CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219132Orig1s000

PRODUCT QUALITY REVIEW(S)

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Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	219132
Applicant Name	IntraBio, Inc.
Drug Product Name	AQNEURSA (levacetylleucine)
Dosage Form	For suspension
Proposed Strength(s)	1 gram (unit-dose)
NDA Classification	Type 1 - NME
Route of Administration	Oral
Maximum Daily Dose	4 grams (for patients ≥ 35kg)
Rx/OTC Dispensed	Rx
Proposed Indication	Treatment of adult and pediatric patients with neurological symptoms of Niemann-Pick Type C (NPC) weighing ≥15 kg
Drug Product Description	IntraBio has submitted this 505(b)(1) new drug application for AQNEURSA® (levacetylleucine) for oral suspension, 1 gram indicated for the treatment of adult and pediatric patients with neurological symptoms of Niemann-Pick Type C (NPC) weighing ≥15 kg. The active ingredient, levacetylleucine has not been previously approved or marketed in the United States and therefore, it is classified as a New Molecular Entity (NME). AQNEURSA® for oral suspension is supplied in a unit-dose packet containing 1.7 gram of white to off-white granules equivalent to 1 gram of levacetylleucine as the active ingredient. The granules also contain hypromellose, isomalt, and strawberry flavor as the inactive ingredients.

	AQNEURSA (levacetylleucine) for oral suspension is supplied in a carton containing 28 unit-dose packets. It is also supplied as a multipack containing 4 cartons providing 112 unit-dose packets. This drug product should be stored at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Based on the stability data provided in the application, an expiration dating period of 24 months is currently granted to this drug product.		
Co-packaged product information	N/A		
Device information	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Sukhamaya Bain, PhD	Lawrence Perez, PhD
	Drug Product/ Labeling	Caroline Strasinger, PhD	Hamid Shafiei, PhD/Julia Pinto, PhD
	Manufacturing	Lloyd Alfonso, PhD	Vaikunth Prabhu, PhD
	Biopharmaceutics	Tapash Ghosh, PhD	Tapash Ghosh, PhD
	Microbiology	N/A	N/A
	Other (Categorical Exclusion)	Caroline Strasinger, PhD	Hamid Shafiei, PhD
	RBPM	Teshara Bouie, M.S.A	
	ATL	Hamid Shafiei, PhD	
Consults	N/A		

2. Final Overall Recommendation - Approval

At the time of submission of this application the dosage form for this drug product was proposed as (b) (4) However, during the review of this application (b) (4) (b) (4) (b) (4) the Agency recommended that the dosage form for this drug product be changed to “for oral suspension”. This was discussed with the applicant during the midcycle communication, and the applicant agreed to revise the dosage form from (b) (4) to “for oral suspension”. Based on the revised dosage form, the Agency’s Biopharmaceutics reviewer requested that the applicant should propose a dissolution test and acceptance criterion as a quality attribute associated with a “for suspension” dosage form and to update the drug product specification for testing of the future batches of the drug product. The applicant agreed and submitted the dissolution test method, acceptance criterion, method validation, and updated drug product specification to be implemented for release and stability testing following approval of the application. The current specification provided in this NDA remains in effect for the approval of this application since the current batches were not tested at release and during stability for dissolution. The updated drug product specification is intended for testing of the drug product after the approval of the application and therefore, it was not captured in the drug product chapter of the IQA because the agreement regarding the addition of the dissolution testing as a quality attribute was reached after the drug product review was completed. The updated specification for the post-approval release and stability testing of the drug product submitted to the application on September 10, 2024 is provided below:

TESTS	METHODS	SPECIFICATIONS
APPEARANCE	Visual method	White to off-white granules
IDENTIFICATION (HPLC/UV) - Retention time	906800	The retention time corresponds to that of the reference standard
- UV Spectrum		The UV spectrum corresponds to that of the reference standard
ASSAY(HPLC/UV)	906800	(b) (4) %/LC
RELATED SUBSTANCES(HPLC/UV) - N-acetyl-L-isoleucine (RRT ≈ (b) (4)) - Single unspecified impurity - Total impurities	906800	(b) (4) % % %
UNIFORMITY OF DOSAGE UNIT (HPLC/UV) (content uniformity) - Level 1 : Acceptance Value - Level 2 : Acceptance Value All individuals (Level 2)	906800 Ph.Eur (2.9.40) / USP <905>	Conforms (b) (4) Complies
(b) (4)	(b) (4)	(b) (4) %
DISSOLUTION TEST - Maxi - Mini - Average - Stage	925600	(b) (4) % (Q) (b) (4)
MICROBIOLOGICAL QUALITY - ENUMERATION : . Total aerobic microbial count (TAMC) . Total combined yeast/mould count (TYMC)	Ph. Eur (2.6.12) / USP <61>	≤ 1000 CFU/g ≤ 100 CFU/g
- TEST FOR SPECIFIED MICROORGANISMS : . *Escherichia coli*	Ph. Eur (2.6.13) / USP <62>	Absence /1g

The updated prescribing information PI as well as container and carton labels submitted to the application on August 21, 2024 indicate that all CMC labeling and label revisions recommended by the Agency have been accepted by the applicant. Therefore, from all OPQ review disciplines this application is recommended for approval with currently granted drug product expiration dating period of 24 months.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

- The applicant of this 505(b)(1) new drug application has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug substance, levacetylleucine and the drug product, AQNEURSA® (levacetylleucine) for oral suspension, 1 gram.
- The Office of Pharmaceutical Manufacturing Assessment (OPMA) has made the overall recommendation of adequate for the facilities involved in this application.
- The CMC-recommended revisions and comments regarding PI labeling as well as container and carton labels have been adequately addressed.
- The applicant's request for categorical exclusion from the preparation of environmental assessment has been found adequate and is granted.

Therefore, this application is recommended for approval from the OPQ perspective with an expiration dating period of 24 months.

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	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): Yes

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Application Technical Lead Name and Date:

Hamid Shafiei, Ph.D.
Senior Pharmaceutical Quality Assessor
DPQA VII/OPQA II/OPQ

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CHAPTER IV: LABELING

For more details about the items in this template, please see Chapter IV (Labeling) of the NDA IQA Guide (OPQ-ALL-WI-0006)

NDA Number	219132
Assessment Cycle Number	1
Drug Product Name	AQNEURSA (levacetylleucine) for oral suspension, 1 g (b) (4)

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate ("N/A" otherwise)
Prescribing Information Labeling	Adequate	**0061**
Patient Information	Adequate	**0061**
Instruction for Use (IFU)	N/A	
Container Labels	Adequate	**0055**
Carton Labeling	Adequate	**0061**

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0001	01-24-24	PI
0019	04-12-24	Packet
0035	05-29-24	Carton/Multipak
0054	08-02-24	PI
0055	08-05-24	Carton/Multipak
0061	08-21-24	PI/Carton

1.0 PRESCRIBING INFORMATION[1]

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights[2] [21 CFR 201.57(a)(2)]		
Established name(s)[3]	Adequate	Update to (levacetylleucine) for oral suspension Applicant agreed to this change on 8/2/2024
Route(s) of administration	Adequate	
Controlled drug substance symbol (if applicable)	N/A	
Initial U.S. Approval [§201.57(a)(3)]	Adequate	
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		

[1] Labeling Review Tool (LRT) (March 2022), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

[2] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

[3] Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not "USP" descriptor in the product title or within the Highlights (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s)[4] and strength(s) in metric system[5]	Adequate	Update to "for oral suspension" Update (b) (4) to "packet" throughout the PI Applicant agreed to this change on 8/2/2024 Change (b) (4) to unit-dose Applicant agreed to this change on 8/23/2024
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).[6]	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."[7]	N/A	
For injectable drug products for parenteral 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.[8]	N/A	

Assessment: *Adequate*

Applicant agreed to use of Packet and the established name of "(levacetylleucine) (b) (4) (b) (4)" on 8/2/2024. Applicant agreed to unit-dose on 8/21/2024.

[4] Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline
[5] Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>
[6] Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1
[7] Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)
[8] Guidance: *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* (October 2018); USP <659>

Note from PQL Mailbox:

The package-type term is "unit-dose" per USP <659> Package and Storage Requirements. (b) (4)

(b) (4) Unit-dose is appropriate for Oral DPs. Although the term Single-unit is on <659>, that is uncommon term used in labeling. HCPs are unfamiliar. Unit-dose is most appropriate.

Noninjection Packaging Systems

Multiple-unit container: A *Container–closure system* that permits withdrawal of successive portions of a noninjection article without changing the safety, strength, quality, or purity of the remaining portion (e.g., bottle of capsules, tablets, oral or topical liquids, and semisolids).

Single-unit container: A *Container–closure system* that holds a quantity of a noninjection article intended for administration as a single dose or a single finished device intended for use promptly after the *Packaging system* is opened.

Unit-dose container: A single-unit *Container–closure system* for an article intended for administration by other than the parenteral route as a single dose.

Unit-of-use container: A *Container–closure system* that contains a specific quantity of an article that is intended to be dispensed as such without further modification except for the addition of appropriate labeling (see (7)). It is not permitted to repackage *Unit-of-use containers* for sale.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)[9]

(b) (4)

[9] See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents and/or soft food[10], storage conditions needed to maintain the stability of the reconstituted or diluted product).	Adequate	Revise for clarity and change, and remove statements (b) (4) (b) (4) as this is a suspension. Applicant agreed to this change on 8/2/2024
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	Adequate	Revise for clarity Applicant agreed to this change on 8/2/2024
For parenteral products: include statement: *"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to*	N/A	

[10] Draft Guidance: Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
administration, whenever solution and container permit."[11]		
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.[12] Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs."	N/A	

Assessment: *Adequate*

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)[13]

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

[11] §201.57(c)(3)(iv)
[12] USP General Notices 2.30 Legal Recognition
[13] See § 201.57(c)(4); Labeling Review Tool (March 2022, page 29)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Remove (b) (4) for naming purposes Applicant agreed to this change on 8/2/2024
Strength(s) in metric system	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Choose an item.	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	Change to unit-dose packet Applicant agreed to this change on 8/21/2024

Assessment: *Adequate*

1.2.3 Section 11 (DESCRIPTION)[14]

(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)[15] [§ 201.57(c)(12)(i)(A)].	Adequate	Add AQNEURSA (levacetylleucine) for oral suspension Applicant agreed to this change on 8/2/2024
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Revise for clarity Applicant agreed to this change on 8/2/2024
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	
List inactive ingredients (not required for oral use, except for	Adequate	

[14] See § 201.57(c)(12); Labeling Review Tool (March 2022, page 56)
[15] Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
colorant) by the USP/NF names in alphabetical order.[16] Avoid brand names. [§ 201.57(c)(12)(i)(C)].		
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. [§ 201.100(b)(5)(iii)].	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	N/A	
Pharmacological/Therapeutic class[17] [§ 201.57(c)(12)(i)(E)].	Adequate	Pharmacological/Therapeutic Class is unknown and thus will be omitted. The phrase "modified amino acid" is acceptable
Chemical name[18], structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	

[16] Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

[17] Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in FDA's Labeling Resources for Human Prescription Drugs for the most recent EPC list.

[18] Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	Add statement on solubility of the API Applicant agreed to this change on 8/21/2024
For oral prescription drug products, include gluten statement[19] (if applicable).	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

Assessment: *Adequate*

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)[20]

(b) (4)

[19] Draft guidance: *Gluten in Drug Products and Associated Labeling Recommendations* (December 2017)
[20] See § 201.57(c)(17); Labeling Review Tool (March 2022, page 70). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	Revise to "for oral suspension" Applicant agreed to this change on 8/2/2024
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Revise (b) (4) to Packet Applicant agreed to this change on 8/2/2024 Change (b) (4) to unit-dose Applicant agreed to this change on 8/21/2024
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	
For injectable drug products for parenteral 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 (see USP <659>).	N/A	

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
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.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Revise for clarity Applicant agreed to this change on 8/2/2024
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."*[21]	N/A	
Include information about child-resistant packaging[22] (if chosen by manufacturer).	N/A	

Assessment: *Adequate*

[21] Guidance: *Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex* (December 2014)
[22] Guidance: *Child-Resistant Packaging Statements in Drug Product Labeling* (August 2019)

1.2.6 Manufacturing Information After Section 17 (for drug products)[23]

Item	Item in Proposed Labeling (choose "Adequate" or "Inadequate")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	

Assessment: *Adequate*

3.0 CONTAINER AND CARTON LABELING[24]

3.1 Container Labels[25]

(b) (4)

[redacted]

[23] § 201.1(h)(5) and 201.1(i); Labeling Review Tool (March 2022, page 74)
[24] Carton and Container Labeling Resources
[25] Per § 201.10(h)(2)(i)(1), if the drug container is too small to bear all labeling information required by section 502(e)(1)(A)(ii) and (B) of the FD&C Act, the container label should bear: proprietary name, established name, lot number, the name of the manufacturer, packer, or distributor of the drug.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name[26], (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	Revise to for oral suspension Applicant accepted this change on 8/5/2024
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)].[27]	Adequate	Yes	1 gram per packet Applicant accepted this change on 8/5/2024
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	N/A	Yes	

[26] Established name = [Drug] [Route of Administration] [Dosage Form]

[27] Express as " XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)].[28]	Adequate	No	Change (b) (4) to unit-dose packets Applicant agreed to this change on 8/21/2024
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	No	Revise storage conditions Store AQNEURSA at room temperature between 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C and 30°C (59°F to 86°F) [see USP Controlled Room Temperature] Applicant accepted this change on 8/5/2024
For injectable drug products for parenteral 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, and these products require a "Not for direct infusion" statement. (See USP <659>).	N/A	Yes	
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for	Adequate	Yes	

[28] § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].			
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	N/A	Yes	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)].[29]	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	No	
"Keep out of reach of children" statement, optional for Rx, required for OTC [§ 201.66(c)(5)(x)].	Adequate	Yes	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	Yes	
No text on Ferrule and Cap overseal of a vial of injectable	N/A	Yes	

[29] See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
products unless a cautionary statement is required. (USP <7>).			
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
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.[30]	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: Choose an item.

In conjunction with OSE/DMEPA comments, the below comments were conveyed to the Applicant in Late Cycle Meeting Communication:

A. General Comments (Container Label(s) & Carton Labeling & Multipack Carton)

1. For consistency with the terminology in the Prescribing Information, we recommend changing the statement of dosage statement [redacted] (b) (4) [redacted] (b) (4) to read "**Recommended Dosage:** See Prescribing Information."

2. As currently presented, it is unclear which format (numerical or alphabetical) you plan to use for your expiration date. Thus, we are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year

[30] USP General Notices 3.20 Indicating Conformance

and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See the FDA guidance for industry *Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers*.

3. The immediate container closure is a packet. Replace the term (b) (4) with packet throughout out all labeling.

4. Revise the storage conditions to read "Store at 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]."

5. Revise the contents to read "Each (b) (4) packet contains 1 gram of levacetylleucine and the inactive ingredients hypromellose, isomalt, and strawberry flavor"

B. Container Label

1. As currently presented, the packet label does not show perforations or visual cue to instruct the user where to cut the packet. We recommend adding a visual perforation line with a scissor to instruct the user of the location to cut the packet.

2. On the principal display panel, we recommend changing (b) (4) to (b) (4) (b) (4) for clarity.

3. The linear barcode is missing on the container label. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label in accordance with 21 CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).

C. Multipack Carton Labeling

1. On the principal display panel, we recommend changing the net quantity statement from (b) (4) to "112 (b) (4) packets (4 cartons of 28 (b) (4) packets)" for clarity.

The above changes were incorporated into all labels on 08/05/2024 and 08/21/2024

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

None

The Label and Labeling of NDA 219132 is now adequate and recommended for approval. Revised labeling was received on 21-AUG-2024 and the Revised label was received on 21-AUG-2024; the applicant agreed to all OPQ requested changes. Additional DMEPA requested changes did not impact the OPQ recommendations.

This application is recommended for approval from the label and labeling perspective.

Primary Assessor Name
Caroline Strasinger, PhD
Master Reviewer
OPQ/OPQAII/DPQAVII

Secondary Assessor Name
Julia Pinto, PhD
Supervisor
OPQ/ OPQAII/DPQAVIII

Caroline Strasinger

Digitally signed by Caroline Strasinger
Date: 8/21/2024 03:23:25PM
GUID: 5051dfdd000013b995075b4d54108ed8
Comments: All OPQ comments agreed to on 08/21/2024

Julia Pinto

Digitally signed by Julia Pinto
Date: 8/21/2024 03:46:54PM
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QUALITY REVIEW

BIOPHARMACUTICS
NDA: NDA 219132
Drug Product Name / Strength: N-Acetyl-L-Leucine (IB 1001)
Route of Administration: Oral
Applicant Name: IntraBio Inc.
Indication: (b) (4)
Submission date: 01/24/2024, 5/29/2024, 9/10/2024, 9/11/2024
Primary Reviewer: Tapash Ghosh, Ph.D.
Recommendation: Adequate

BACKGROUND:

The original NDA was submitted dated January 24, 2024. FDA information requests regarding drug product of the original NDA (Sequence 0001) was issued dated April 29, 2024. The current submission received May 29, 2024 contains sponsor's responses to the aforementioned FDA information request. The sponsor accepted FDA's recommendation to designate the proposed N-acetyl-L-leucine dosage form as "oral suspension" as per the USP definition.

In terms of dissolution, the sponsor reiterated that the solubility of the drug substance, levacytelleucine (NALL) in water is (b) (4) mg/mL. Your product requires solubilizing 1000 mg NALL in 40 mL of water, orange juice, or almond milk (and 1700 mg of granules in 40 mL of reconstitution medium) (b) (4)

The sponsor mentioned that dissolution tests performed during development show a (b) (4) profile with (b) (4) % of the drug dissolved (b) (4) They also mentioned that the observed solubility of drug substance (b) (4) (b) (4) (b) (4) The sponsor has initiated further solubility experiments for the dosage form throughout the physiological pH range and will make the results available to the agency as soon as possible.

Overall, we still believe that dissolution test with appropriate dissolution acceptance criterion is required for QC purpose unless ongoing further solubility experiments for the dosage form throughout the physiological pH range reveals otherwise.

An IR in this regard was communicated to the applicant on August 20, 2004 asking them to implement a dissolution test with appropriate dissolution specification for batch release. In their response dated August 23, 2024, the applicant agreed to set a *preliminary specification* of **Q= (b) (4) % (b) (4)**

However, the Agency proposed to implement Q = (b) (4) % at 15 minutes. In their amendment dated August 27, 2024, the applicant agreed to implement the proposed specification within a week. In their communication dated September 10, 2024, the applicant Officially updated the

Specification for Nacetyl-L-leucine 1000 mg, granules for oral suspension by adding the dissolution test at release with a limit of **Q= (b) (4)% at 15 minutes**.

CONCLUSION AND RECOMMENDATION:

Form a Biopharmaceutics perspective, **NDA 219132 for N-Acetyl-L-Leucine (IB 1001)** Oral suspension is **adequate** for approval (b) (4) (b) (4) with following dissolution method and acceptance criterion:

Dissolution Test – Equipment and operating conditions	
Apparatus	USP apparatus 2 (paddles)
Speed	50 rpm
Temperature	37 ± 0.5°C
Dissolution medium	0.1M Hydrochloric acid
Dissolution volume	900 mL
Sampling time points	Profile for development batches: 5, 10, 15, 30 and 45 minutes
Sampling volume	10 mL
Sinkers	no
Sample solution	(b) (4)
Acceptance Criterion	**Q = (b) (4)% at 15 minutes**.

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Tapash Ghosh

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Date: 9/11/2024 12:51:46PM
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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/

HAMID R SHAFIEI
09/12/2024 01:49:54 PM