# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 217026Orig1s000

# PRODUCT QUALITY REVIEW(S)

# NDA Executive Summary

## 1. Application/Product Information

| | | | |
|---|---|---|---|
| **NDA Number** | 217026 | | |
| **Applicant Name** | Acadia Pharmaceuticals Inc. | | |
| **Drug Product Name** | DAYBUE (trofinetide) | | |
| **Dosage Form** | Oral solution | | |
| **Proposed Strength(s)** | 200 mg/mL | | |
| **Route of Administration** | Oral | | |
| **Maximum Daily Dose** | 24 g | | |
| **Rx/OTC Dispensed** | Rx | | |
| **Proposed Indication** | Treatment of Rett syndrome in adults and pediatric patients 2 years of age and older. | | |
| **Drug Product Description** | Pink to red strawberry flavored solution. | | |
| **Co-packaged product information** | N/A | | |
| **Device information** | N/A | | |
| **Storage Temperature/ Conditions** | Refrigerate, 2°C to 8°C | | |
| **Review Team** | **Discipline** | **Primary** | **Secondary** |
| | *Drug Substance* | Zhixing Shan | Gaetan Ladouceur |
| | *Drug Product/ Labeling* | Grace Chiou | Martha Heimann |
| | *Manufacturing* | Chaoying Ma | Shujun Chen |
| | *Biopharmaceutics* | N/A | N/A |
| | *Microbiology* | Ryan Blower | Erika Pfeiler |
| | *Other (specify):* | N/A | N/A |

| | | |
|---|---|---|
| | *RBPM* | Erica Keafer |
| | *ATL* | Martha Heimann |
| **Consults** | N/A | |

**2. Final Overall Recommendation - Approval**

**3. Action Letter Information**

**a. Expiration Dating:**

18 months when stored at 2°C to 8°C

**b. Additional Comments for Action**

None

**4. Basis for Recommendation:**

**a. Summary of Rationale for Recommendation:**

OPQ recommends **APPROVAL** of NDA 217026 for DAYBUE (trofinetide) oral solution 200 mg/mL. The applicant has provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all facilities associated with this application. The proposed labeling and labels have adequate information to meet the regulatory requirements.

**b. Is the overall recommendation in agreement with the individual discipline recommendations?** Yes

**Recommendation by Subdiscipline:**

**Drug Substance - Adequate**
**Drug Product - Adequate**
**Quality Labeling - Adequate**
**Manufacturing - Adequate**
**Biopharmaceutics - N/A**
**Microbiology - Adequate**

**Environmental Assessment:** Categorical Exclusion - Adequate
**QPA for EA(s):** No

## 5. Life-Cycle Considerations

**Established Conditions per ICH Q12: No**
**Comments**:

**Comparability Protocols (PACMP): No**
**Comments:**

**Additional Lifecycle Comments:**

There are no outstanding issues or lifecycle considerations.

Martha Heimann

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# CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

## 1.0 PRESCRIBING INFORMATION

**Assessment of Product Quality Related Aspects of the Prescribing Information:** Labeling was submitted in eCTD 0001. There does not appear to be a medication guide.

## 1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Product Title in Highlights** | | |
| Proprietary name | DAYBUE™ (trofinetide) oral solution | Adequate |
| Established name(s) | | |
| Route(s) of administration | | |
| **Dosage Forms and Strengths Heading in Highlights** | | |
| Summary of the dosage form(s) and strength(s) in metric system. | Oral solution: 200 mg/mL (3) | Adequate |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | NA | NA |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | NA | NA |

## 1.2 FULL PRESCRIBING INFORMATION

### 1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

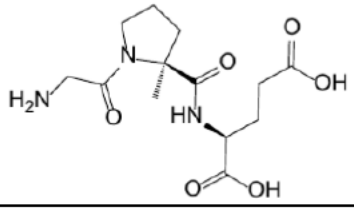
| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE AND ADMINISTRATION section** | | |
| Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product) | DAYBUE can be given orally or via gastrostomy (G) tube4; doses administered via gastrojejunal (GJ) tubes must be administered through the G-port.<br>A calibrated measuring device should be obtained from the pharmacy to measure and deliver the prescribed dose accurately. A household measuring cup is not an adequate measuring device.<br>(b) (4)<br>14 days of opening the bottle [see How Supplied/Storage and Handling (16.2)]5. | Adequate<br><br>Note: The DMEPA review is recommending removal of, "(b) (4) ." Additionally, there is a recommendation to use the following language, "Discard any unused oral solution after 14 days of first opening the bottle" or something similar as there is a recommendation to include a "(b) (4)" statement on the carton/container labels.<br><br>From a CMC perspective, we recommend the language follow a similar format to RADICAVA ORS i.e, "Dispose of any DAYBUE that is not used within 14 days after opening the bottle." |

### 1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DOSAGE FORMS AND STRENGTHS section** | | |
| Available dosage form(s) | Trofinetide oral solution: 200 mg/mL | Adequate |
| Strength(s) in metric system | | |
| If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance | (b) (4) | |
| A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting | of a pink to red, strawberry flavored solution. | |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | NA | NA |
| For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package. | NA | NA |

### 1.2.3 Section 11 (DESCRIPTION)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **DESCRIPTION section** | | |
| Proprietary and established name(s) | DAYBUE is a pink to red, oral solution with each 5 mL containing 1 g of trofinetide (200 mg/mL). The oral solution also contains purified water, maltitol, strawberry flavor, sucralose, methylparaben sodium, propylparaben sodium, and FD&C Red No. 40 as inactive ingredients. | Inadequate<br>Revise to alphabetize inactive ingredients. |
| Dosage form(s) and route(s) of administration | | |
| If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance. | | |
| List names of all inactive ingredients. Use USP/NF names. Avoid Brand names. | | |
| For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. | NA | NA |
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | NA | NA |
| Statement of being sterile (if applicable) | NA | NA |
| Pharmacological/ therapeutic class | | Inadequate<br>Revise to include therapeutic class. |

| | | |
|---|---|---|
| Chemical name, structural formula, molecular weight | Trofinetide is designated chemically as (2S)-2-{[(2S)-1-(2-aminoacetyl)-2-methylpyrrolidine-2-carbonyl]amino}pentanedioic acid (IUPAC). Its empirical formula is $C_{13}H_{21}N_3O_6$ and its molecular weight is 315.33 g/mol. The chemical structure is:  | Adequate |
| If radioactive, statement of important nuclear characteristics. | NA | NA |
| Other important chemical or physical properties (such as pKa or pH) | Trofinetide is a white to off-white solid and is freely soluble in water. | Adequate |

**Section 11 (DESCRIPTION) Continued**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| For oral prescription drug products, include gluten statement if applicable | NA | NA |
| Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity" | NA | NA |

### 1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **HOW SUPPLIED/STORAGE AND HANDLING section** | | |
| Available dosage form(s)<br>Strength(s) in metric system<br>Available units (e.g., bottles of 100 tablets)<br>Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number | Store DAYBUE in an upright position refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze.<br>(b) (4)<br>Keep the child-resistant cap tightly closed.<br>(b) (4)<br>(b) (4) | Adequate<br><br>DMEPA is recommending strength presented as 200 mg/mL. This is acceptable from a CMC perspective. Additionally, DMEPA is recommending revision of,<br>(b) (4)<br>to be in alignment with language discussed in Dosage and Administration. Refer to the comments above. |
| Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored" | NA | NA |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. | NA | NA |

**Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)**

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|

| | | |
|---|---|---|
| Special handling about the supplied product (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.) | See above | Adequate |
| If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.” | NA | NA |
| Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. | | |
| 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.” | NA | NA |
| Include information about child-resistant packaging | See above | Adequate |

### 1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

### *1.2.6* Manufacturing Information After Section 17 (for drug products)

| Item | Information Provided in the NDA | Assessor's Comments |
|---|---|---|
| **Manufacturing Information After Section 17** | | |
| Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer | Marketed by: Acadia Pharmaceuticals Inc. San Diego, CA 92130 USA | Adequate |

## 2.0 PATIENT LABELING

**Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):**

***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

## 3.0 CARTON AND CONTAINER LABELING

### 3.1 Container Label

(b) (4)

### 3.2 Carton Labeling

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| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Proprietary name, established name, and dosage form (font size and prominence |  | Adequate |
| Dosage strength | 200 mg/mL | |
| Route of administration | For oral or G-tube administration only | |
| If the active ingredient is a salt, include the equivalency statement per FDA Guidance | | |
| Net contents (e.g. tablet count) | 450 mL | Adequate<br><br>Also, DMEPA recommends the storage statement be amended to, "Must be refrigerated. Store at 2°C to 8°C (36°F to 46°F)." CMC does not agree and will recommend a revision of, "Store DAYBUE refrigerated between 2°C to 8°C (36°F to 46°F)." |
| "Rx only" displayed on the principal display | Present | |
| NDC number | NDC 63090-660-01 | |
| Lot number and expiration date | (b) (4) | |
| Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD. | (b) (4) | |
| For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use) | NA | NA |
| Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement. | | |

| | | |
|---|---|---|
| If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol | | |
| Bar code | See above | Adequate |

| Item | Information Provided in the NDA | Assessor's Comments about Carton Labeling |
|---|---|---|
| Name of manufacturer/distributor | MARKETED BY<br>Acadia Pharmaceuticals Inc.<br>San Diego, CA 92130 | Adequate |
| Medication Guide (if applicable) | NA | NA |
| No text on Ferrule and Cap overseal | No text present | Adequate |
| When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. | NA | NA |
| And others, if space is available | | |

**Assessment of Carton and Container Labeling:** ***Adequate***

***Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."***

## ITEMS FOR ADDITIONAL ASSESSMENT

**NA**

***Overall Assessment and Recommendation:***

**This application is recommended for approval per labeling/labels perspective once the following changes (in red) have been made to the label.**

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Martha Heimann

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# CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

| | |
|---|---|
| **Product Information** | |
| **NDA Number** | 217026 |
| **Assessment Cycle Number** | 01 |
| **Drug Product Name/ Strength** | Trofinetide/ 200 mg/mL |
| **Route of Administration** | Oral Solution |
| **Applicant Name** | Acadia Pharmaceuticals Inc. |
| **Therapeutic Classification/ OND Division** | |
| **Manufacturing Site** | (b) (4) |
| **Method of Sterilization** | N/A; non-sterile |

***Assessment Recommendation:*** **Adequate**

***Assessment Summary:*** The application is adequate from the standpoint of product quality microbiology.

**List Submissions being assessed (table):**

| Document(s) Assessed | Date Received |
|---|---|
| 0002 SD 2 | 07/29/2022 |
| 0001 SD 1 | 07/12/2022 |

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

**Remarks:** The drug product is a non-sterile clear pink to red oral solution indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older that comes in a 500 mL round high-density polyethylene (HDPE) bottles with a 28 mm (b) (4) child resistant closure with a heat

induction seal. Trofinetide is a multi-dose product [redacted] (b) (4)

**Concise Description of Outstanding Issues: N/A**

**Supporting Documents:** N/A

## S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

## P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Section 3.2.P.1. The drug product is a multi-dose non-sterile oral solution that contains 200 mg/mL Trofinetide.

- **Drug product composition –** Section 3.2.P.1

| Ingredient | Quantity per (mg/mL) | Function |
|---|---|---|
| Trofinetide | 200 | Active ingredient |
| Maltitol | [redacted] (b) (4) | |
| Methylparaben sodium | | |
| Proplparaben Sodium | | |
| FD&C Red No. 40 | | |
| Strawberry flavor[a] | | |
| Sucralose | | |
| Purified water | | |

[a] Strawberry flavor [redacted] (b) (4)

[redacted] (b) (4)

- **Description of container closure system –** Section 3.2.P.1, p.4 of 4. 3.2.P.7

| Component | Description | Manufacturer |
|---|---|---|

| | | |
|---|---|---|
| Bottle | 500 mL HDPE (b) (4) round bottle | (b) (4) |
| Closure | 28 mm child resistant closure with (b) (4) liner | |

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

## P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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