CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219132Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	219132
PDUFA Goal Date	September 24, 2024
Nexus TTT #	2024-8005
Reviewer Name(s)	Theresa Ng, PharmD, BCPS
Team Leader	Yasmeen Abou-Sayed, PharmD
Deputy Division Director	Laura Zendel, PharmD
Review Completion Date	September 20, 2024
Subject	Evaluation of Need for a REMS
Established Name	Levacetylleucine or N-Acetyl-L-Leucine (NALL)
Trade Name	Aqneursa
Name of Applicant	IntraBio Inc.
Therapeutic Class	Amino Acid Replacement
Formulation(s)	1 g (b) (4) of granules (b) (4)
Dosing Regimen	(b) (4)

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aqneursa (levacetylleucine) is necessary to ensure the benefits outweigh its risks. IntraBio Therapeutics, Inc. submitted a New Drug Application (NDA) 219132 for Aqneursa with the proposed indication (b) (4) (b) (4) Based on the results from clinical trials, pharmacological data, and pharmacokinetic modeling, the indication was revised "for the treatment of neurologic symptoms in adult and pediatric patients with NPC who are 15 kg and greater." The risk associated with Aqneursa is embryo-fetal toxicity. The Applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Rare Diseases and Medical Genetics (DRDMG) determined that a REMS is not needed to ensure the benefits of Aqneursa outweigh its risk. There is limited animal data on embryo-fetal toxicity and no available human pregnancy data with levacetylleucine. Dose-range studies in rats and rabbits exposed to levacetylleucine at 1.4-fold and 6-fold, respectively, the maximum recommended human dose of 4 gram/day, demonstrated embryo-fetal toxicity adverse outcomes such as post-implantation loss and skeletal malformation. The risk of embryo-fetal toxicity will be communicated in labeling in Warnings and Precautions with a recommendation to verify patients of reproductive potential are not pregnant prior to initiating therapy, and for use of effective contraception during treatment and for 7 days after discontinuation of Aqneursa. Additionally, the Applicant will be required to conduct a postmarketing study to further characterize this risk.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Aqneursa (levacetylleucine) is necessary to ensure the benefits outweigh its risks. IntraBio Therapeutics, Inc. (IntraBio) submitted a New Drug Application (NDA) 219132 for Aqneursa with the proposed indication (b) (4) (b) (4) This application is under review in the Division of Rare Diseases and Medical Genetics (DRDMG). The Applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Aqneursa (levacetylleucine) is a new molecular entity (NME)[a] consisting of active drug substance N-acetyl-L-leucine (NALL) that targets underlying neurological dysfunction caused by mutations in the *NPC1* or *NPC2* genes. The mechanism of action for Aqneursa is unknown. Aqneursa is proposed for the

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

(b) (4) It is formulated as 1 gram (b) (4) granules (b) (4) The proposed dose is presented in table 1 below.

Table 1. Aqneursa Dosing Regimen

(b) (4)

NALL was granted both Fast Tract designation (March 2020) and Orphan drug designation (September 2021). Aqneursa is not currently approved in any jurisdiction.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219132 relevant to this review:

- 3/19/2020: Fast track designation granted for NALL under investigational new drug (IND) application 134369 for NPC.
- 9/8/2021: Orphan drug designation granted for NALL (DRU-2021-8361).
- 1/24/2024: NDA 219132 submission (b) (4) (b) (4) received.
- 5/17/2024: Mid-cycle meeting minutes issued informing the Applicant that there were no major safety concerns identified at this time that require a REMS for Aqneursa.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Niemann-Pick disease Type C (NPC) is a rare, progressive, life-limiting, neurodegenerative, autosomal-recessive lysosomal disorder caused by mutations in the NPC1 (95%) or NPC2 genes (5%) involved with intracellular cholesterol trafficking, resulting in the accumulation of multiple tissue specific lipids in the lysosomes.[1c] The principal manifestations are age dependent. The perinatal period and infancy are

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

predominantly visceral, with hepatosplenomegaly, jaundice, and (in some instances) pulmonary infiltrates. From late infancy onward, the presentation is dominated by neurologic manifestations with progressive motor and cognitive impairment, supranuclear gaze palsy, dysphagia, dysarthria, ataxia, and epilepsy. Older teenagers and young adults may present predominantly with apparent early-onset dementia or psychiatric manifestations. The prevalence of NPC has been estimated at 1:150,000 live births and causes premature death due to relentless neurodegeneration as well as lung and liver dysfunction.[2d] The majority of NPC patients are children and die before the age of 20. The median age of death was 13 years with a range from 0.1-69 years.[3]

3.2. Description of Current Treatment Options

Current treatment is limited to symptomatic management and off label use of miglustat in United States (US). There is no curative treatment for NPC.

Zavesca (miglustat) NDA 21348, a glucosylceramide synthase inhibitor was approved in 2003 for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option. Miglustat is approved in the European Union, Canada, and Japan for the treatment of the progressive neurological manifestations of NPC in pediatric and adult patients. Though not approved in the US, miglustat is used off-label and considered by clinical experts as standard of care for the treatment of NPC. Adverse events associated with miglustat include peripheral neuropathy, tremor, diarrhea and weight loss, and reduction in platelet count. Miglustat has been shown to delay disease progression and to stabilize neurological symptoms in several randomized controlled clinical trials, observational studies, and long-term extension studies.[4] Despite this, disease progression continues, therefore, there remains a high unmet medical need for novel treatments for NPC.

4. Benefit Assessment

The efficacy and safety of NALL, also known as IB1001 in the clinical development program, for NPC is based on the pivotal phase 3 study IB1001-301, NCT05163288, with confirmatory evidence from a phase 2 study IB1001-201, NCT03759639, and their respective extension periods in NPC patients. The Applicant also provided additional information from in vitro studies, animal model studies of NPC, clinical pharmacology data and published literature to support the mechanism of action of IB1001 in NPC to support the confirmatory evidence of effectiveness of IB1001 on NPC.

IB1001-301 is a multinational, randomized, double-blinded, placebo-controlled, crossover study involving 7-non-US countries. A total of 60 subjects aged 5 to 67 years with a confirmed diagnosis of NPC were randomized in a 1:1 ratio into two treatment groups: 30 subjects in IB1001 and 30 subjects in placebo. The study consisted of three periods: a baseline period, a 12-week first treatment period ("Treatment Period I"), and a 12-week second treatment period ("Treatment Period II"). The mean age

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

of patients in the study was 26.4 (range 5 to 67 years), 38.3% were pediatric patients (< 18 years), 90% were White, and 85% used miglustat at baseline. The primary endpoint, defined as the difference in the mean change in the modified Scale for the Assessment and Rating of Ataxia (mSARA) scores[e] from pretreatment baseline to week 12, measured (b) (4) (b) (4) Due to concern for the interpretability of the mSARA, the Agency recommended rescoring of the data using select Scale for the Assessment and Rating of Ataxia (SARA)[f] domains.[5] A similar pattern was seen using the Agency's recommended rescoring of the SARA (or ARSARA[g]) with estimated ARSARA of -0.45 (95% CI: -0.70, -0.2; p-value < 0.001). Both analyses did not show significant carryover effects and there is no evidence for differential treatment effect across demographic subgroups.

Study IB1001-201, a multinational, rater-blinded open label study in 33 subjects (aged 7 to 64 years) consisting of 6 weeks of treatment period (Visit 2 to Visit 4) and 6 weeks washout period (Visit 4 to Visit 6) with NPC provided support for the confirmatory evidence of efficacy for IB1001. The overall mean age of the subjects was 28.8 years, 88% were White, and 91% used miglustat at baseline. The primary endpoint was the Clinical Impression of Change in Severity (CI-CS)[h], anchored with an eight minute walk test (8MWT) or Nine-Hole Peg Test (9HPT)[i], in the treatment and washout study periods. The median difference in CI-CS score between the two study periods was 1.0 (90% CI: 0.3, 1.8; p-value 0.03).

The clinical reviewer concluded the ARSARA results in study IB1001-301 demonstrated clinically meaningful improvement with IB1001 compared with placebo for NPC.[j] Confirmatory evidence is provided from study IB101-201 based on the CI-CS results and from nonclinical data, including the pharmacokinetics (PK)/ pharmacodynamics (PD) of IB1001 that is consistent with the pathophysiology of disease. The clinical reviewer also concluded while no subjects under 5 years of age were enrolled, extrapolation of data from subjects 10 years and older in IB1001-301 to those less than 10 years old is justified based on similar underlying disease pathophysiology and manifestations in children with NPC, and the expected same therapeutic MOA of IB1001 across age groups. PK findings from the clinical trials

---

[e] mSARA scores is a six-item clinical rating scale consisting of 6 domains (gait, speech disturbance, finger-chase test, nose-finger test, fast alternating movements, and heel-shin test) with scores ranging from 0-30, where 0 is the best neurological status and 30 the worst.

[f] SARA is a clinical scale made up of 8 items related to gait, stance, sitting, speech, finger-chase test, nose-finger test, fast alternating movements and heel-shin test to determine the severity of ataxia. The SARA total score ranges from 0 to 40, where 0 is the best neurological status and 40 the worst.

[g] ARSARA contains the SARA domains of only the four SARA domains of gait, stance, sitting, and speech with total score ranges from 0 to 16.

[h] CI-CS scoring is based on comparing videos of the subject's performance on the predefined anchor test ranked on a 7 point Likert-scale (-3 = significantly worse to +3 = significantly improved).

[i] 9-HPT is a standardized, quantitative assessment used to measure finger dexterity and upper extremity function.

[j] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

support this extrapolation. Additionally, the therapeutic MOA of IB-1001 is expected to be the same across all age groups.

Durability of treatment effect was assessed in 54 patients in the extension phase (EP) of Study IB1001-301. The clinical reviewer determined data of continued mean improvement and/or relative stability in neurological symptoms after one year provided reasonable scientific justification for the long-term use of NALL and support use for chronic therapy.

The clinical reviewer also recommended changes to limit the proposed indication to those with neurological symptoms of NPC and dosing regimen to those ≥ 15 kg for IB1001. The pivotal study, IB1001-301, evaluated changes in neurological symptoms associated with NPC; the study did not evaluate for improvements in visceral symptoms (e.g., jaundice, hepatomegaly, and splenomegaly) with NPC. Additionally, the data submitted on the proposed dosing regimen is based on body weight (b) (4) (b) (4) (b) (4) Therefore, the clinical reviewer determined the label indication should be revised to "for the treatment of adult and pediatric patients with neurological symptoms of Niemann-Pick Type C (NPC) weighing ≥ 15 kg". These changes were communicated to the Applicant via labeling communications, dated July 25, 2024 [6] and the Applicant submitted labeling amendment to reflect these changes on August 21, 2024.[7]

5. Risk Assessment & Safe-Use Conditions

The primary evidence of the safety of IB1001 is based on Study IB1001-301 with added support from IB1001-201 and data from their respective open label extension (OLE) phases (for additional 2 years). The NPC combined safety population (including study IB1001-301 and IB1001-201) consisted of a total of 84 patients who were 5 years of age and older (range 5-67 years). There was a total of 28 pediatric patients (7 were less than 10 years old) and 56 adult patients. No safety data is available for patients under 5 years of age. To avoid the impact of potential carry over effects, Treatment Period I was the primary portion of study IB1001-301 reviewed for common adverse reactions.

In IB1001-301, there were no SAEs that led to withdrawal from the study. Overall, 58% of subjects experienced a treatment-emergent adverse event (TEAE) versus 51% while on placebo. During IB1001-301 Treatment Period 1, TEAEs with a risk difference ≥ 6.7 were abdominal pain, dysphagia, nasopharyngitis, upper respiratory tract infections and vomiting. Of note, Rosacea (2%) was reported as possibly related to treatment in IB1001-301 and will be included as an adverse reaction in labeling. In IB1001-301 OLE, 43% of subjects experienced treatment adverse events; the most common System Organ Classes (SOC) were Infections and Infestations (16.7%) followed by Gastrointestinal disorders (13%).

In study IB1001-201, TEAEs were reported by more patients exposed to IB1001 than during the washout period (70% vs 21%). In the overall cohort, there were 6 reported serious adverse events (SAEs) in 4 subjects.

Thrombocytopenia with platelets < $100X10^3$ cells/uL was observed in four patients during Treatment Period 1, and all were receiving miglustat. Thrombocytopenia is included as a warning in miglustat's labeling. A causal relationship of levacetylleucine with thrombocytopenia has not been established with IB1001 but will be included in labeling as an adverse reaction.

Hypersensitivity reactions including anaphylaxis, skin rash, urticaria, laryngeal edema, and abdominal pain have been reported for racemate of IB1001, Tanganil (N-Acetyl-Dl-Leucine) approved in France for symptomatic treatment of vertigo. However, Tanganil contains a wheat-based excipient which may contribute to the hypersensitivity reaction. There were no clear hypersensitivity reactions reported for IB1001 similar to those reported with Tanganil in Trial IB1001-301. (b) (4)

(b) (4)

There was one death of a study subject in IB1001-301 that occurred after withdrawal from the study due to physician decision after complications from a planned surgical procedure. The clinical reviewer concurred that the death was not related to the study drug. No deaths were reported for IB1001-201. There have been no deaths reported in the OLE period thus far.

5.1. Embryo-fetal toxicity

There is limited data on embryo-fetal toxicity for IB1001 in the clinical development program. Dose-range findings in rats and rabbits demonstrated embryo-fetal toxicity due to IB1001. Post-implantation loss (resorptions) and skeletal malformation were observed in pregnant rats and rabbits at a dose that was approximately 1.4-fold and 6-fold, respectively, the maximum recommended human dose (MRHD) of 4 gram/day of levacetylleucine. The clinical reviewer recommends including the risk of embryo-fetal toxicity in Warnings and Precautions in labeling. Females of reproductive potential should not be pregnant prior to initiating treatment with IB1001 and should use effective contraception during treatment and for 7 days after discontinuation of therapy. The clinical reviewer also recommends a postmarketing requirement (PMR) study for fertility and early embryonic development toxicity, and pre/post-natal development toxicity in rodents.

6. Expected Postmarket Use

Neurologists and medical geneticists are the primary providers in the care of patients with NPC with supportive management provided by a multi-disciplinary team involving physical therapy, occupational therapy, speech therapy, nutrition, feeding, psychology, and social work. Given NPC is a rare autosomal recessive disease that can be passed to offspring by both male and female carriers, parental testing for NPC should be offered to all at risk couples and requires careful counseling by clinical geneticists and NPC specialists.[8]

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Aqneursa beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Aqneursa on the basis of the efficacy and safety information currently available. NPC is a rare, serious progressive disease with no FDA-approved therapeutic options for patients at the time of this review.

The benefit-risk of IB1001 is favorable for the treatment of pediatric and adults with confirmed NPC. The clinical reviewer concluded IB1001-301 provided an adequate well-controlled trial in children and adults with NPC with significant and clinically meaningful treatment difference in neurologic symptom outcome with ARSARA of -0.45 (95% CI: -0.70, -0.2, p-value < 0.001). Confirmatory support was provided from IB1001-201 with median difference in CI-CS score of 1.0 (90% CI: 0.3, 1.8, p-value 0.03) and from PK/PD data and published literature on MOA on the effect of IB1001 on NPC. Though the youngest subject enrolled in IB1001-301 was 5 years old, the clinical reviewer determined the efficacy data in IB1001-301 along with the PK/ PD data and knowledge on the progressive nature of NPC disease lend to the justification for extrapolation for the effectiveness of IB1001 to younger pediatric patients. Additionally, the indication statement was revised to, "for the treatment of adult and pediatric patients with neurological symptoms of Niemann-Pick Type C (NPC) weighing ≥ 15 kg" to reflect that the clinical studies evaluated only for neurological symptoms in NPC patients and results of the Agency's PK extrapolation analysis on dosing.

The available safety data show that IB1001 is safe for its intended use. Common adverse reactions include dysphagia, abdominal pain and vomiting. Nonclinical dose-range findings in rodents and rabbits demonstrated potential for embryo-fetal toxicity risk. However, the data is limited and there is no data on human pregnancy. The clinical reviewer concluded that this risk can be communicated in labeling in Warnings and Precautions with recommendations to verify patients of reproductive status are not pregnant prior to initiating treatment, and for use of effective contraception during treatment, and for 7 days after discontinuation of therapy. A PMR is also recommended by the clinical reviewer to further help characterize this risk. Family planning and genetic counseling by specialists (e.g., endocrinologists and geneticists) should be offered to patients with NPC to mitigate passing of this genetic condition to offspring.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for Aqneursa to ensure the benefits outweigh the risk. At the time of this review, evaluation of safety information and labeling are ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

1. Vanier MT, Millat G. Niemann-Pick disease type C. *Clin Genet*. Oct 2003;64(4):269-81. doi:10.1034/j.1399-0004.2003.00147.x
2. Vance JE, Karten B. Niemann-Pick C disease and mobilization of lysosomal cholesterol by cyclodextrin. *J Lipid Res*. Aug 2014;55(8):1609-21. doi:10.1194/jlr.R047837
3. Bianconi SE, Hammond DI, Farhat NY, et al. Evaluation of age of death in Niemann-Pick disease, type C: Utility of disease support group websites to understand natural history. *Mol Genet Metab*. Apr 2019;126(4):466-469. doi:10.1016/j.ymgme.2019.02.004
4. Patterson MC, Mengel E, Vanier MT, Moneuse P, Rosenberg D, Pineda M. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease Type C: a final report of the NPC Registry. *Orphanet J Rare Dis*. Apr 25 2020;15(1):104. doi:10.1186/s13023-020-01363-2
5. Doan J. DRDMG. Type C Meeting Minutes for IND 134369, dated June 14, 2021.
6. Doan J. Labeling Discussion Comments for NDA 219132, dated July 25, 2024.
7. IntraBio. Labeling/ Package Insert Draft, dated August 21, 2024.
8. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet Journal of Rare Diseases*. 2018/04/06 2018;13(1):50. doi:10.1186/s13023-018-0785-7

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/

THERESA N NG
09/20/2024 10:43:41 AM

YASMEEN I ABOU-SAYED
09/20/2024 10:49:39 AM

LAURA A ZENDEL
09/20/2024 11:34:26 AM