

NDA 219132

NDA APPROVAL

IntraBio Inc
c/o Strategic Drug Development Services, LLC
Attention: Scott A. Oglesby, PhD
Executive Consultant
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:

Please refer to your new drug application (NDA), dated and received January 24, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Aqneursa (levacetylleucine) for oral suspension.

This NDA provides for the use of Aqneursa (levacetylleucine) for oral suspension for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥ 15 kg.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.¹ Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Instructions for Use) as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.²

The SPL will be accessible via publicly available labeling repositories.

¹ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

² We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved NDA 219132.**” Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Aqneursa (levacetylleucine) for oral suspension shall be 24 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F).

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA. This priority review voucher (PRV) has been assigned a tracking number, PRV **NDA 219132**. All correspondences related to this voucher should refer to this tracking number.

This PRV entitles you to designate a single human drug application submitted under section 505(b)(1) of the FDCA or a single biologics license application submitted under section 351(a) of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the PRV must notify FDA of its intent to submit an application with a PRV at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”
- This PRV may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the PRV may be transferred, but each person to whom the PRV is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this PRV, you should refer to this letter as an official record of the voucher. If the PRV is transferred, the sponsor to whom the PRV has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the PRV was transferred.

- FDA may revoke the PRV if the rare pediatric disease product for which the PRV was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a PRV must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
 - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
 - the estimated demand in the U.S. for the product, and
 - the actual amount of product distributed in the U.S.

You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.³

ADVISORY COMMITTEE

Your application for Aqneursa was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal

³ <https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs>

of serious risks with levacetylleucine use related to embryofetal development, fertility, early embryonic development, pre- and postnatal development, and carcinogenicity.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

PMR 4683-1 Conduct an embryo-fetal development (EFD) toxicity and toxicokinetic study with levacetylleucine in the rodent.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

PMR 4683-2 Conduct an embryo-fetal development toxicity and toxicokinetic study with levacetylleucine in the non-rodent.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

PMR 4683-3 Conduct a juvenile toxicity and toxicokinetic study with levacetylleucine.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 05/2025

PMR 4683-4 Conduct a fertility and early embryonic development (FEED) toxicity study with levacetylleucine.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2024

PMR 4683-5 Conduct a pre- and postnatal development (PPND) toxicity study with levacetylleucine.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2025

PMR 4683-6 Conduct a 26-week carcinogenicity study with levacetylleucine, administered by daily oral gavage, in an appropriate transgenic mouse model.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 01/2025
Final Protocol Submission: 06/2025
Study Completion: 06/2026
Final Report Submission: 03/2027

Submit the draft protocol as a special protocol assessment (SPA).⁴ Include the report of a dose-ranging study with accompanying SEND data to support your SPA.⁵

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁶

PMR 4683-7 Conduct a long-term (2-year) GLP-complaint carcinogenicity study by oral gavage administration in rats.

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 06/2025
Final Protocol Submission: 12/2025
Study Completion: 06/2028
Final Report Submission: 06/2029

⁴ See the FDA guidance for industry, *Special Protocol Assessment* (April 2018), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/special-protocol-assessment-guidance-industry>.

⁵ See the guidance for industry, *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals* (November 2022), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1br1-addendum-s1b-testing-carcinogenicity-pharmaceuticals>.

⁶ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Submit the draft protocol as an SPA.⁷ Include the report and accompanying SEND data for a toxicology study intended to inform the dose selection and support your SPA.⁸

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.⁹

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected serious risk of drug-drug interactions with P-gp substrates.

Therefore, based on appropriate scientific data (in vitro P-gp efflux transporters inhibition study results), FDA has determined that you are required to conduct the following trial:

PMR 4683-8 Conduct a clinical drug-drug interaction (DDI) trial in healthy volunteers to evaluate the effect of levacetylleucine on a probe substrate of P-gp to thoroughly assess its inhibitory potential and its impact on patient safety. Design and conduct the trial in accordance with FDA guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2025
Final Protocol Submission:	09/2025
Trial Completion:	09/2026
Final Report Submission:	09/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.¹⁰

⁷ See the FDA guidance for industry, *Special Protocol Assessment* (April 2018), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/special-protocol-assessment-guidance-industry>.

⁸ See the guidance for industry, *S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals* (November 2022), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s1br1-addendum-s1b-testing-carcinogenicity-pharmaceuticals>.

⁹ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

¹⁰ See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Submit clinical protocol(s) to your IND 134369 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:

Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

PMC 4683-9 Conduct a dedicated food effect trial to evaluate the impact of food on exposure of levacetylleucine granules for oral suspension in accordance with FDA guidance for industry *Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry* (June 2022).

The timetable you agreed to in your submission dated September 18, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2024
Final Protocol Submission:	03/2025
Trial Completion:	09/2025
Final Report Submission:	03/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 134369 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.¹¹

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.¹² Information and Instructions for completing the form can be found at FDA.gov.¹³

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

¹¹ For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/media/128163/download>.

¹² <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

¹³ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website¹⁴.

If you have any questions, contact Jenny Doan, Regulatory Project Manager, at (301) 796-1023 or Jenny.Doan@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Janet W Maynard, MD, MHS
Director
Office of Rare Diseases, Pediatrics,
Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Instructions for Use
- Carton and Container Labeling

¹⁴ <https://www.uspnf.com/>

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/

JANET W MAYNARD
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