
eCTD-0047 (SDN-47) PI and IFU	02/10/2021

1.0 PRESCRIBING INFORMATION

Assessor's comment: Issues were identified for Sections 11 and 16 of Prescribing Information labeling submitted in eCTD-0042. Subsequently, updated Prescribing Information labeling, based on the Agency's recommendation, was submitted in eCTD-0047, which is summarized below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1. **PRODUCT TITLE**

NULIBRY (fosdenopterin) for injection, for intravenous use
Initial U.S. Approval: 2021

2. **DOSAGE FORMS AND STRENGTHS**

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

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	NULIBRY (fosdenopterin) for injection	**Acceptable**
Dosage form, route of administration	for injection, intravenous	**Acceptable**
Initial U.S. Approval	2021	**Acceptable** The drug substance is an NME. The year this drug is approved should be listed.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage forms and strengths in metric system	For injection, 9.5 mg	**Acceptable** Strength is expressed on the free base content.
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: Satisfactory

The proposed proprietary name "NULIBRY" was evaluated by Sarah Vee on 5/4/2020 and concluded to be acceptable. The established name "fosdenopterin" has been listed in USAN Online.

Product Title and Initial U.S. Approval are acceptable. Critical information per 21 CFR 201.57(a)(8) is also included in Dosage Forms and Strengths section. Per Labeling Review Tool (page 13), which recommends including limited packaging information. The color of the solid does not need to be included in Highlights.

The drug product is a powder for reconstitution before injection, the word "for" is inserted in front of the route of administration and dosage form.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

2.3 Preparation and Administration Instructions

NULIBRY must be reconstituted prior to use. Use aseptic technique during preparation and follow these instructions:

1. Determine the total dose, number of vials needed, and total reconstituted dose volume based on the patient's weight and prescribed dose.
2. Remove the required number of vials from the freezer to allow them to reach room temperature (by hand warming or exposing to ambient air).

3. Reconstitute each required NULIBRY vial with 5 mL of Sterile Water for Injection, USP. Gently swirl the vial continuously until the powder is completely dissolved. DO NOT shake. After reconstitution, the final concentration of NULIBRY reconstituted solution is 9.5 mg/5 mL (1.9 mg/mL).
4. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Reconstituted NULIBRY is a clear and colorless to pale yellow solution. Do not use, if there are particles present or if the solution is discolored.
5. Administer the total reconstituted dose.

2.4 Storage of Reconstituted Solution

Reconstituted NULIBRY may be stored at room temperature [15°C to 25°C (59°F to 77°F)] or refrigerated [2°C to 8°C (36°F to 46°F)] for up to 4 hours. If reconstituted NULIBRY is refrigerated, allow it to come to room temperature (by hand warming or exposing to ambient air) before administration. Do not heat. Do not re-freeze NULIBRY after reconstitution. Do not shake.

Discard all unused reconstituted NULIBRY solution 4 hours after reconstitution.

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	NULIBRY must be reconstituted prior to use. Reconstituted NULIBRY may be stored at room temperature [15°C to 25°C (59°F to 77°F)] or refrigerated [2°C to 8°C (36°F to 46°F)]. Do not heat. Do not re-freeze NULIBRY after reconstitution. Do not shake. Discard all unused reconstituted NULIBRY solution 4 hours after reconstitution.	**Acceptable**

Conclusion: Satisfactory

The proposed storage temperature and the hold time of the reconstituted solution are supported by the stability data. The information is acceptable.

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

For injection: 9.5 mg of fosdenopterin, as a white to pale yellow lyophilized powder or cake in a single-dose vial for reconstitution

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	For injection	**Acceptable**
Strengths: in metric system	9.5 mg	**Acceptable**
Active moiety expression of strength (if applicable)	Strength is expressed on the free base content.	**Acceptable**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	a white to pale yellow lyophilized powder or cake	**Acceptable**
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

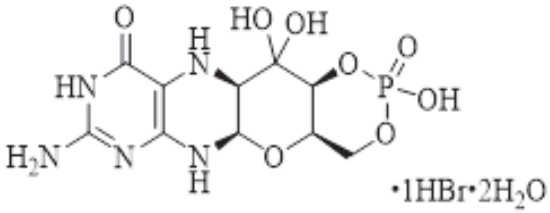
*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: S**atisfactory**

Information in DOSAGE FORMS AND STRENGTHS meets the regulatory requirements.

1.2.3 Section 11: DESCRIPTION

NULIBRY (fosdenopterin) for injection is cyclic pyranopterin monophosphate (cPMP). Fosdenopterin is present as a dihydrate of the hydrobromide salt with the chemical name (4a*R*,5a*R*,11a*R*,12a*S*)-8-amino-4a,5a,6,9,11,11a,12,12a-octahydro-2,12,12-trihydroxy-1,3,2-dioxaphosphorino[4',5':5,6]pyrano[3,2-*g*]pteridin-10(4*H*)-one 2-oxide. Fosdenopterin hydrobromide as a dihydrate is a crystalline solid. The molecular formula is $C_{10}H_{14}N_5O_8P \cdot HBr \cdot 2H_2O$ and the molecular weight is 480.16. The chemical structure is:



NULIBRY is supplied as a sterile, preservative-free, white to pale yellow lyophilized powder or cake in a single-dose, clear glass vial for reconstitution for intravenous infusion. Each vial contains 9.5 mg fosdenopterin (equivalent to 12.5 mg fosdenopterin hydrobromide as a dihydrate). Each vial also contains the following inactive ingredients: 10 mg ascorbic acid USP, 187.5 mg mannitol USP, and 62.5 mg sucrose NF. Sodium hydroxide NF and hydrochloric acid NF are used to adjust pH to 5.0-7.0.

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	NULIBRY (fosdenopterin) for injection	**Acceptable**
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	For injection, intravenous infusion	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	Each vial contains 9.5 mg fosdenopterin (equivalent to 12.5 mg fosdenopterin hydrobromide as a dihydrate).	**Acceptable**
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).	Each vial also contains the following inactive ingredients: 10 mg ascorbic acid USP, 187.5 mg mannitol USP, and 62.5 mg sucrose NF. Sodium hydroxide NF and hydrochloric acid NF are used to adjust pH to 5.0-7.0.	**Acceptable**
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	A sterile statement is provided.	**Acceptable**
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	cyclic pyranopterin monophosphate (cPMP)	**Acceptable**
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	Chemical name and structural formula are provided.	**Acceptable**
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	pH 5.0 – 7.0.	**Acceptable**
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: S**atisfactory**

Information in DESCRIPTION meets the regulatory requirements.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

NULIBRY (fosdenopterin) for injection is a white to pale yellow lyophilized powder or cake in a single-dose clear glass vial for reconstitution. Each NULIBRY vial contains 9.5 mg of fosdenopterin.

Each carton of NULIBRY contains one vial (NDC 73129-001-01).

Components are not made with natural rubber latex.

Storage

Store NULIBRY frozen between -25°C and -10°C (-13°F and 14°F). Store the vial in its original carton to protect from light. For storage recommendations for the reconstituted solution, *see Dosage and Administration (2.4).*

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	for injection	**Acceptable**
Strength of dosage form in metric system	9.5 mg	**Acceptable**
Available units (e.g., bottles of 100 tablets)	One carton contains one vial	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number.	a white to pale yellow lyophilized powder or cake	**Acceptable**
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store the vial in its original carton to protect from light.	**Acceptable**
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store NULIBRY frozen between -25°C and -10°C (-13°F and 14° F).	**Acceptable**
Latex: If product does not contain latex and manufacturing of product and container did not	Components are not made with natural rubber latex.	**Acceptable**

include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."		
Package type (for injectable products).*	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: Satisfactory

Information in HOW SUPPLIED/STORAGE AND HANDLING meets the regulatory requirements.

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	**Manufactured by:** Alcami Carolinas Corporation, Charleston, SC **Distributed by:** Origin Biosciences, Inc., Boston, MA	**Acceptable**

Conclusion: Satisfactory

Information in PATIENT COUNSELING INFORMATION meets the regulatory requirement.

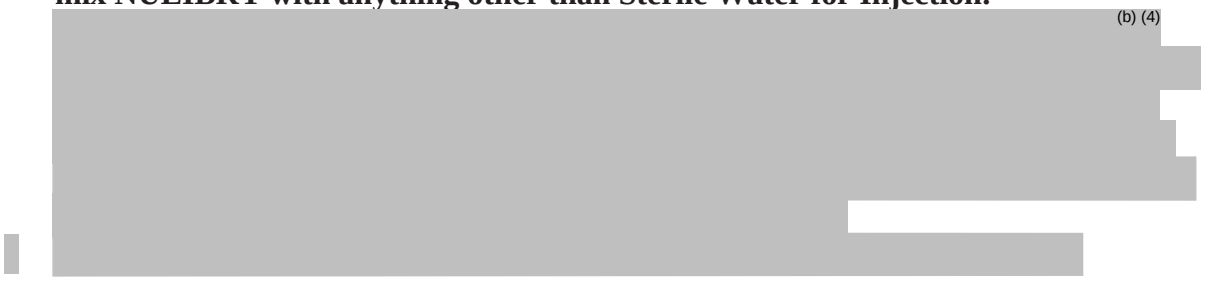
2.0 PATIENT LABELING (INSTRUCTIONS FOR USE)

The information provided in eCTD-0047 is summarized below.

Assessor's comment: Only relevant quality labeling information is included below.

Important information you need to know before preparing and infusing NULIBRY:

- NULIBRY comes as a powder or cake in a vial. Each vial of NULIBRY must be mixed with Sterile Water for Injection to mix (dissolve) the powder or cake before use. **Do not mix NULIBRY with anything other than Sterile Water for Injection.**



[redacted] **NULIBRY**

Frozen vials:

- Store NULIBRY in the freezer between -13°F to 14°F (-25°C to -10° C). Keep NULIBRY vials in its original carton to protect from light until you are ready to use it.

Vials of NULIBRY after mixing:

- Store vials of NULIBRY that have been mixed at room temperature 59°F to 77°F (15°C to 25°C) or refrigerated 36°F to 46 °F (2°C to 8°C) [redacted], until you are ready to give the [redacted].

Vials of NULIBRY are for 1 time use only. Throw the vial away after use, even if there is medicine left in the vial. **Do not** save for later use. [redacted]

Step 6: Mix (dissolve) NULIBRY

- Remove the flip-off cap from the vial of NULIBRY.
- Wipe the rubber stopper on the vial of NULIBRY with a new alcohol wipe.
- Hold the NULIBRY vial firmly on your work surface. Take the syringe with the Sterile Water for Injection and slowly insert the needle into the center of the vial stopper.
- Slowly push down on the plunger all the way to push the Sterile Water for Injection into the vial. Then carefully remove the needle from the vial. Throw away (dispose of) the used needle and syringe in your sharps disposal container right away. Do not try to recap the needle. **See the section "How should I throw away (dispose of) used [redacted] needles and syringes."**
- Gently swirl the vial continuously until the powder is completely dissolved. **Do not** shake the vial.
- **Repeat steps 4 through 6 if more than 1 vial of NULIBRY is needed to prepare your child's prescribed NULIBRY dose. Use a new 5 mL syringe and new needle for each vial of NULIBRY.**

Note: When mixed, the NULIBRY solution should be clear, and colorless to pale yellow.

- **Do not** use the solution if it is discolored or cloudy, or if there are any particles in it. If the solution is discolored or cloudy, tell your pharmacist and ask for a replacement vial.
- **Do not** throw the vial away because the pharmacist may ask that you return it.

What are the ingredients in NULIBRY?

Active ingredient: fosdenopterin

Inactive ingredients: ascorbic acid, mannitol, sucrose. Sodium hydroxide and hydrochloric acid are used to adjust the pH.

Manufactured by:	Distributed by:
Alcami Carolinas Corporation	Origin Biosciences, Inc.
Charleston, SC	Boston, MA

Conclusion: Satisfactory

Adequate quality labeling information is provided in INSTRUCTION FOR USE, including Nulibry storage temperature [between -13°F and 14°F (-25°C and -10° C)] in its original carton, the appearance of the reconstituted solution (clear and colorless to pale yellow), storage condition of the reconstituted solution [59°F to 77°F (15°C to 25°C) or refrigerated 36°F to 46 °F (2°C to 8°C)] for up to 4 hours, and one time use of the vials.

3.0 CARTON AND CONTAINER LABELS

The following issues were identified in Assessment Cycle #1 dated 02-Oct-2020.

1. Replace "(b) (4) (container label) and "(b) (4) " (carton label) with "Recommended Dosage: See Prescribing Information" for both the container and carton labels.
2. Address the following issues for the container label:
   a Include the statement "equivalent to 12.5 mg fosdenopterin hydrobromide" underneath the strength "9.5 mg/vial".
   b Add a statement for quantitative inactive ingredients information, i.e., "Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH."
3. Address the following issues for the carton label:
   a Replace "L-ascorbic acid, USP, Mannitol, USP, and Sucrose NF" with "10 mg ascorbic acid, USP, 187.5 mg mannitol, USP, and 62.5 mg sucrose, NF. Hydrochloric acid and sodium hydroxide are added to adjust pH."
   b Allocate the locations for Lot number and expiration date.

Revised container and carton labels were provided in eCTD-0030, including the newly proposed sample container and carton labels. Based on DMEPA's recommendation to relocate the equivalency statement to the side panel, an updated version of the container and carton labels, as shown below, were provided in eCTD-0040.

3.1 CONTAINER LABEL

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	9.5 mg/vial equivalent to 12.5 mg fosdenopterin hydrobromide	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	9.5 mg/vial	**Acceptable** Expression of strength for dry powder products should be expressed in terms of the total amount of drug per vial as "9.5 mg/vial" or "9.5 mg per vial" [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH.	**Acceptable**
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	The locations for Lot No and expiration date are allocated.	**Acceptable**
Storage conditions	MUST BE FROZEN	**Acceptable**

	PROTECT FROM LIGHT STORE IN CARTON	
Bar code [21CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: See Prescribing Information	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Discard unused portion Reconstitute prior to use	**Acceptable** Because space is limited, instructions for reconstituting the product and the resultant concentration can be omitted [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].
Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: **Satisfactory**

The information provided for container label meets the regulatory requirements.

3.2 SAMPLE CONTAINER LABEL

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**

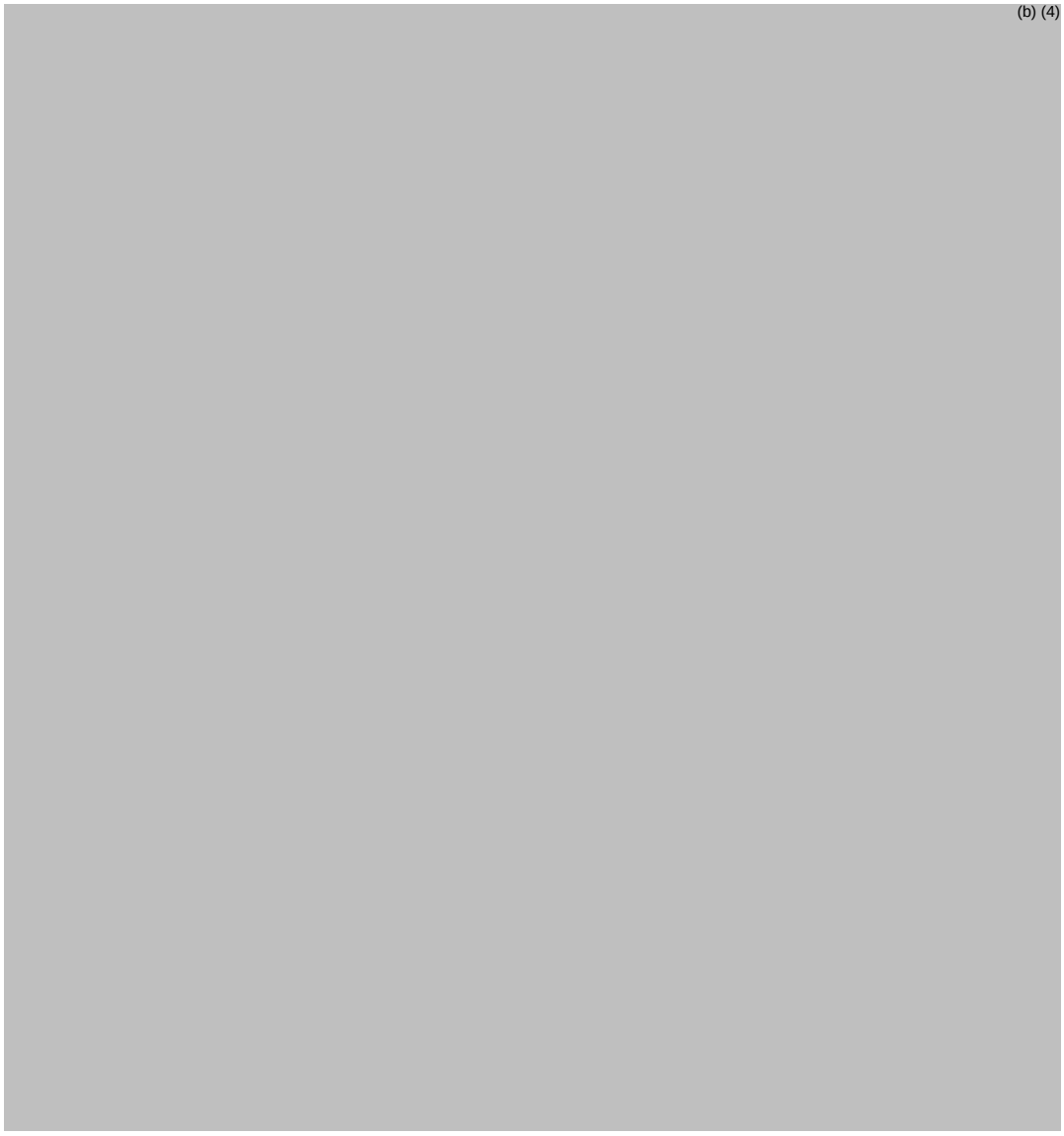
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	9.5 mg/vial equivalent to 12.5 mg fosdenopterin hydrobromide	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	9.5 mg/vial	**Acceptable** Expression of strength for dry powder products should be expressed in terms of the total amount of drug per vial as "9.5 mg/vial" or "9.5 mg per vial" [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH.	**Acceptable**
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-99	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	The locations for Lot No and expiration date are allocated.	**Acceptable**
Storage conditions	MUST BE FROZEN PROTECT FROM LIGHT STORE IN CARTON	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: See Prescribing Information	**Acceptable**

Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Discard unused portion Reconstitute prior to use	**Acceptable** Because space is limited, instructions for reconstituting the product and the resultant concentration can be omitted [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].
Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: **Satisfactory**

The information provided for sample container label meets the regulatory requirements.

3.3 CARTON LABEL



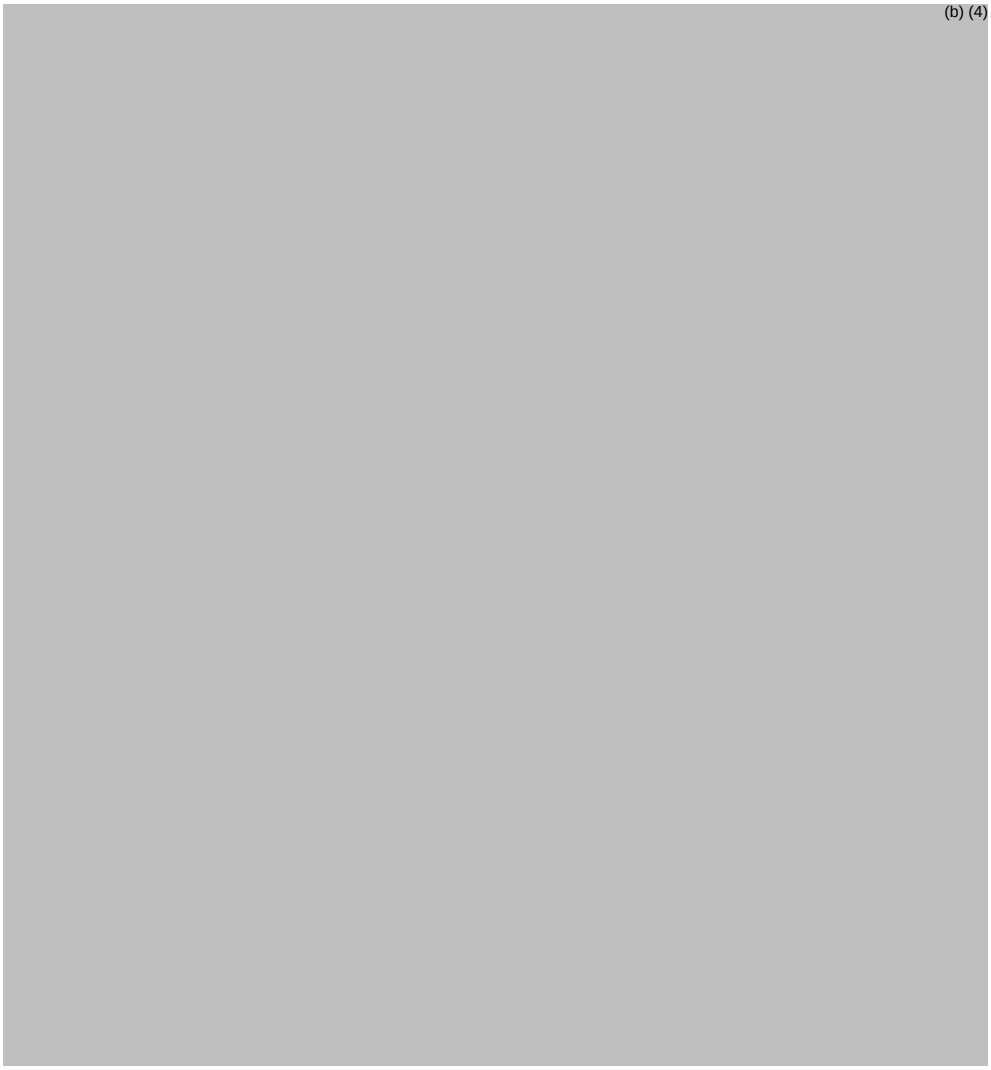
Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each vial contains 9.5 mg fosdenopterin equivalent to 12.5 mg fosdenopterin hydrobromide Contains 1 vial	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	9.5 mg/vial	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	10 mg ascorbic acid, USP, 187.5 mg mannitol, USP, and 62.5 mg sucrose, NF. Hydrochloric acid and sodium hydroxide are added to adjust pH.	**Acceptable**
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	Not provided	**Acceptable** "Sterile" statement is required for the Full Prescribing Information, but not required for the carton label.
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	MUST BE FROZEN between -25°C and -10°C (-13°F and 14°F)	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]	Provided	**Acceptable**

Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: See Prescribing Information	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not provided	**Acceptable** The statement is optional for Rx drugs.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Reconstitute prior to use. Reconstitute each vial with 5 mL Sterile Water for Injection, USP. The resulting concentration is 1.9 mg/mL. Discard unused portion.	**Acceptable**
Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: Satisfactory

The information provided meets the regulatory requirements.

3.4 SAMPLE CARTON LABEL



Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21	Each vial contains 9.5 mg fosdenopterin equivalent to 12.5 mg fosdenopterin hydrobromide	**Acceptable**

CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Contains 1 vial	
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	9.5 mg/vial	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	10 mg ascorbic acid, USP, 187.5 mg mannitol, USP, and 62.5 mg sucrose, NF. Hydrochloric acid and sodium hydroxide are added to adjust pH.	**Acceptable**
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	Not provided	**Acceptable** "Sterile" statement is required for the Full Prescribing Information, but not required for the carton label.
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-99	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Provided	**Acceptable**
Storage conditions	MUST BE FROZEN between -25°C and -10°C (-13°F and 14°F)	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	Recommended Dosage: See Prescribing Information	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not provided	**Acceptable** The statement is optional for Rx drugs.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Reconstitute prior to use. Reconstitute each vial with 5 mL Sterile Water for Injection, USP. The resulting concentration is 1.9 mg/mL. Discard unused portion.	**Acceptable**

Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: Satisfactory

The information provided for sample carton label meets the regulatory requirements.

Jane Chang

Digitally signed by Jane Chang
Date: 2/11/2021 11:08:16AM
GUID: 5034f819000053b21e2574590781f330

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 2/11/2021 11:44:10AM
GUID: 50816dbc000085595ca3284bbca465a8

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HITESH N SHROFF
02/15/2021 04:21:12 PM

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Not Ready for Approval –Labeling Pending
☐ Complete Response

NDA 214018
Assessment 1

Drug Product Name	Nulibry (fosdenopterin) for Injection
Dosage Form	Powder, for injection
Strength	9.5 mg/vial
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Origin Biosciences, Inc.; Boston, MA
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Jun 29, 2020	OPQ
Amendment	Jul 27, 2020	OPMA
Amendment	Jul 31, 2020	OPMA
Amendment	Sep 4, 2020	ONDP
Amendment	Sep 30, 2020	ONDP
Amendment	Oct 1, 2020	ONDP
Amendment	Oct 8, 2020	DMA
Amendment	Oct 26, 2020	DMA
Amendment	Nov 12, 2020	OPMA, ONDP
Amendment	Nov 18, 2020	ONDP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Lawrence Perez	Donna Christner
Drug Product	Jane Chang	Wendy Wilson
Manufacturing / Facilities	Yan Xu	Joanne Wang
Microbiology	Shannon Heine	Erika Pfeiler
Environmental	Jane Chang	Wendy Wilson
Regulatory Business Process Manager	Oumou Barry	
Application Technical Lead	Hitesh Shroff	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The applicant has provided sufficient CMC information to assure the identity, strength, purity, and quality of the proposed Nulibry (fosdenopterin) for Injection.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made a final overall "**Approval**" recommendation for the facilities involved in this application,

The claim for the Categorical Exclusion for the Environmental Assessment is granted.

The label/labeling has not been finalized as of this review.

Therefore, from the OPQ perspective, this NDA is ***not*** deemed ready for approval in its present form per CFR 314.125(b)(6) until the label/labeling is finalized.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Nulibry is a sterile, preservative-free, white to yellow lyophilized powder for injection. It is supplied in a single-dose clear glass vial. Each vial contains 9.5 mg of fosdenopterin. It must be reconstituted with 5 mL of sterile water for injection (WFI) prior to intravenous administration.

<table>
<tr><td>Proposed Indication(s) including Intended Patient Population</td><td>Nulibry is a synthetic form of cyclic pyranopterin monophosphate (cPMP) indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.</td></tr>
<tr><td>Duration of Treatment</td><td>As needed</td></tr>
<tr><td>Maximum Daily Dose</td><td>The reconstituted solution should be administered as an intravenous infusion at a rate of 1.5 mL/minute.

• Pediatric patients less than 12 months – Dosage should be titrated to the target dose of 0.9 mg/kg/day over a period of 3 months.

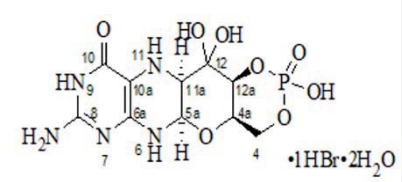
<table>
<tr><th>Titration Schedule</th><th>Gestational Age ≥ 37 weeks mg/kg</th><th>Gestational Age < 37 weeks mg/kg</th></tr>
<tr><td>Initial Dose</td><td>0.55 mg</td><td>0.40 mg</td></tr>
<tr><td>Month 1</td><td>0.75 mg</td><td>0.70 mg</td></tr>
<tr><td>Month 3</td><td>0.90 mg</td><td>0.90 mg</td></tr>
</table>

Patients 1 year or older - the recommended dosage is 0.90 mg/kg administered once daily.</td></tr>
<tr><td>Alternative Methods of Administration</td><td>None</td></tr>
</table>

B. Quality Assessment Overview

Drug Substances: Adequate

Fosdenopterin hydrobromide is the drug substance in Nulibry for injection. It is a white to pale yellow/light orange/brown/red solid. The drug substance registration batches were light orange to dark red/brown in color. It is practically insoluble in water, methanol, ethanol and at low pH. However, it is very soluble at high pH e.g. 0.1 N KOH. It is hygroscopic. It is produced in a dihydrate crystalline form. It is a chiral molecule containing four chiral centers, C5a*R*, C11a*R*, C12a*S* and C4a*R*. The chemical name of fosdenopterin hydrobromide as dihydrate is (4a*R*,5a*R*,11a*R*,12a*S*)-8-Amino-2,12,12- t rihydroxy-4,4a,5a,6,9,10,11,11a,12,12a-decahydro-2H-1,3,5-trioxa-6,7,9,11-tetraaza-2λ^5-phosphatetracene- 2,10-dione (hydrobromide dihydrate). The molecular weight of fosdenopterin is 480.16 as hydrobromide dihydrate and 363.23 as free base. The chemical structure is:



Fosdenopterin hydrobromide is manufactured at (b) (4)

(b) (4)

(b) (4)

The identity, purity and quality of the drug substance, Fosdenopterin hydrobromide, is assured by its specification for appearance, identity by IR and HPLC; assay by HPLC, impurities by HPLC, elemental impurities by ICP-MS per USP <233>, residual solvents by GC; powder X-ray diffraction and microbial limits testing per USP <61> and <62>. The potential genotoxic impurities were evaluated by AMES test per ICH M7. The drug substance and potential impurities showed negative response in AMES test. The non-compendial analytical methods were validated per ICH Q2R1.

The batch analyses of multiple drug substance batches (b) (4) used in nonclinical, clinical, and stability studies met the proposed drug substance specification and confirmed that the drug substance manufacturing process is robust.

Based on the long-term stability testing of multiple batches of Fosdenopterin hydrobromide, a retest period of (b) (4) months is supported when stored at (b) (4) C in proposed container closure systam (b) (4)

The drug substance reviewer, Dr. Lawrence B. Perez, concluded that the applicant has submitted adequate CMC information regarding the regulatory starting material, raw materials, intermediates, manufacturing process as well as the specification for identity, purity and quality of the drug substance, Fosdenopterin hydrobromide. (see the **Drug Substance** review).

Drug Product: Adequate

Nulibry, a substrate replacement therapy, is a synthetic form of cyclic pyranopterin monophosphate (cPMP). Nulibry (fosdenopterin) for injection is supplied as a sterile, white to pale yellow, lyophilized powder or cake in 10 mL single-dose USP (b) (4) clear glass vials. Each vial contains 9.5 mg fosdenopterin (equivalent to 12.5 mg fosdenopterin hydrobromide). Each vial also contains the following inactive ingredients: 10 mg L-ascorbic acid USP, 187.5 mg Mannitol USP, and 62.5 mg sucrose NF. Sodium hydroxide NF and hydrochloric acid NF are used to adjust pH to 5.0-7.0. (b) (4) The vials are stoppered with 20 mm (b) (4) stoppers and capped with 20 mm (b) (4) flip-off caps. Nulibry must be reconstituted with 5.0 mL sterile water for injection prior to administration. The intravenous administration of Nulibry must be completed within 4 hours of reconstitution. Reconstituted Nulibry may be stored at room temperature (15°C to 25°C/59°F to 77°F) or refrigerated (2°C to 8°C/35°F to 47°F). The unused reconstituted Nulibry vials must be discarded after 4 hours since reconstitution.

The specification for drug product as a lyophilized powder or cake and reconstituted solution includes the acceptance limits and following tests: visual appearance, reconstitution time, pH, water content per USP <921>, identity by UV and HPLC, strength by UHPLC assay, ascorbic acid assay, degradation products by UHPLC, content uniformity per USP <905, particulate matter per USP <788>, container closure integrity per USP <1207> and sterility per USP <71>, Bacterial endotoxin per USP <85>. The in-house developed, non-compendial analytical methods were validated per ICH Q2(R1). The overall control strategy for the drug product's identity, strength, purity and quality is deemed adequate based on the proposed drug product specification.

Based on the satisfactory drug product stability data provided, a 12-month of expiration dating period is granted when stored at -10°C to -25°C in the proposed container closure system. (See the **Drug Product** review by Dr. Jane Chang)

Manufacturing: Adequate

Nulibry (fosdenopterin) for injection is manufactured at Alcami Carolinas Corporation, SC. The drug product manufacturing process involves (b) (4)

[redacted] (b) (4) The proposed drug product manufacturing process for commercial manufacture at [redacted] (b) (4) scale was reviewed by Dr. Yan Xu and was found to be reasonable with low risk. (See the **Manufacturing Integrated Assessment** review)

Microbiology: Adequate

Nulibry is a sterile, lyophilized powder in a single-dose 10 mL clear glass vial for intravenous infusion after reconstitution. The microbiology reviewer, Dr. Shannon Heine, reviewed the drug product manufacturing steps, environmental monitoring program, component/equipment sterilization, depyrogenation of vials, bioburden, [redacted] (b) (4), bacterial endotoxin and container closure integrity method and validation in drug product specification; stability data and post-approval stability plan; and concluded that the applicant has met regulatory expectations for the drug product release. (see **Microbiology** review)

Labeling: Inadequate

The label/labeling has not been finalized as of this review. (see the **Labeling** review).

Facilities Adequate

The Office of Process and Facilities (OPF) reviewer, Dr. Yan Xu has made an "Adequate" recommendation for the drug substance and drug product manufacturing and testing facilities. (see the **Manufacturing Integrated Assessment** review).

Environmental Assessment Adequate

The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances per 21 CFR 25.31(b) because the estimated concentration at the point of entry into the aquatic environment is estimated to be substantially below 1 part per billion. The claim of categorical exclusion is acceptable. (see the **Drug Product** Review).

Post-marketing Commitments (PMC): None

Lifecycle Management Considerations: None

C. LIST OF DEFICIENCIES:

A. Regarding PI

a) Full Prescribing Information

Section 2: Dosage and Administration

1. Replace the temperature [redacted (b) (4)] with "36°F to 46°F" in Section 2.2.

Section 3: Dosage Forms and Strengths

2. Add product description "as a white to pale yellow lyophilized powder or cake"

Section 11: Description

3. Include the route of administration by adding "for reconstitution for intravenous infusion".
4. Add "a synthetic form of cyclic pyranopterin monophosphate (cPMP)".
5. Add description for the drug substance "Fosdenopterin hydrobromide as a dihydrate is a crystalline solid" and the molecular formula "$C_{10}H_{14}N_5O_8P \cdot HBr \cdot 2H_2O$"
6. Revise the chemical name to "(4a*R*,5a*R*,11a*R*,12a*S*)-8-amino-2,12,12-trihydroxy-4a,5a,6,7,11,11a,12,12a-octahydro-2*H*-2λ^5-[1,3,2]dioxaphosphinino[4',5':5,6]pyrano[3,2-*g*]pteridine-2,10(4*H*)-dione, hydrobromide, hydrate (1:1:2)"
7. Add "as a dihydrate" after the drug substance established name "fosdenopterin hydrobromide" for the salt equivalence statement for clarity.
8. Use the title of USP/NF monographs as the established name for inactive ingredients. List the inactive ingredients in lower case. That is, ascorbic acid (instead of L-ascorbic acid) and mannitol (instead of Mannitol).

Section 16: How Supplied/Storage and Handling

9. Replace drug product description "[redacted] with "white to pale yellow lyophilized powder or cake".
10. Delete [redacted]
11. Delete [redacted] *[see Dosage and Administration (2.2)]*.

B. Regarding the Container/Carton Labels

12. Replace '[redacted] (container label) and "[redacted] (carton label) with "Recommended Dosage: See Prescribing Information" for both the contain and carton labels.
13. Address the following issues for the container label:
    a Include the statement "equivalent to 12.5 mg fosdenopterin hydrobromide" underneath the strength "9.5 mg/vial".
    b Add a statement for quantitative inactive ingredients information, i.e., "Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH."
14. Address the following issues for the carton label:
    a Replace "L-ascorbic acid, USP, Mannitol, USP, and Sucrose NF" with "10 mg ascorbic acid, USP, 187.5 mg mannitol, USP, and 62.5 mg sucrose, NF. Hydrochloric acid and sodium hydroxide are added to adjust pH."
    b Allocate the locations for Lot number and expiration date.

Application Technical Lead Name and Date:

Hitesh Shroff, Ph.D.
Application Technical Lead, Branch V
Division of New Drug Products II
November 27, 2020

Hitesh N. Shroff -S

Digitally signed by Hitesh N. Shroff -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000348333, cn=Hitesh N. Shroff -S
Date: 2020.11.27 20:27:55 -05'00'

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	Active	N/A	LOA: Dec 10, 2019
	III			Active	N/A	LOA: Jul 31, 2020
	IV			Active	Oct 30, 2020, Adequate	LOA: Nov 26, 2019

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	117502	Rely on all information and clinical trials conducted under this IND.
		(b) (4)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

87 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List Submissions being reviewed:

Document Reviewed (eCTD #)	Date Received
eCTD-0004 (SDN-4)	06/29/2020
eCTD-0007 (SDN-7)	07/09/2020

1.0 PRESCRIBING INFORMATION

The information provided in eCTD-0004 is summarized below. In eCTD-0007, a word version of the proposed labeling was provided.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

1. **PRODUCT TITLE**

NULIBRY (fosdenopterin) for injection, for intravenous use
Initial U.S. Approval: XXXX

2. **DOSAGE FORMS AND STRENGTHS**

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Drug name [201.57(a)(2)]		
Proprietary name and established name	NULIBRY (fosdenopterin) for injection	**Acceptable**
Dosage form, route of administration	for injection, intravenous	**Acceptable**
Initial U.S. Approval	XXXX	**Acceptable** The drug substance is an NME. The year this drug is approved should be listed.
Dosage Forms and Strengths [201.57(a)(8)]		
Dosage forms and strengths in metric system	For injection, 9.5 mg	**Acceptable** Strength is expressed on the free base content.
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: Satisfactory

The proposed proprietary name "NULIBRY" was evaluated by Sarah Vee on 5/4/2020 and concluded to be acceptable. The established name "fosdenopterin" was adopted by USAN

Council on 12/18/2019 (see https://www.ama-assn.org/about/united-states-adopted-names).

Product Title and Initial U.S. Approval are acceptable. Critical information per 21 CFR 201.57(a)(8) is also included in Dosage Forms and Strengths section. Minor edits as shown below are recommended for Dosage Forms and Strengths per Labeling Review Tool (page 13), which recommends including limited packaging information. Of not, the color of the solid does not need to be included in the Highlights.

DOSAGE FORMS AND STRENGTHS

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

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2: DOSAGE AND ADMINISTRATION

(b) (4)

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4)	**Unacceptable** The temperature range of 2°C - 8°C corresponds to 36°F-46°F.

Conclusion: Unsatisfactory

The recommended revisions are shown below:

(b) (4)

1.2.2 Section 3: DOSAGE FORMS AND STRENGTHS

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Available dosage forms	For injection	**Acceptable**
Strengths: in metric system	9.5 mg	**Acceptable**
Active moiety expression of strength (if applicable)	Strength is expressed on the free base content.	**Acceptable**
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	(b) (4)	**Unacceptable** Add " or cake" after "powder".
Package type (for injectable products).* See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: **Unsatisfactory**

Per Labeling Review Tool (page 27), it is recommended including limited packaging information. The recommended revisions are shown below:

(b) (4)

For injection: 9.5 mg of fosdenopterin (b) (4) as a white to pale yellow lyophilized powder or cake in a single-dose vial for reconstitution

1.2.3 Section 11: DESCRIPTION

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name and established name [21 CFR 201.57(c)(12)(i)(A)]	NULIBRY (fosdenopterin) for injection	**Acceptable**
Dosage form and route of administration [21 CFR 201.57(c)(12)(i)(B)]	(b) (4)	**Unacceptable** Add "for intravenous infusion" as the route of administration.
Active moiety expression of strength with equivalence statement (if applicable) per 21 CFR 201.100(b)(4)	Each vial contains 9.5 mg fosdenopterin (equivalent to 12.5 mg fosdenopterin hydrobromide).	**Acceptable with a minor editorial change** Add "as a dihydrate" after "fosdenopterin hydrobromide", i.e., fosdenopterin hydrobromide as dihydrate.
Inactive ingredient information [21 CFR 201.57(c)(12)(i)(C)] [quantitative, if injectables 21CFR201.100(b)(5)(iii), listed by USP/NF names (if any)]. Not required for oral use, except for colorant. For ingredients added to adjust the	Each vial also contains the following inactive ingredients: 10 mg L-ascorbic acid USP, 187.5 mg Mannitol USP, and 62.5 mg sucrose NF. Sodium hydroxide NF and hydrochloric acid NF are used to adjust pH.	**Unacceptable** Use lowercase for mannitol. The title of the USP/NF monograph should be used as the established name, i.e., "ascorbic acid" instead of "L-ascorbic acid".

pH or make isotonic, include the name and statement of effect. If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F (15.56 °C) per 21 CFR 201.10(d)(2).		
Statement of being sterile [if applicable, 21 CFR 201.57(c)(12)(i)(D)]	A sterile statement is provided.	**Acceptable**
Pharmacological/ therapeutic class [21 CFR 201.57(c)(12)(i)(E)]	Not provided	**Unacceptable** Add "cyclic pyranopterin monophosphate (cPMP)".
Chemical name, structural formula [21 CFR 201.57(c)(12)(i)(F)]	Chemical name and structural formula are provided.	**Unacceptable** The chemical name is incorrect. Update the structural formula without the atom position denotation for clarity.
Other important chemical or physical properties (such as pKa or pH) [21 CFR 201.57(c)(12)(ii)]	pH 5.0 – 7.0.	**Acceptable**
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	N/A
Package type (for injectable products)*. See USP <659> for other package type terms including pharmacy bulk package and imaging bulk package.	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: **Unsatisfactory**

The recommended revisions are shown below:

NULIBRY (fosdenopterin) for injection (b) (4) -is a synthetic form of cyclic pyranopterin monophosphate (cPMP). Fosdenopterin is present as a dihydrate of the hydrobromide salt with the ~~The~~ chemical name (b) (4) (b) (4)

Fosdenopterin hydrobromide as a dihydrate is a crystalline solid. The molecular formula is $C_{10}H_{14}N_5O_8P \cdot HBr \cdot 2H_2O$ and the molecular weight (b) (4) is 480.16. (b) (4) The chemical structure is:

(b) (4)

NULIBRY (b) (4) is supplied as a sterile, preservative-free, white to pale yellow, lyophilized powder or cake in a single-dose, clear glass vial for reconstitution for intravenous infusion. Each vial contains 9.5 mg fosdenopterin (equivalent to 12.5 mg fosdenopterin hydrobromide as a dihydrate). Each vial also contains the following inactive ingredients: 10 mg ~~L~~ ascorbic acid USP, 187.5 mg ~~Mannitol~~ mannitol USP, and 62.5 mg sucrose NF. Sodium hydroxide NF and hydrochloric acid NF are used to adjust pH (b) (4) to 5.0-7.0.

1.2.4 Section 16: HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Dosage form	for injection	**Acceptable**
Strength of dosage form in metric system	9.5 mg	**Acceptable**
Available units (e.g., bottles of 100 tablets)	One carton contains one vial	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number.	lyophilized powder	**Unacceptable** The color of the lyophilized powder or cake should be provided.
Special handling (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store the vial in its original carton to protect from light.	**Acceptable**
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store (b) (4) NULIBRY frozen between −25°C and −10°C (−13°F and 14° F).	**Acceptable**
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	Components not made with natural rubber latex.	**Acceptable**
Package type (for injectable products).*	single-dose	**Acceptable**

*See Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use

Conclusion: Unsatisfactory

The long-term stability study of the drug product was conducted at -20±5°C per ICH Q1A. The temperature range for storage of NULIBRY is stated as "between -25°C and -10°C (−13°F and 14°F)", which is consistent with the freezer temperature per USP <659>; therefore, it is acceptable.

The recommended revisions are shown below:

16.1 How Supplied

NULIBRY (fosdenopterin) for injection is (b) (4) white to pale yellow lyophilized powder or cake in a single-dose clear glass vial for (b) (4) reconstitution. Each NULIBRY vial contains 9.5 mg of fosdenopterin.

Each carton of NULIBRY contains one vial (b) (4) (NDC 73129-001-01).

Components not made with natural rubber latex.

16.2 Storage (b) (4)

Store (b) (4) NULIBRY frozen between −25°C and −10°C (−13°F and 14° F). Store the vial in its original carton to protect from light.

(b) (4)

[see Dosage and Administration (2.2)].

(b) (4)

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

Item	Information Provided in NDA	Assessor's Comments and Recommendations
Manufacturer/distributor name [21 CFR 201.1(h)(5)]	Manufactured by: Alcami Carolinas Corporation Charleston, SC Distributed by: Origin Biosciences, Inc. Boston, MA	**Acceptable**

Conclusion: Satisfactory

Information in PATIENT COUNSELING INFORMATION meets the regulatory requirement.

2.0 PATIENT LABELING (INSTRUCTIONS FOR USE)

Assessor's comment: Only relevant quality labeling information is included below.

Important Information You Need to Know Before Preparing and (b) (4) NULIBRY

(b) (4)

Step 6: (b) (4) (Dissolve) NULIBRY

(b) (4)

Step 8: (b) (4)

(b) (4)

Conclusion: Satisfactory

Adequate quality labeling information is provided in INSTRUCTION FOR USE, including Nulibry storage temperature [between −13°F and 14°F (−25°C and −10° C)] in its original

carton, reconstitution time (b) (4), the appearance of the reconstituted solution (clear and colorless to pale yellow), use of the reconstituted solution within four hours after reconstitution, and one time use of the vials.

3.0 CARTON AND CONTAINER LABELS

The information provided in eCTD-0004 is summarized below.

3.1 CONTAINER LABEL

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**
Route of administration, if it is not for oral use [21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	9.5 mg/vial	**Unacceptable** Salt equivalence statement should be included.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)][&]	9.5 mg/vial	**Acceptable** Expression of strength for dry powder products should be expressed in terms of the total amount of drug per vial as "9.5 mg/vial" or "9.5 mg per vial" [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].

Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	Not provided	**Unacceptable** Quantitative inactive ingredients information should be included.
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	The locations for Lot No and expiration date are allocated.	**Acceptable**
Storage conditions	(b) (4) FROZEN PROTECT FROM LIGHT STORE IN CARTON	**Acceptable**
Bar code [21CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)	(b) (4)	**Unacceptable** Replace with "Recommended Dosage: See Prescribing Information"
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Discard unused portion Reconstitute prior to use	**Acceptable** Because space is limited, instructions for reconstituting the product and the resultant concentration can be omitted [see FDA draft guidance entitled *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (file:///C:/Users/CHANGJa/Downloads/FDA-2013-D-0401-0002_content%20(1).pdf)].
Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: **Unsatisfactory**

In an email communication dated 8/9/2019 with DMEPA assessor for labeling of another NDA, the assessor stated that based on DMEPA management's involvement with the Labeling Workgroup, it was recently determined that the usual dosage statement be changed from (b) (4) (b) (4) to "Recommended Dosage: See Prescribing Information".

The recommended revisions are shown below:

1. Include the statement "equivalent to 12.5 mg fosdenopterin hydrobromide" underneath the strength "9.5 mg/vial".
2. Replace "(b) (4) with "Recommended Dosage: See Prescribing Information".
3. Add a statement for quantitative inactive ingredients information, i.e., "Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH."

3.2 CARTON LABEL

(b) (4)

Items	Information Provided in NDA	Assessor's Comments and Recommendations
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	Nulibry (fosdenopterin) for injection	**Acceptable**
Route of Administration [not required for oral, 21 CFR 201.100(b)(3)]	For intravenous infusion only	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	Each vial contains 9.5 mg fosdenopterin equivalent to 12.5 mg fosdenopterin hydrobromide Contains 1 vial	**Acceptable**
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	9.5 mg/vial	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]	L-ascorbic acid, USP, Mannitol, USP, and Sucrose NF	**Unacceptable** Quantitative information for each excipient should be provided. Use lower case for mannitol and sucrose. The title of the USP/NF monograph should be used as the established name, i.e., "ascorbic acid" instead of "L-ascorbic acid".
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Provided	**Acceptable**
Statement of being sterile (if applicable)	Not provided	**Acceptable** "Sterile" statement is required for the Full Prescribing Information, but not required for the carton label.
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 73129-001-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	Not provided	**Unacceptable**
Storage conditions	STORE FROZEN between -25°C and -10°C (-13°F and 14°F)	**Acceptable**
Bar code [21 CFR 201.25(c)(2)]	Provided	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR	(b) (4)	**Unacceptable**

201.5] or "Recommended Dosage: See Prescribing Information" (21 CFR 201.55)		Replace with "Recommended Dosage: See Prescribing Information"
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Not provided	**Acceptable** The statement is optional for Rx drugs.
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by: Origin Biosciences, Inc., Boston, MA 02116	**Acceptable**
And others, if space is available	Reconstitute prior to use. Reconstitute each vial with 5 mL Sterile Water for Injection, USP. The resulting concentration is 1.9 mg/mL. Discard unused portion.	**Acceptable**
Package type (for injectable products).	Single-dose vial	**Acceptable**

Conclusion: Unsatisfactory

The recommended revisions are shown below:

1. Replace "L-ascorbic acid, USP, Mannitol, USP, and Sucrose NF" with "10 mg ascorbic acid USP, 187.5 mg mannitol USP, and 62.5 mg sucrose NF. Hydrochloric acid and sodium hydroxide are added to adjust pH."

   Per 21 CFR 201.100(b)(5)(iii), the quantity of inactive ingredients is required for parenteral injection drugs. The title of USP/NF monographs should be used as the established name. Provide the inactive ingredients in lower case.

2. Allocate the locations for Lot number and expiration date.
3. Replace "(b) (4)" with "Recommended Dosage: See Prescribing Information".

4.0 LIST OF DEFICIENCIES:

A. Regarding PI

a) Full Prescribing Information

Section 2: Dosage and Administration

1. Replace the temperature "(b) (4)" with "36°F to 46°F" in Section 2.2.

Section 3: Dosage Forms and Strengths

2. Add product description "as a white to pale yellow lyophilized powder or cake"

Section 11: Description

3. Include the route of administration by adding "for reconstitution for intravenous infusion".
4. Add "a synthetic form of cyclic pyranopterin monophosphate (cPMP)".
5. Add description for the drug substance "Fosdenopterin hydrobromide as a dihydrate is a crystalline solid" and the molecular formula "$C_{10}H_{14}N_5O_8P \bullet HBr \bullet 2H_2O$"
6. Revise the chemical name to "(4a*R*,5a*R*,11a*R*,12a*S*)-8-amino-2,12,12-trihydroxy-4a,5a,6,7,11,11a,12,12a-octahydro-2*H*-2λ^5-[1,3,2]dioxaphosphinino[4',5':5,6]pyrano[3,2-*g*]pteridine-2,10(4*H*)-dione, hydrobromide, hydrate (1:1:2)"
7. Add "as a dihydrate" after the drug substance established name "fosdenopterin hydrobromide" for the salt equivalence statement for clarity.
8. Use the title of USP/NF monographs as the established name for inactive ingredients. List the inactive ingredients in lower case. That is, ascorbic acid (instead of L-ascorbic acid) and mannitol (instead of Mannitol).

Section 16: How Supplied/Storage and Handling

9. Replace drug product description "(b) (4)" with "white to pale yellow lyophilized powder or cake".
10. Delete (b) (4)
11. Delete information relevant to Dosage and Administration. Add "(b) (4)) *[see Dosage and Administration (2.2)]*.

B. Regarding the Container/Carton Labels

12. Replace "(b) (4) (container label) and (b) (4)) with "Recommended Dosage: See Prescribing Information" for both the contain and carton labels.
13. Address the following issues for the container label:
    a Include the statement "equivalent to 12.5 mg fosdenopterin hydrobromide" underneath the strength "9.5 mg/vial".
    b Add a statement for quantitative inactive ingredients information, i.e., "Each vial contains 10 mg ascorbic acid, 187.5 mg mannitol, and 62.5 mg sucrose. Hydrochloric acid and sodium hydroxide are added to adjust pH."
14. Address the following issues for the carton label:
    a Replace "L-ascorbic acid, USP, Mannitol, USP, and Sucrose NF" with "10 mg ascorbic acid, USP, 187.5 mg mannitol, USP, and 62.5 mg sucrose, NF. Hydrochloric acid and sodium hydroxide are added to adjust pH."
    b Allocate the locations for Lot number and expiration date.

OVERALL ASSESSMENT:

Issues on the product description, incorrect chemical name, inactive ingredient established name, salt equivalence statement, and lack of route of administration, pharmacological/

therapeutic class, quantitative inactive ingredients information, and lot number and expiration date are identified.

Recommendation:

From the ONDP perspective, this application is ***not*** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Jane Chang, Ph.D.
Master Chemistry Reviewer
DNDP II/ONDP
10/1/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson-Lee, Ph.D.
Division Director (Acting Chief, Branch 4)
DNDP II/ONDP
10/1/2020

Jane Chang

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Wendy Wilson- Lee

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	
NDA Number	214018
Assessment Cycle Number	1
Drug Product Name / Strength	fosdenopterin (b) (4) for injection, 9.5 mg/vial
Route of Administration	Intravenous (IV) infusion
Applicant Name	Origin Biosciences, Inc.
Manufacturing Site	Alcami Carolinas Corporation 4221 Faber Place Drive Charleston, SC 29405, USA FEI: 1000110990 DUNS: 832394733
Method of Sterilization	(b) (4)

Assessment Recommendation: *Adequate*

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ Media Fill Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:*

N/A

Assessment Summary:

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Seq 0003	5 May 2020
Seq 0004	29 June 2020
Seq 0007	9 July 2020
Seq 0013	4 September 2020
Seq 0025	8 October 2020
Seq 0031	26 October 2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is a sterile, white to pale yellow lyophilized powder for IV infusion. The drug product is packaged in 10 mL tubular single dose glass vials, stoppered, and sealed. The drug product is indicated for the treatment of Molybdenum Cofactor Deficiency Type A. The drug product received Orphan Drug Designation on 5 November 2009, Breakthrough Therapy Designation on 23 October 2013, and Rare Pediatric Disease Designation on 15 June 2017. The applicant's proposal for a Rolling Review NDA was accepted on 18 November 2019. Deficiencies were conveyed to the applicant in Product Quality Microbiology Information Requests dated 25 September 2020 and 20 October 2020.

The submission is recommended for approval from the standpoint of product quality microbiology.

Concise Description of Outstanding Issues: N/A

Supporting Documents:

- Microbiology Review of DMF (b) (4)), dated 28 August 2019, for (b) (4) (b) (4)
- Type V DMF (b) (4) for the (b) (4) manufacturing operations and facility in Charleston, SC (Alcami Carolinas Corporation).
- Type III DMF (b) (4) for the (b) (4)
- Type III DMF (b) (4) for (b) (4)
- Microbiology Review of DMF (b) (4) dated 19 April 2017 for (b) (4)
- Microbiology Review of DMF (b) (4) dated 30 October 2020, for (b) (4)
- Microbiology Review of DMF (b) (4) dated 25 June 2019 for (b) (4)
- Microbiology Review of DMF (b) (4) dated 15 December 2011 for (b) (4)

Select Number of Approved Comparability Protocols: 0

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance was not performed since the drug is sterilized during the drug product manufacturing process.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product**

(See Section 3.2.P.1 (Seq 0004), *Description and composition of the drug product*)

The subject drug product is a sterile, white to pale yellow lyophilized powder for Intravenous (IV) infusion. The drug product is packaged in 10 mL clear and colorless tubular single dose glass vials, stoppered, and sealed.

Note: The strength of the drug product is 9.5 mg/vial when listed as fosdenopterin free base. The applicant indicates that prior submissions and documents list the strength as 12.5 mg/vial, which is the equivalent for fosdenopterin hydrobromide dihydrate. The concentration of fosdenopterin is 1.9 mg/mL as the free base when in solution, either prior to lyophilization or after reconstitution, which is equivalent to 2.5 mg/mL fosdenopterin HBr. The applicant states that either concentration may be listed in reports and documents with “free base” being designated when used. (See Section 3.2.P.1 (Seq 0004), pg.1 of *Description and composition of the drug product*)

- **Drug product composition**

Fosdenopterin for Injection, 9.5 mg/vial

Ingredient	Quantity per vial*	Concentration after reconstitution	Function
Fosdenopterin HBr	(b) (4)	1.9 mg/mL	Active Pharmaceutical Ingredient
L-Ascorbic acid		(b) (4)	(b) (4)
Mannitol			
Sucrose			
Water for injection			
Hydrochloric acid			pH adjustment
Sodium hydroxide			pH adjustment
			(b) (4)
		(b) (4)	

The quantity presented included the overfill.

- **Description of container closure system**

(See Section 3.2.P.7 (Seq 0004), pg. 2 of *Container Closure System*)

Component	Description	Manufacturer
Vial	(b) (4)	
Stopper		
Seal		

Assessment: ***Adequate***
The applicant provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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