

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219132Orig1s000

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: September 4, 2024

To: Jenny Doan, Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Carrie Newcomer, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for AQNEURSA™ (levacetylleucine) for oral suspension

NDA: 219132

Background:

In response to DRDMG's consult request dated January 25, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for AQNEURSA™ (levacetylleucine) for oral suspension.

PI/IFU:

OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on August 29, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed IFU, and comments were sent under separate cover on August 30, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling accessed from SharePoint on September 3, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at 301-796-1233 or carrie.newcomer@fda.hhs.gov.

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CARRIE A NEWCOMER
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 30, 2024
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 219132
Product Name, Dosage Form, and Strength:	Aqneursa (levacetylleucine) for oral suspension, 1 gram per packet
Applicant Name:	IntraBio Inc.
FDA Received Date:	August 21, 2024,
TTT ID #:	2024-8004-3
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

IntraBio Inc. submitted revised container label and carton labeling received on August 21, 2024 for Aqneursa. The revisions are in response to recommendations that we made during a previous label and labeling review.^a The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container label and carton labeling for Aqneursa (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

The proposed container label, and carton labeling are acceptable from a medication error perspective. We have no further recommendations at this time.

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^a Mahmoud, S. Label and Labeling Review Memo for Aqneursa (NDA 219132). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 AUG 12. TTT ID: 2024-8004-2.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: August 30, 2024

To: Jenny Doan, MSN, BSN
Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, MSN, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Helen Young, MSN, MPH, CRRN, PHN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): AQNEURSA (levacetylleucine)

Dosage Form and Route: for oral suspension

Application Type/Number: NDA 219132

Applicant: IntraBio Inc. c/o Strategic Drug Development Services, LLC

1 INTRODUCTION

On January 24, 2024, IntraBio Inc. c/o Strategic Drug Development Services, LLC submitted for the Agency's review an original New Drug Application (NDA) 219132 for AQNEURSA (levacetylleucine) for oral suspension. AQNEURSA (levacetylleucine) is, indicated for the treatment of adult and pediatric patients with neurological symptoms of Niemann-Pick Type C (NPC) weighing ≥ 15 kg.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rare Diseases and Medical Genetics (DRDMG) on August 6, 2024 and January 25, 2024, respectively, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for AQNEURSA (levacetylleucine) for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on August 12, 2024.

2 MATERIAL REVIEWED

- Draft AQNEURSA (levacetylleucine) for oral suspension IFU received on January 24, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 22, 2024.
- Draft AQNEURSA (levacetylleucine) for oral suspension Prescribing Information (PI) received on January 24, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 22, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the PI
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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BARBARA A FULLER
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**MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING**

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	August 12, 2024
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 219132
Product Name, Dosage Form, and Strength:	Aqneursa (levacetylleucine) for oral suspension, 1 gram per packet
Applicant Name:	IntraBio Inc.
FDA Received Date:	August 2, 2024, August 5, 2024 and August 7, 2024
TTT ID #:	2024-8004-2
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

IntraBio Inc. submitted revised container label and carton labeling received on August 5, 2024 for Aqneursa. IntraBio Inc. also submitted a proposed Instructions for Use (IFU) in response to The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed IFU, revised container label and carton labeling for Aqneursa (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The proposed IFU, container label, and carton labeling are unacceptable from a medication error perspective. The principal display panel contains incorrect and incomplete information that may lead to medication errors. We provide specific recommendations for Division of Rare Diseases and Medical Genetics (DRDMG) in Section 3 and IntraBio in Section 4.

3 RECOMMENDATIONS FOR DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

Please see Appendix B for specific recommendations for the proposed Instructions for Use.

4 RECOMMENDATIONS FOR INTRABIO INC.

A. General Comments (Container Label and Carton Labeling)

1. We recommend revising the package type term from (b) (4) to “unit-dose” per USP <659> Package and Storage Requirements for oral drug products.

B. Container Label

1. On the principal display panel, revise the statement (b) (4) to “**Directions:** See enclosed Instructions For Use for administration instructions. Use within 30 minutes.” to direct the patients to the IFU for preparation and administration instructions to ensure safe use of the product.
2. On the back panel, separate storage information as a separate paragraph to minimize confusion and information overcrowding. Ensure there is sufficient white space between each paragraph to improve readability. For example:

Recommended Dosage: See Prescribing Information.

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].

Keep out of reach of children.

C. Carton labeling

^a Mahmoud, S. Label and Labeling Review Addendum for Aqneursa (NDA 219132). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 JUL 31. TTT ID: 2024-8004-1.

1. On the principal display panel, add the statement “**Directions:** See enclosed Instructions For Use for administration instructions. Use within 30 minutes.” to direct the patients to the IFU for preparation and administration instructions to ensure safe use of the product.

D. Carton labeling for the multipack

1. On the side panel, separate the storage information as a separate paragraph to minimize confusion and information overcrowding. Ensure there is sufficient white space between each paragraph to improve readability. For example:

Recommended Dosage: See Prescribing Information.

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].

Keep out of reach of children.

APPENDIX A. LABELS AND LABELING

Instructions for Use, received on August 2, 2024, available from

<\\CDSESUB1\evsprod\NDA219132\0054\m1\us\114-labeling\draft\labeling\patient-instructions-for-use-02aug2024.docx>

Container Label received on August 5, 2024



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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of New Drugs
Office of Rare Diseases Pediatrics and Reproductive Medicine
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Memorandum

Date: 8/7/2024 **Date Consulted:** 1/24/2024

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health
DPMH

Lynne Yao, MD, DPMH Director

To: Division of Rare Diseases and Medical Genetics (DRDMG)

NDA: 219132

Drug: Aqueursa (levacetylleucine)

Proposed
Indication: Niemann-Pick disease, Type C (NPC) in adults and pediatrics

Applicant: IntraBio Therapeutics

Subject: Pregnancy and Lactation Labeling and Postmarketing Requirements

Materials Reviewed:

- Applicant's submitted Clinical Summary of Safety, submitted 1/24/2024
- Prior DPMH Review of Olipudase alfa BLA 761261 by Jane Liedtka, MD, dated 4/12/22, DARRTs Reference ID: 4971622.¹
- Prior DPMH Review of Arimoclomol NDA 214927 by Jacqueline Yancy, PhD, dated 2/25/21. DARRTs Reference ID: 4752992.¹

¹ The Olipudase alfa and Arimoclomol reviews were part of the materials reviewed but were not a source replied upon for the labeling recommendations in this consult review.

Consult Question: “DRDMG requests participation from DPMH in the NDA review process to provide input and recommendations as appropriate.”

INTRODUCTION

On 1/24/24, the applicant, IntraBio Therapeutics, submitted an original NDA for a new molecular entity (NME) for Aqneursa (levacetylleucine) for the treatment of Niemann-Pick disease, Type C (NPC) in adults and pediatric patients. DRDMG consulted DPMH Maternal Health Team on 1/24/24 to request assistance for the proposed prescribing information to comply with the Pregnancy and Lactation Labeling Rule (PLLR) and potential postmarketing studies required for this NME.

BACKGROUND

Regulatory History

- The applicant received orphan drug designation for levacetylleucine on 8/9/21.

Drug Characteristics²

- *Dosage and administration:* based on patient’s (b) (4) body weight in kilograms (kg) to be administered orally up to three times daily as per below.



- *Mechanism of Action (MOA):* The MOA of levacetylleucine in treatment of NPC is unknown.
- *Molecular Weight:* 173.21
- *Half-life:* 1 hour
- *Contraindications:* none
- *Warnings and Precautions:* (b) (4)
- *Adverse Reactions:* rosacea

Niemann-Pick disease type C (NPC) and Pregnancy³

- *Etiology:* NPC is caused by pathogenic variants of the NPC1 and NPC 2 genes that result in impaired cellular processing and transport of low-density lipoprotein (LDL) cholesterol and other macromolecules, including glycosphingolipids.
- *Incidence:* estimated as 1:120,000 livebirths in Europe.
- *Onset and clinical presentation:* variable; NPC can present from the perinatal period until late adulthood. Most patients have onset in middle to late childhood after normal early development. These patients typically have cerebellar involvement characterized by clumsiness and gait problems. Progressive dystonia, dysarthria, and dysphagia occur, eventually impairing oral feeding. Approximately one-third of patients develop seizures

² Applicant’s proposed labeling as reviewed by the DRDMG Clinical and Clinical Pharmacology Review Teams.

³ Overview of Niemann-Pick disease by Raphael Schiffmann, MD, dated 3/12/24 literature current through 6/2024. UpToDate.com

and death typically occurs from aspiration pneumonia in the 2nd or 3rd decade of life.^{Error!}
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- *Treatment*: There is currently no approved therapy to modify onset, neurological progression, or prolong lifespan. Miglustat has been used off-label. Cholesterol-lowering agents lower the free cholesterol in the liver, but the clinical course is unchanged. Disease management is mostly supportive.
- *Pregnancy*: This reviewer searched Embase for pregnancy reports using search terms “Neimann-Pick Type C disease” and “pregnancy.” No pregnancy cases were identified.

REVIEW

PREGNANCY

Nonclinical Experience⁴

In a dose-range finding rat embryo-fetal development study, doses of up to 1000 mg/kg/day oral levacetylleucine were administered daily during organogenesis (Gestation Day [GD] 6 through GD 17). Increases in the mean number of resorptions, mean post-implantation losses and skeletal malformations (thoracic arch of the vertebra-fused thoracic arch, misaligned thoracic arch, hemicentric thoracic centrum, and misaligned thoracic centrum; vertebral column-scoliosis, and ribs-absent costal cartilage and short rib) were observed at doses greater than 300 mg/kg/day, which is 0.7-fold the 4g/day maximum recommended human dose (MRHD) of levacetylleucine based on body surface area.

In a dose-range finding rabbit embryo-fetal development study, doses of up to 2500 mg/kg/day oral levacetylleucine were administered daily to pregnant females during organogenesis (GD 7 through GD 19). Increased embryo-fetal death (post implantation loss/resorption), decreased fetal body weight, and increase in external (open or partially open eyes, hyperflexion of limbs) and skeletal malformations (misshapen maxillae and premaxillae, and small interparietal bones) were observed at doses greater than 675 mg/kg/day, which is 3-fold the MRHD of levacetylleucine based on body surface area.

For details, refer to the Nonclinical Review by Saryu Goel, PhD.

Reviewer's Comment

DPMH discussed the nonclinical data described above with the Nonclinical Review Team who noted the applicant has only provided a draft study report rather than full study report and the nonclinical reproductive toxicology studies are incomplete. However, the findings from the preliminary nonclinical studies are concerning for embryo-fetal toxicity in two species (rat and rabbit) at low exposure multiples based on body surface area. Therefore, the Nonclinical Review Team recommends including a Warning and Precaution in Aqneursa (levacetylleucine) labeling.

DPMH discussed the concern for embryo-fetal toxicity based on the currently available nonclinical data with the DRDMG Review Team. The determination was made to include labeling recommendations for pregnancy testing and contraceptive use in females of reproductive potential. The Nonclinical Review Team recommends issuing postmarketing requirement (PMR) studies to further evaluate the effects of levacetylleucine on embryofetal

⁴ DRDMG Nonclinical Review Team labeling recommendations.

development, fertility and early embryonic development, and pre-and postnatal development, which can be used to further inform pregnancy safety and labeling recommendations.

Clinical Experience

Clinical Trials

- Pregnant women were excluded from clinical trials with levacetylleucine. The applicant stated that no pregnancy cases have been reported during the clinical development program.

Review of Published Literature

- The applicant did not submit a review of published literature for this NME
- This Reviewer performed a search in PubMed, Embase, Micromedex⁵, TERIS⁶, Reprotox⁷, and Briggs⁸ to find relevant articles not cited by the applicant. Search terms included “levacetylleucine” AND “pregnancy,” “pregnant women,” “birth defects,” “congenital malformations,” “stillbirth,” “spontaneous abortion,” OR “miscarriage.”
 - No relevant literature was identified.

LACTATION

Nonclinical Experience

Animal lactation studies were not performed with levacetylleucine. For details, refer to the Nonclinical Review by Saryu Goel, PhD.

Clinical Experience

Clinical Trials

- Lactating women were excluded from clinical trials with levacetylleucine. No lactation cases were reported during the clinical development program.

Review of Published Literature

- The applicant did not submit a review of published literature for this NME
- This Reviewer performed a search in *Medications and Mother's Milk*⁹, LactMed¹⁰, Micromedex⁵, Reprotox⁷, Briggs⁸, PubMed, and Embase using the terms “levacetylleucine” AND “lactation” OR “breastfeeding.”
 - No relevant literature was identified.

⁵ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 7/9/24.

⁶ TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/9/24.

⁷ Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/9/24.

⁸ Briggs GG, et al. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 9th Ed. 2011.

⁹ Hale, Thomas (2017) *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

¹⁰ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 7/9/24.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

Studies of fertility and early embryonic development and pre-and postnatal toxicology were not conducted with levacetylleucine. For details, refer to the Nonclinical Review by Saryu Goel, PhD.

Clinical Experience

Published literature

- The applicant did not submit published literature for this NME
- This Reviewer performed a search in PubMed, Embase, and Reprotox⁷ using the terms “levacetylleucine” AND “fertility,” “contraception,” “oral contraceptives,” OR “infertility.”
 - No relevant published literature was identified.

DISCUSSION and CONCLUSIONS

Pregnancy

There are no available data on levacetylleucine use in pregnant women to evaluate a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. However, based on animal reproduction studies, levacetylleucine may cause embryo-fetal harm when administered during pregnancy. The DRDMG Nonclinical Review Team recommends including a Warning and Precaution in Aqneursa labeling to advise pregnant women of the potential risk to the fetus. Pregnancy testing and contraception recommendations will also be included. The decision to continue or discontinue treatment during pregnancy should consider the patient’s need for Aqneursa, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal disease.

Due to the likely low prevalence of pregnancy in women with NPC and the fatality of this disease, DPMH does not believe that collection of data through the issuance of a postmarketing requirement (PMR) pregnancy registry or descriptive pregnancy safety study (DPSS) would be feasible. Pharmacovigilance can be used to monitor for any pregnancy exposure cases and safety outcomes.

Lactation

There are no available published literature or postmarketing data on the presence of levacetylleucine in human milk, the effects on the breastfed infant, or the effects on milk production. Therefore, DPMH recommends including the following benefit/risk statement in Subsection 8.2 labeling, “The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Aqneursa and any potential adverse effects on the breastfed infant from Aqneursa or from the underlying maternal condition.”

Due to the likely low prevalence of lactation in women with NPC and the fatality of this disease, DPMH does not believe that collection of lactation data through the issuance of PMR would be feasible. Pharmacovigilance can be used to monitor for lactation exposure cases and safety outcomes.

Females and Males of Reproduction Potential

There are no available human data to suggest levacetylleucine adversely effects male or female fertility. However, based on animal studies, levacetylleucine may cause fetal harm. Therefore, subsection 8.3 of labeling will include headings for pregnancy testing and contraception. The Nonclinical and Clinical Pharmacology team recommend a duration of 7 days for contraception after discontinuation of treatment based on the short-half life and potential reproductive toxicity.

LABELING RECOMMENDATIONS

DPMH revised Highlights, subsection 2.1, 5.1, 8.1, 8.2, 8.3, and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed the PLLR labeling recommendations below with the DRDMG Review Team on July 17, 2024. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Aqneursa (levacetylleucine) Pregnancy and Lactation Labeling

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LABEL AND LABELING REVIEW ADDENDUM

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 31, 2024
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 219132
Product Name, Dosage Form, and Strength:	Aqneursa (levacetylleucine) for oral suspension, 1 gram per packet
Applicant Name:	IntraBio Inc.
FDA Received Date:	April 12, 2024; May 29, 2024
TTT ID #:	2024-8004-1
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Acting Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF ADDENDUM

This memorandum is an addendum to our previous labels and labeling review.^a Since our previous labels and labeling review, there has been a change in the dosage form and the package term ((b) (4) packet) for Aqneursa. Thus, the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the container label and the revised carton labeling for Aqneursa (Appendix A) to determine if they are acceptable from a medication error perspective.

2 DISCUSSION

On May 29, 2024, IntraBio submitted updated Prescribing Information (PI) in response to FDA Information Request^a and clarified that only water has been studied when reconstituting Aqneursa for administration via Gastrostomy Tube (G-Tube). Additionally, IntraBio updated Section 2.3 Preparation and Administration instructions in the Aqneursa PI to explain that for G-tube administration, the mixture should be administered via G-tube immediately.

Furthermore, the DRDMG Review Team made additional edits for Section 2.3 Preparation and Administration instructions for clarity. Since the instructions now involve more steps (b) (4) there is insufficient space on the carton labeling and container label to adequately convey complete Aqneursa preparation and administration instructions to patients. Thus, we recommend the Applicant to propose an Instructions for Use (IFU) to communicate complete Aqneursa preparation and administration instructions to patients.

3 CONCLUSION

The proposed Aqneursa container label and carton labeling are unacceptable from a medication error perspective. We provide additional recommendations for IntraBio Inc. in Section 4.

4 RECOMMENDATIONS FOR INTRABIO INC.

A. General Comments (Instructions for Use)

1. We refer to you the FDA recommendations for PI Section 2.3 Preparation and Administration Instructions, where the instructions now involve many more steps (b) (4). Thus, there is insufficient space on the carton labeling and container label to adequately convey complete Aqneursa preparation and administration instructions to patients. We recommend you to propose an Instructions for Use (IFU) to provide complete Aqneursa preparation and administration instructions to patients, including visuals if appropriate, in a patient-friendly manner. An adequate number copies of the proposed IFU should be supplied in each carton. You may refer to our guidance for industry *Instructions for Use — Patient*

^a Doan, J. Information request for Aqneursa (NDA 219132). Silver Spring (MD): FDA, CDER, OND, DRDMG (US); 2024 MAY 06.

B. 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 (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 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 *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021)*.

C. Carton Labeling

1. On the principal display panel, we recommend changing (b) (4) to “28 unit-dose packets” for clarity.

D. 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 “1 unit-dose packet” 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).

E. Multipack Carton Labeling

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

APPENDIX A. IMAGES OF LABELS AND LABELING

Container Label received on April 12, 2024



1 Page(s) of Draft Labeling has been Withheld in Full
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Clinical Inspection Summary

Date	Jul 24, 2024
From	Cheryl Grandinetti, Pharm.D. Clinical Pharmacologist Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Jenny Doan, MSN, BSN, Regulatory Project Manager Maura Ruzhnikov, MD, Medical Officer Jacqueline Karp, MD, Clinical Team Lead Catherine Pilgrim-Grayson, MD, MPH, Division Director (Acting) Division of Rare Disease and Medical Genetics (DRDMG)
NDA #	219132
Applicant	IntraBio, Ltd.
Drug	Aqneursa (levacetylleucine, N-Acetyl-L-Leucine)
NME	Yes
Proposed Indication	Treatment of Neimann-Pick disease, type C
Consultation Request Date	Feb 26, 2024
Summary Goal Date	Jul 24, 2024
Action Goal Date	Sep 24, 2024
PDUFA Date	Sep 24, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators, Drs. Gascon-Bayarri, Bremova-Ertl, and Martakis, were inspected in support of NDA 219132, covering two clinical trials, IB1001-201 and IB1001-301. During the clinical investigator inspections, source records documenting the following were reviewed and verified against the applicant's data line listings:

- For Protocol IB1001-201 for all 10 participants enrolled by Dr. Gascon-Bayarri, the treating physician's clinical impression of change in severity (CI-CS) scores for the 9-Hole Peg Test of the dominant hand (9HPT-D) or 8-Meter Walk Test (8MWT) and the central blinded rater's CI-CS scores for 9HPT-D or 8MWT (i.e., primary efficacy endpoint).
- For Protocol IB1001-301 for all 12 randomized participants at Dr. Bremova-Ertl site and for all 9 randomized participants at Dr. Martakis' site, the mean change of modified Scale for the Assessment and Rating of Ataxia (mSARA) (i.e., primary efficacy endpoint) and the original SARA (i.e., key secondary efficacy endpoint).

No discrepancies were noted. However, a data reliability concern was noted in the Visit 6 mSARA and SARA assessment for participant (b) (6) (enrolled in Protocol IB1001-301 by

Dr. Bremova-Ertl). The investigator noted in this participant that the mSARA/SARA was performed remotely over videoconference using “WhatsApp” for Visit 6. In addition, the investigator performed the assessment on (b) (4) (Visit 6) but did not document the assessment and scores until (b) (4). The investigator also made multiple changes to the individual assessment domains on (b) (4) as follows:

- **Gait:** Changed from 3 (considerable staggering, difficulties in half-turn, but without support) to 1 (slight difficulties, only visible when walking 10 consecutive steps)
- **Right nose-finger:** changed from 1 (tremor with amplitude <2 cm) to 0 (No tremor)
- **Right heel-shin slide:** changed from 1 (slightly abnormal, contact to shin maintained) to 0 (normal)
- **Left heel-shin slide:** changed from 3 (severely abnormal, goes off shin 4 or more times during 3 cycles) to 1 (slightly abnormal, contact to shin maintained)

It is difficult to rule out the potential for recall bias for the Visit 6 mSARA and SARA assessment performed in Participant (b) (6) for the following reasons:

- Visit 6 mSARA and SARA assessments were performed remotely and were not documented in a contemporaneous fashion (i.e., the 6 and 8 individual domain assessments were documented on the source record approximately 5 days after Visit 6 occurred).
- The investigator made multiple changes to 4 of the 6 individual domain assessments for the mSARA and 4 of the 8 individual domains for the SARA approximately 13 days after they were documented as noted above.
- There was no documented justification for the assessment changes.

A sensitivity analysis is recommended with regard to the Visit 6 assessment for the mSARA and SARA data generated from participant (b) (6). Notwithstanding the above concern with how the data was documented for Participant (b) (6) in Protocol IB1001-301, the studies appear to have been conducted adequately. The study data, including the primary and key secondary efficacy endpoint data for the two studies (i.e., Protocol IB1001-201 and IB1001-301), generated by these three sites appear acceptable in support of the respective indication.

II. BACKGROUND

NDA 219132 was submitted in support of the use of Aqneursa (levacetylleucine, N-Acetyl-L-Leucine) for the treatment of pediatric and adult patients with Niemann-Pick Type C (NPC) disease. The pivotal studies supporting the application were the following:

- IB1001-201, “Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C: A multinational, multicenter, open-label, rater-blinded Phase II study”
- IB1001-301, “Effects of N-Acetyl-L-Leucine on Neimann-Pick disease type C (NPC): A Phase III, randomized, placebo-controlled, double-blind, crossover study”

Protocol IB1001-201 was a multi-center, open-label, rater-blinded Phase II study. The primary objective was to evaluate the efficacy of N-Acetyl-L-Leucine based on blinded raters’ clinical

impression of change in severity (CI-CS) in the treatment of NPC.

Participants:

- Parent Study Period: 34 participants were screened, 33 were enrolled and treated, and 31 completed treatment.
- Extension Phase: 19 participants continued into the Extension Phase, 17 participants completed Visit 10, and 13 participants completed Visit 12.

Sites: 9 sites in the United Kingdom (4 sites), Spain (1 site), Germany (2 sites), Slovakia (1 site), and United States (1 site)

Study Initiation and Completion Dates:

- Parent Study Period: (b) (6) (first participant, first visit); (b) (6) (last participant, last visit)
- Extension Phase: (b) (6) (first participant, first visit); (b) (6) (last participant, last visit)

Data cutoff: Jun 22, 2020

Database Lock Dates: Apr 5, 2023

Participants were assessed during three study periods:

1. **Baseline period with or without a study run-in (Visits 0, 1, and 2):** At the initial screening visit, participants with a confirmed diagnosis of NPC (i.e., a positive genetic test for mutations in both copies of NPC1 or in both copies of NPC2) were classified as either “naïve” or “non-naïve” depending on their use of prohibited medications within the past 42 days.
 - “Naïve” participants were participants who confirmed they had not used any prohibited medications within the past 42 days. For naïve participants, the initial screening visit was treated as Visit 1 (Baseline 1) and Visit 2 (Baseline 2/Start of treatment period) took place 14 days (+7 days) after Visit 1.
 - “Non-naïve” participants were participants who confirmed they had used (or were unable to confirm or deny if they had used) any prohibited medication within the past 42 days or participants whose urine sample unexpectedly detected levels of N-Acetyl-D-Leucine above the permitted threshold. For non-naïve participants, the initial screening visit was treated as Visit 0, which commenced the study run-in period where participants underwent a washout from prohibited medications. Non-naïve participants were eligible to return for Baseline 1 after a minimum of 42 days washout. The second visit was treated as Visit 1 (Baseline 1) and Visit 2 (Baseline 2/Start of treatment period) and took place 14 days (+7 days) after Visit 1.
2. **Treatment period (Visits 3 and 4):** All participants received N-Acetyl-L-Leucine for approximately 42 days (+7 days). Visit 3 (Treatment 1) occurred at Day 28 (+7 days) of the treatment period and Visit 4 (Treatment 2) occurred after the full 42 days (+7 days) of treatment.

3. **Washout period (Visits 5 and 6):** An approximately 42-day (+7 days) washout period occurred following treatment with N-Acetyl-L-Leucine. Visit 5 (Washout 1) was scheduled for Day 28 (+7 days) of the washout period and Visit 6 (Washout 2) was scheduled after the full 42 days (+7 days) of washout.

A trial participant was considered to have completed the Parent Study if he/she had completed all phases of the Parent Study including the last visit (Visit 6).

Extension Phase: Participants who completed the Parent Study were offered the opportunity to participate in the Extension Phase if the clinical investigator determined it was in their best interest. Participants who completed Visit 6 of the Parent Study and continued into the Extension Phase were assessed approximately 6 times over a 116-week period.

During each Treatment Period (1 and 2), the dosing of the treatments (IB1001 or placebo) was as follows:

- Adults and children aged ≥ 13 years were to take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Children aged 6-12 years weighing ≥ 35 kg were to take 4 g per day: 2 g in the morning, 1 g in the afternoon and 1 g in the evening (as per adults).
- Children aged 6-12 years weighing 25 to < 35 kg were to take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Children aged 6-12 years weighing 15 to < 25 kg were to take 2 g per day: 1 g in the morning and 1 g in the evening.

The study drug was to be taken 30 minutes before, or at least 2 hours after a meal.

The **primary efficacy endpoint** was defined as the clinical impression of change in severity (CI-CS) comparing the end of treatment (Visit 4) with baseline (Visit 2) minus the CI-CS comparing the end of washout (Visit 6) with the end of treatment (Visit 4). The primary analysis was based on two independent raters' blinded assessment of videos documenting the patients' performance on the 9-Hole Peg Test of the Dominant Hand (9HPT-D) or 8-meter Walk Test (8MWT).

The treating physicians selected, based on the patient's unique clinical symptoms, either the 9HPT-D or the 8MWT as an anchor test for the CI-CS. The treating physician based this decision on their assessment of the patient at Visit 1 (Baseline 1), before the start of treatment with N-Acetyl-L-Leucine. The treating physician performed a cognitive assessment at Visit 1 according to the standard procedures of the clinical site to assist with the selection of the anchoring functional test appropriate for each patient from both a cognitive and a motor perspective. The treating physician also selected the anchor test based on interactions with the patient, their family, and caregivers, to ensure the selected scale is considerate of their quality of life. At each study visit, the treating physician documented their CI-CS assessment on a paper CI-CS Scoring Form and then the data was entered electronically into the eCRFs. The paper scoring forms were kept in the patient source data.

Each site video recorded the assessments (9HPT-D and 8MWT). Site staff used the same video-recording devices and received the same standardized training and instructions to create homogeneity in the video recordings. The site staff uploaded their videos to the ClinTrak Imaging Windows Client Application for collection, quality control (QC), central review and storage. All submitted videos underwent QC within 2 business days of receipt by Medpace Core Laboratory.

Use of Blinded Raters:

All videos were reviewed and scored by the blinded raters who were independent senior raters, who had ideally performed the 9HPT, 8MWT, and Clinical Global Impression (CGI) in a clinical setting. Medpace Core Laboratories was responsible for randomizing the anchor test videos and assigning and releasing the cases to the blinded raters via Medpace Core Laboratories ClinTrak Imaging System. The blinded raters were to receive the same standardized training and instructions to create homogeneity in the assessments of patient's clinical change in severity while performing the 9HPT-D/8MWT. Two "primary raters" were responsible for the initial comparison of the video pairs, while the third acted as an adjudicator for cases where the 2 initial reviewers differ in their assessment of the primary CI-CS score by more than 1 point.

Protocol IB1001-301 was a randomized, placebo-controlled, double-blinded, crossover phase III study. The primary objective was to evaluate the efficacy of levacetylleucine for the chronic treatment of NPC based on the Scale for the Assessment and Rating of Ataxia (SARA) (a measurement of neurological signs and symptoms and functioning). Participants who participated in the parent study were offered the opportunity to rollover into an Extension Phase which is still ongoing.

Participants: 64 participants were screened, 60 were enrolled and treated, and 59 completed both treatment periods with levacetylleucine and placebo.

Sites: 14 sites with 11 sites that recruited participants

Study Initiation and Completion Dates: Jun 30, 2022 (first participant, first visit); Jun 13, 2023 (last participant, last visit)

Data cutoff: Jun 20, 2023

Database Lock Dates: Jun 20, 2023

Unblinding Date: Jun 21, 2023

The Parent Study comprised of the following:

1. **Study Run-in and Baseline Period (i.e., Visits 0, 1, and 2):** At the initial screening visit, participants were classified as either "naïve" or "non-naïve" depending on their use of prohibited medications within the past 42 days.
 - Naïve participants were participants who, at the initial screening visit, confirmed they had

not used any prohibited medications within the past 42 days. For naive participants, the initial screening visit was treated as Visit 1 (Baseline 1) and Visit 2 (Baseline 2/Start of treatment period) took place 14 days (+7 days) after Visit 1.

- Non-naïve participants were participants who confirmed they had used (or were unable to confirm or deny if they had used) any prohibited medication within the past 42 days or participants whose urine sample unexpectedly detected levels of N-Acetyl-D-Leucine above the permitted threshold. For non-naïve participants, the initial screening visit was treated as Visit 0. Visit 0 commenced the study run-in period, where participants underwent a washout from prohibited medications. Participants were eligible to return for Baseline 1 after a minimum of 42 days washout. The second visit was treated as Visit 1 (Baseline 1) and Visit 2 (Baseline 2/Start of treatment period) took place 14 days (+7 days) after Visit 1.
2. **Treatment Period I (i.e., Visits 3 and 4):** During Treatment Period I, all participants were planned to receive either levacetylleucine or placebo for approximately 84 days (+7 days). Visit 3 was scheduled for Day 42 (+7 days) of the period and Visit 4 was scheduled after the full 84 days (+7 days) of treatment. At Visit 2 (Baseline 2), participants were randomly assigned by using an IRT system in a 1:1 ratio to 2 randomization sequences:
- Sequence 1: Starting Visit 2 (Baseline 2), participants received levacetylleucine during Treatment Period I and immediately crossed over to receive placebo during Treatment Period II.
 - Sequence 2: Starting Visit 2 (Baseline 2), participants received placebo during Treatment Period I and immediately crossed over to receive levacetylleucine during Treatment Period II.
3. **Treatment Period II (i.e., Visits 5 and 6):** At the end of Treatment Period I (Visit 4), participants immediately crossed over to receive the opposite treatment (levacetylleucine or placebo) during Treatment Period II. Visit 5 occurred on Day 42 (+7 days) of Treatment Period II and Visit 6 occurred after the full 84 days (+7 days) of Treatment Period II.

During each Period I and II, the dosing of the treatments (levacetylleucine or placebo) was as follows:

- Participants aged ≥ 13 years were to take 4 g per day: 2 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Participants aged 4-12 years weighing 15 to <25 kg were to take 2 g per day: 1 g in the morning and 1 g in the evening.
- Participants aged 4-12 years weighing 25 to <35 kg were to take 3 g per day: 1 g in the morning, 1 g in the afternoon, and 1 g in the evening.
- Participants aged 4-12 years weighing ≥ 35 kg were to take 4 g per day: 2 g in the morning, 1 g in the afternoon and 1 g in the evening (as per patients aged ≥ 13).

The planned maximum dosage of levacetylleucine or placebo for patients ≥ 13 years or aged 4-12 weighing ≥ 35 kg was 4 g per day for 84 days (+7 days). Patients aged 4 to 12 years and <35 kg were to receive 2 g or 3 g per day for 84 days (+7 days) of levacetylleucine and placebo, in accordance with their body weight (see above).

The study duration for all participants, from the first day of dosing with treatment (levacetylleucine or placebo) (Visit 2) to the final follow-up visit (Visit 6), was approximately 168 days. A participant was considered to have completed the Study if he/she completed all phases of the Study including the last visit (Visit 6).

4. Safety Follow-Up Phone Call: Occurred only for participants who did not enter the extension phase.

The **primary efficacy endpoint** was the mean change of modified Scale for the Assessment and Rating of Ataxia (mSARA) from baseline to Visit 4 or Visit 6. In the U.S., the mSARA was the primary endpoint, consisting of 6 of the 8 SARA domains: gait, speech disturbance, finger chase test, nose-finger test, fast alternating movements, and heel-shin test.

Key **secondary efficacy endpoint** was the original SARA, an 8 item clinical rating scale that includes gait, stance, sitting, speech disturbance, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test. The scores range from 0 (no ataxia) to 40 (most severe ataxia).

The complete SARA (including mSARA) should have been assessed by the investigator or qualified member of the study team and by the same investigator or qualified member of the study team at each study visit. The complete SARA (including mSARA) was performed at baseline Visit 1 (Day -14)), Visit 2 (Day 1, start of IMP), Visit 3 (Day 42), Visit 4 (day 84), Visit 5 (Day 126) and Visit 6 (Day 168, EOS)

III. RESULTS (by site):

1. Jordi Gascon-Bayarri, MD

Site #34-01

Hospital Universitari De Bellvitge

Department Of Neurology

Carrer De La Feixa Llarga, S/N

L'Hospitalet De Llobregat

8907 BARCELONA, Spain

PDUFA Inspection Dates: May 21 to 24, 2024

At this site for Protocol IB1001-201, 10 participants were screened and randomized, and 9 participants completed the study. Participant (b) (6) discontinued from the study due to an adverse event (i.e., increased seizures).

A full audit of the study records for the 10 randomized participants was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records including those related to verification of the primary efficacy endpoint (i.e., treating physician's CI-CS scores for 9-hole peg test of the dominant hand (9HPT-D) or 8-meter walk

test (8MWT); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters; and other regulatory documentation (e.g., financial disclosures).

There was no evidence of under-reporting of adverse events. Source records documenting the treating physician's CI-CS scores for the 9HPT-D or 8MWT were reviewed against the sponsor's data line listings for all 10 randomized participants. No discrepancies or issues were noted.

A post-inspection videoconference was held with representatives from Medpace Laboratories and IntraBio, Ltd. and this reviewer to verify the central blinded rater's CI-CS scores for 9HPT-D or 8MWT against the applicant's data line listings for all 10 participants. During this videoconference, Medpace Laboratories provided guided access to the ClinTrak Imaging System that contained the source data for the central blinded rater data. In addition, the source data's associated audit trails were reviewed to ensure that data were entered by trained blinded central raters and that no unauthorized changes were made to the data after initial entry by the central raters. Processes and procedures for randomizing, assigning, and releasing the anchor test videos to the blinded raters were also reviewed. No discrepancies or issues were noted.

2. **Tatiana Bremova-Ertl, MD**

Site #41-1

Inselspital, Universitaetsspital Bern

Department Of Neurology

Freiburgstrasse 20

3010 BERN, Switzerland

PDUFA Inspection Dates: May 13 to 17, 2024

At this site for Protocol IB1001-301, 13 participants were screened, 12 were randomized and 12 participants completed the study.

A full audit of the study records for the 13 participants (i.e., screened and randomized) was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; IEC submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints (i.e., SARA and mSARA, respectively); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters, and other regulatory documentation (e.g., financial disclosures).

There was no evidence of under-reporting of adverse events. Source records documenting the SARA and mSARA were reviewed against the sponsor's data line listings for the 12 randomized participants. No discrepancies were noted.

Of note, for participant (b) (6), the investigator documented that the SARA was performed remotely over videoconference using "WhatsApp" for Visit 6. In addition, the investigator performed the assessment on (b) (4) (Visit 6) but did not document the assessment and scores until (b) (4). The investigator also made multiple changes to the individual

assessment domains on (b) (4) as follows:

- **Gait:** Changed from 3 (considerable staggering, difficulties in half-turn, but without support) to 1 (slight difficulties, only visible when walking 10 consecutive steps)
- **Right nose-finger:** changed from 1 (tremor with amplitude <2 cm) to 0 (no tremor)
- **Right heel-shin slide:** changed from 1 (slightly abnormal, contact to shin maintained) to 0 (normal)
- **Left heel-shin slide:** changed from 3 (severely abnormal, goes off shin 4 or more times during 3 cycles) to 1 (slightly abnormal, contact to shin maintained)

Reviewer's comment: *It is difficult to rule out the potential for recall bias for the Visit 6 mSARA and SARA assessment performed in Participant (b) (6) for the following reasons:*

- *Visit 6 mSARA and SARA assessments were performed remotely and were not documented in a contemporaneous fashion (i.e., the 6 and 8 individual domain assessments were documented on the source record approximately 5 days after Visit 6 occurred).*
- *The investigator made multiple changes to 4 of the 6 individual domain assessments for the mSARA and 4 of the 8 individual domains for the SARA approximately 13 days after they were documented as noted above.*
- *There was no documented justification for the assessment changes.*

A sensitivity analysis is recommended with regard to the Visit 6 assessment for the mSARA and SARA data generated from participant (b) (6).

3. Kyriako Martakis, MD

Site #49-4

Universitaetsklinikum Giessen Und Marburg GmbH,

Feulgenstr. 10-12

Department Of Neurology

35392 Giessen, Germany

PDUFA Inspection Dates: May 27 to 29 and 31, 2024

At this site for Protocol IB1001-301, 9 participants were screened and randomized, and 8 participants completed the study. Participant (b) (6) terminated from the study early due to a serious adverse event (i.e., death).

A full audit of the study records for the 9 randomized participants was conducted. Records reviewed during the inspection included, but were not limited to, the study protocol and amendments; Independent Ethics Committee (IEC) submissions, approvals, and correspondence; eligibility criteria; informed consent process and forms; source records including those related to verification of the primary and key secondary efficacy endpoints (i.e., mSARA and SARA, respectively); adverse event reporting; protocol deviations; drug accountability logs; monitor logs and follow-up letters, and other regulatory documentation (e.g., financial disclosures).

There was no evidence of under-reporting of adverse events. Source records documenting the SARA and mSARA were reviewed against the sponsor's data line listings for all 9

randomized participants. No discrepancies or issues were noted.

{ See appended electronic signature page }

Cheryl Grandinetti, Pharm.D.
Clinical Pharmacologist
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{ See appended electronic signature page }

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Jenn Sellers, M.D. Ph.D.
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cc:

Central Doc. Rm. NDA 219132
DG/Project Manager/Jenny Doan
DG/Medical Reviewer/Maura Ruzhnikov
DG/Medical Team Leader/Jacqueline Karp
DG/Division Director/Catherine Pilgrim-Grayson
OSI/Office Director/David Burrow
OSI/DCCE/Division Director/Kassa Ayalew
OSI/DCCE/Acting Branch Chief/Jenn Sellers
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/GCP Program Analysts/Yolanda Patague

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/

CHERYL A GRANDINETTI
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PHILLIP D KRONSTEIN
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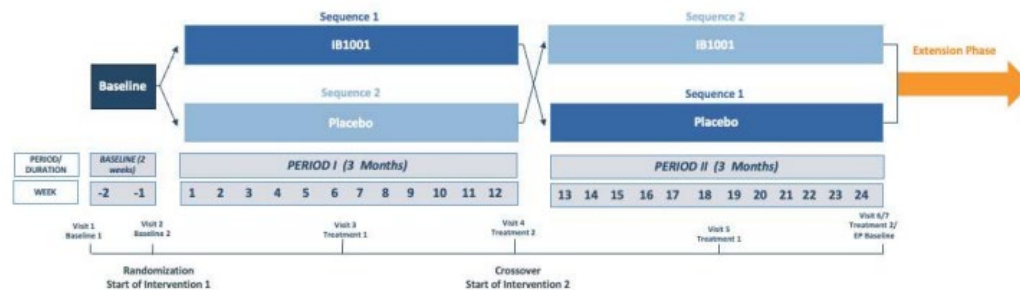
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Division of Neurology 1 (DN1) Consult Memo

NDA (Serial Number)	NDA 219132
Sponsor:	IntraBio Ltd.
Drug:	N-Acetyl-L-leucine (1B1001)
Proposed Indication:	Niemann-Pick disease type C
Material Submitted:	NDA package
Date Consult Received:	2/13/2024
Date Review Completed	5/14/2024
Reviewer:	Peggy Lazerow, MD
Division Director/Team Leader:	Emily Freilich, MD

BACKGROUND for CONSULT REQUEST

The Division of Rare Diseases and Medical Genetics (DRDMG) requested a consult from DN1 to provide input on the use of the Scale for Assessment and Rating of Ataxia (SARA) measurements in pediatric populations, to comment on the Applicant's assertion of axial ataxia measurement, and to help ensure concordance across Divisions to Applicants on SARA-related advice. The Applicant has submitted information regarding their study: Effects of N-Acetyl-L-Leucine on Niemann-Pick disease type C (NPC), a Phase III randomized, placebo-controlled, double blind, crossover study. The Applicant analyzed data from 60 subjects with a confirmed diagnosis of NPC aged ≥ 4 years.



Abbreviations: EP = extension phase.

The proposed primary endpoint in the United States was change from baseline compared to placebo in the modified SARA (mSARA, defined below) with a key secondary endpoint of change from baseline compared to placebo on the full, original SARA. Improvement from baseline compared to placebo on the axial SARA (defined below) was proposed as an exploratory endpoint.

The consult request noted that the Applicant "did not use Agency's previously suggested response categories (i.e., response options 0-4) on SARA domains 1-4 (gait stance, sitting, and speech disturbances)." DRDMG requests DN1's input regarding "SARA-related advice."

The Applicant described their approach to the SARA and its scoring as follows:

Total Original SARA = total score of 0 (no ataxia) to 40 (most severe ataxia)

1. Gait (0-8 points)
2. Stance (0-6 points)
3. Sitting (0-4 points)
4. Speech disturbance (0-6 points)
5. Finger chase (0-4 points)
6. Nose-finger test (0-4 points)
7. Fast alternating hand movement (0-4 points)
8. Heel-shin slide (0-4 points)

Once each of the 8 categories has been assessed, the total is calculated to determine the severity of ataxia. For motor activities of the four extremities (items 5-8), assessments are performed bilaterally, and the mean values are used to obtain the total score.

Modified SARA (mSARA) = total score of 0 to 30

The Applicant's mSARA is a six-item clinical rating scale that consisted of the original Gait, Speech Disturbance, Finger Chase, Nose-Finger test, Fast Alternating, Hand Movement, and Heel-shin slide domains (Domain 1, and domains 4-8).

It ranges from a score of 0-30, where 0 is the best neurological status and 30 the worst. The scoring appears similar to original scoring for each domain.

Axial SARA = total score of 0 to 24

The axial SARA includes only the first 4 domains (gait, stance, sitting, speech) of the original SARA. The axial SARA was scored using similar scoring strategy (i.e., total score) for each domain.

Previous input on the COA for the drug (IND 134369) was provided by Dr. Teresa Buracchio during the clinical development phase. On January 31, 2019, Dr. Buracchio (with COA input) wrote the following regarding the SARA scale:

"The SARA is not acceptable as a primary clinical endpoint in its original, unmodified form because several of the domains assess neurologic exam findings that do not reflect clinically meaningful change in a patient's ability to perform daily functions and scoring of other items may not capture clinically meaningful changes."

Dr. Buracchio referenced advice previously given to the Sponsor under PIND (b) (4)

"The domains assessed by the first four items of the SARA scale (gait, stance, sitting, and speech) are acceptable because they assess patients' daily functional ability. However, the response items need to be modified to reflect a clinically meaningful change in function." These recommendations including collapsing of the scoring to 0-4 for the first four items, labeled the modified SARA (mSARA). To note, these modifications are different from the mSARA that was utilized by the Applicant.

The Applicant provided an instruction and training manual for physicians performing the evaluations and provided some additional insight regarding scoring, based on the input of their advising neurologists.

For the gait assessment (Item 1), their advising neurologists felt that the scores should not be collapsed (i.e. – 0-4) as the Agency had previously recommended, but rather that the original 0-8 scoring was necessary to maintain the granularity when capturing differences in function. They also recommended that the speech scoring (Item 4) should be kept at 0-6 and provided some additional clarification on scoring certain items of the scale.

The subject of SARA testing has been discussed in depth with the Sponsor. Some relevant correspondence is listed below:

1. Type C Meeting Minutes dated June 14, 2021 (DARRTS Reference ID: 4810823):
 - At this meeting, IntraBio expressed concerns about the lack of validation data for the modified version of SARA (mSARA) recommended for use by FDA, but FDA assured that additional validation data would not be necessary to support the FDA-recommended changes.
 - FDA expressed concern regarding the interpretability of the SARA in younger patients (4 to 10 years) and recommended stratification of randomization by age.
2. Advice Letter dated December 20, 2021 (DARRTS Reference ID: 4907307)
 - The Agency requested evidence supporting the reliability of the SARA in children ages 4 years and older noting reliability concerns from published literature for children younger than 8 years of age.
 - The Agency advised to include sitting and stance tasks in the Applicant's version of the mSARA (Domains 1, 4-8) to ensure comprehensive assessment of ataxia.
 - The Agency provided response options and scoring to be used for sitting task of SARA.
 - The Agency advised revised response categories for gait and all other mSARA items based on the example of response categories ranging from 0 to 4.
 - The Agency asked the Applicant to record the use of any assistive device to walk on the CRF and that walking should be assessed in the same manner (e.g., use of orthotics and/or assistive devices must be the same) during all assessments.
3. Advice Letter dated March 22, 2022 (DARRTS Reference ID: 4955181):
 - The Agency continued to express concerns about measurement approach for the Applicant's proposed mSARA as the primary endpoint.
 - The Agency reiterated that there does not appear to be adequate evidence to support that SARA items 5-8 (finger chase, nose-finger test, fast alternating hand movements, heel shin slide) measure clinically relevant and meaningful functions.
 - The Agency recommended that the Sponsor omit SARA items 5-8 from computation of the primary endpoint.

To better understand the current scoring approaches in the NDA submission, DCOA/PFSS sent an IR. The Applicant's response explained that the SARA assessment was administered at each site by a qualified physician using a provided manual. At all visits, the original 8-domain SARA assessment was administered. The Applicant's mSARA and the Axial SARA were calculated based on the statistical

evaluations of their respective subset of SARA domains following the database lock. For each test, the total score was derived as the cumulative score.

DRDMG requests DN1 to help guide the Applicant on how to collapse current SARA response categories and re-score their SARA responses for both primary and secondary efficacy endpoint results.

DN1 Response:

The Scale for Assessment and Rating of Ataxia (SARA) is a 40-point clinician-rated scale that consists of 8 domains based on neurologic exam findings (gait, stance, sitting, speech disturbance, finger chase, nose-finger test, fast alternating hand movements, and heel-shin slide). The axial SARA score uses a similar strategy, but only on the first 4 domains (gait, stance, sitting, speech). The Division has suggested a collapsing strategy for each score which can be done by modifying the original SARA domains.

The total SARA as currently constructed may not be able to establish a clinically meaningful change in patient function. Several items of the scale, such as Finger Chase, Nose to Finger, Fast Alternating Hand Movements and Heel to Shin measure the same clinical sign, dysmetria, and do not directly assess the ability to function; hence, these domains appear inadequate to establish a clinically meaningful benefit. For certain items, patients are asked to complete distinct tasks, yet the scoring combines these distinct tasks, making it difficult to clearly identify what function improved or declined. In addition, the scoring of these elements is variable, with gait scored from 0 to 8, stance and speech scored from 0 to 6 and sitting scored from 0 to 4. The different weights for the domains make it difficult to interpret the total score.

We note that some elements of the SARA, such as gait, stance, speech disturbance, and possibly sitting (Items 1-4), may be capable of reflecting a clinically meaningful benefit if properly reconstructed. Your outcome assessment should be able to capture both improvement and decline in daily function.

. DN1 has previously made recommendations to sponsors for modifications to the SARA scale to make it acceptable to the primary endpoint (with input from COA). Such recommendations include using only the first four items of the SARA scale (gait, stance, sitting, and speech) because they assess patients' daily functional ability and may be capable of reflecting a clinically meaningful benefit if properly reconstructed... A possible outcome assessment should be static and non-comparative, with a limited number of categories. Each category should be distinct, clearly defined, non-overlapping and should represent a clinically meaningful gradation (both improvement and decline) in the functional ability in patients. The scoring categories should contain the same number of items (e.g., 0 to 4) for each domain, and should be based on clearly defined and clinically important distinctions. Please see attachment at the end of this document for collapsing SARA responses for the Applicant's modified SARA version.

DN1 recommends giving more weight to the Applicant's Axial SARA which was proposed at an exploratory endpoint, since this is more consistent with what DRDMG and the Agency initially requested of the Applicant.

Attachment 1: Agency recommended rescored axial SARA

SARA Item	Original Item Score	Modified Item Score
Item 1: Gait	0 = Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)	0
	1 = Slight difficulties, only visible when walking 10 consecutive steps in tandem	1
	2 = Clearly abnormal, tandem walking >10 steps not possible	1
	3 = Considerable staggering, difficulties in half-turn, but without support	2
	4 = Marked staggering, intermittent support of the wall required	2
	5 = Severe staggering, permanent support of one stick or light support by one arm required	2
	6 = Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)	3
	7 = Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)	3
	8 = Unable to walk, even supported	4
Item 2: Stance	0 = Normal, able to stand in tandem for > 10 s	0
	1 = Able to stand with feet together without sway, but not in tandem for > 10s	1
	2 = Able to stand with feet together for > 10 s, but only with sway	1
	3 = Able to stand for > 10 s without support in natural position, but not with feet together	2
	4 = Able to stand for >10 s in natural position only with intermittent support	3
	5 = Able to stand >10 s in natural position only with constant support of one arm	3
	6 = Unable to stand for >10 s even with constant support of one arm	4
Item 3: Sitting	0 = Normal, no difficulties sitting >10 sec	0
	1 = Slight difficulties, intermittent sway	1
	2 = Constant sway, but able to sit > 10 s without support	2
	3 = Able to sit for > 10 s only with intermittent support	3
	4 = Unable to sit for >10 s without continuous support	4

Item 4: Speech disturbance	0 = Normal	0
	1 = Suggestion of speech disturbance	1
	2 = Impaired speech, but easy to understand	1
	3 = Occasional words difficult to understand	2
	4 = Many words difficult to understand	3
	5 = Only single words understandable	4
	6 = Speech unintelligible / anarthria	4

The assessment and rating of the modified SARA should be done at the in-clinic visits in order to ensure that ratings are prospective. All raters should receive mandatory training on the modified SARA and be subject to testing and be certified during the conduct of the protocol.

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/

PEGGY R LAZEROW
05/14/2024 10:47:37 AM

EMILY R FREILICH
05/14/2024 02:45:42 PM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 7, 2024
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 219132
Product Name, Dosage Form, and Strength:	Aqneursa (levacetylleucine) granules (b) (4) 1 gram
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	IntraBio Inc.
FDA Received Date:	April 12, 2024
TTT ID #:	2024-8004
DMEPA 2 Safety Evaluator:	Sali Mahmoud, PharmD, BCPS
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 INTRODUCTION

As part of the approval process for Aqneursa (levacetylleucine) granules (b) (4) the Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Aqneursa Prescribing Information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219132.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
<i>We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance.</i>	

3 CONCLUSION

The proposed Aqneursa Prescribing Information (PI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Rare Diseases and Medical Genetics (DRDMG) in Section 5 and for IntraBio Inc. in Section 6.

4 RECOMMENDATIONS FOR THE DIVISION OF RARE DISEASES AND MEDICAL GENETICS (DRDMG)

A. Prescribing Information

1. Highlights of Prescribing Information

- To section 2 Dosage and Administration, we recommend specifying the allowed liquids for dissolving Aqneursa. To “40 mL (b) (4)” specify “water, orange juice or almond milk” for completeness.

2. Section 2 Dosage and Administration

- We recommend deleting (b) (4) from the dosage tables to improve readability. Consider adding a sentence before Table 1 and 2 (b) (4)
- To section 2.2 Recommended Dosage we recommend adding gastrostomy tube to the route of administration for completion. Consider

“Administer AQNEURSA orally, or via gastrostomy tube, after dissolving...”

- c. The preparation instructions do not include (b) (4). We recommend including a step to check the dose and select the correct number (b) (4) before mixing. Consider adding another step to repeat the dissolution process (b) (4) if needed.
- d. Clarify if dissolved Aqneursa is to be discarded after 30 minutes if not used immediately. Add a step to discard after 30 minutes if not taken administered immediately.
- e. There are inconsistent references to the final form of Aqneursa once it is in solution. We recommend consistently using (b) (4) to facilitate accurate understanding of preparation and administration steps.

5 RECOMMENDATIONS FOR INTRABIO INC.

A. General Comments (Multi-pack & Carton Labeling)

1. As currently presented, the format for the expiration date is not defined. 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 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 Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).
2. Side panel
 - a. We recommend changing the title (b) (4) to “administration instructions” to align with prescribing information.
 - b. We recommend specifying the allowed liquids in statement 1 of the preparation instructions. Stating this information on side panel will facilitate access at the time of administration. Add “water, orange juice or almond milk” to statement 1.

- c. For consistency with the prescribing information we recommend changing the statement of dosage (b) (4) to “Recommended Dosage: See Prescribing Information.”

B. Container Label(s)

1. 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 and carton labeling in accordance with 21CFR 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).
2. (b) (4) labeling does not show perforations or visual cue to mark where to cut. We recommend adding an image to the corner where user can access the drug product.
3. As currently presented, the preparation instructions on the principal display panel are incomplete and unclear (b) (4). We recommend adding the complete preparation instructions to the back (b) (4).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Aqneursa^a received on April 12, 2024 from IntraBio Inc.

Table 2. Relevant Product Information for Aqneursa	
Initial Approval Date	NA
Active Ingredient	levacetylleucine
Indication	(b) (4)
Dosage Form	granules (b) (4)
Strength	1 gram
Route of Administration	Oral

^a Prescribing Information for Aqneursa. Tenaflly (NJ): IntraBio; 2024 JAN 24. Available from: <\\CDSESUB1\EVSPROD\nda219132\0001\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-10jan2024.docx>

Table 2. Relevant Product Information for Aqneursa	
Dose and Frequency	(b) (4)

Table 2. Relevant Product Information for Aqneursa	
How Supplied	(b) (4) Each (b) (4) contains 1.7 g white to off-white granules, equivalent to 1 g Levacetylleucine <NDC no.>: Carton containing 28 (b) (4) (b) (4)
Storage	Store at room temperature, 15°C to 25°C (59°F and 77°F); excursion permitted up to 30°C (86°F) [see USP Controlled Room Temperature].
Container Closure	(b) (4)

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Aqneursa labels and labeling submitted by IntraBio Inc.

- Prescribing Information received on April 12, 2024, available from <\\CDSESUB1\EVSPROD\nda219132\0019\m1\us\114-labeling\draft\labeling\uspi-11apr2024-tracked-change.docx>
- Container label(s) received on April 12, 2024
- Carton labeling received on April 12, 2024

B.2 Container Label(s) and Carton Labeling Images

Container label(s)



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

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On April 16, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, levacetylleucine. Our search identified no previous reviews.

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/

SALI MAHMOUD
05/07/2024 02:34:11 PM

ASHLEIGH V LOWERY
05/07/2024 02:35:32 PM