



National Tay-Sachs &
Allied Diseases Association

Use of Aqneursa in GM1 and GM2 Gangliosidoses

The following guidance for healthcare providers (HCPs) considering off-label use of Aqneursa for individuals with GM1 or GM2 gangliosidoses. This document is not intended to provide medical advice. This information is designed for HCPs treating affected individuals living in the US; the approval status of medications may vary from country to country. Countries outside of the US may have different availability of, or processes for, accessing medications via off-label drug use.

- Background
 - Aqneursa (levacetyl-leucine or N-acetyl-L-leucine; NALL) is an acetylated form of the amino acid L-leucine
 - N-acetylation is believed to enhance the transport of compounds across the blood-brain barrier. NALL then boosts flux through the Krebs cycle increasing ATP production. Downstream effects include reduced lysosomal volume and reduced neuroinflammation.
 - Aqneursa was approved for use in Niemann-Pick disease type C (NPC) in September 2024
 - Neurodegenerative diseases like NPC, GM2 gangliosidoses (GM2), GM1 gangliosidosis (GM1), and others are believed to share pathogenic features
 - NALL has been shown to improve motor function and lifespan in mouse models of both NPC and GM2
 - NALL is the L-enantiomer of N-acetyl-DL-leucine (brand name Tanganil), which is approved for ataxia in France and has been used by many in the NTSAD community
- Approved uses
 - Aqneursa was approved for use in Niemann-Pick disease type C (NPC) in patients weighing more than 15kg in September 2024. Aqneursa is made by IntraBio. It was previously referred to as IB1001.
 - Approval was based on a double-blind, placebo-controlled, crossover trial
 - 60 subjects aged 5 to 67 years were randomized 1:1 to receive NALL for 12 weeks followed by placebo for 12 weeks or vice versa

- The primary endpoint was the Scale for the Assessment and Rating of Ataxia (SARA, a clinical measure of cerebellar ataxia severity) with lower scores indicating less ataxia. A modified version of the SARA scale (used in previous studies in other ataxias) was also used at the request of the FDA
 - Mean change from baseline in SARA total score was -1.97 ± 2.43 after 12 weeks receiving NALL and -0.60 ± 2.39 points after placebo (least-squares mean difference -1.28 points; 95% CI, -1.91 to -0.65 ; $p < 0.001$)
 - Mean change from baseline in the mSARA total score was similar (least-squares mean difference -0.96 points; 95% CI, -1.45 to -0.46)
- Available data in GM2 gangliosidosis
 - Open-label, rater-blinded study
 - 30 subjects ≥ 6 years old received NALL for 6 weeks followed by 6-week washout period
 - Primary endpoint based on predetermined “anchor test” of either 8-meter walk test or 9-hole peg test for each subject based on their abilities; performances were recorded and evaluated centrally by raters blinded to either treatment or washout period
 - Met primary endpoint using Clinical Impression of Change in Severity (CI-CS) analysis (mean difference 0.71 , SD = 2.09 , 90% CI 0.00 to 1.50 ; $p = 0.039$)
 - Specifically, subjects had improvements in CI-CS during the treatment period with a mean difference of 0.34 (SD = 1.59 , median = 0.5) and worsening of CI-CS during the washout period with a mean difference -0.36 (SD = 1.33 , median = -0.5)
 - IntraBio has applied to the FDA for approval for Aqneursa for GM2 gangliosidosis via Supplemental Drug Application and is currently appealing the FDA's request for a placebo-controlled study
 - IntraBio applied to the FDA for a supplemental drug application for the use of Aqneursa in GM2 gangliosidosis. The application is pending.
- There is no available data on the use of NALL in GM1 gangliosidosis but the mechanism of action suggests there may be a similar effect
- On-label recommended dosing (per package insert)
 - 15kg to less than 25kg - 1gm BID (morning and evening)
 - 25kg to less than 35kg - 1gm TID (morning, afternoon, evening)
 - 35kg or more - 2gm in morning, 1gm in afternoon, 1gm in evening
 - Aqneursa is supplied in 1gm packets
 - May be taken orally or via G-tube; see package insert for administration instructions

- Safety profile
 - Adverse events (AEs) in the NPC trial that occurred in $\geq 5\%$ of subjects and more commonly in those taking NALL compared to placebo include URI, abdominal pain, dysphagia, and vomiting
 - No subjects discontinued NALL due to AEs in the NPC trial
- Other considerations
 - HCPs prescribing any medications via OLDU should consider methods of assessing efficacy of such use. This may include video recordings of an individual's development and skills, tracking of mobility, falls, or ability to perform activities of daily living, or use of standardized patient -reported outcome or clinical assessments
- Known drug interactions/contraindications
 - NALL should not be taken with N-acetyl-DL-leucine or N-acetyl-D-leucine as these compete with NALL for transporter uptake and may reduce the efficacy of NALL
 - HCPs should monitor more frequently for P-glycoprotein (P-gp) transporter related adverse events when used concomitantly with Aqneursa. Examples of medications that are substrates of P-gp efflux pump include: apixaban, colchicine, cyclosporine, dabigatran, digoxin, edoxaban, rivaroxaban, and tacrolimus
 - Contraindicated in pregnancy and may cause fetal harm; Females of reproductive potential should be verified not to be pregnant before starting NALL and should use effective contraception while taking NALL and for 7 days after the last dose
 - Use of an available drug interaction checker is recommended (such as this one: https://www.drugs.com/drug_interactions.html)
- An enrollment form can be accessed through the Aqneursa website: <https://www.aqneursahcp.com/>

This document was organized by the National Tay-Sachs & Allied Diseases Association (NTSAD) Research Committee working group. It was authored by Staci Kallish, DO, from Penn Medicine with input from other NTSAD Research Committee members and members of the NTSAD Scientific Advisory Committee.

If you have additional questions, please contact research@ntsad.org.

References:

- 1) Aqneursa Package Insert: <https://www.aqneursahcp.com/wp-content/prescribing-information.pdf>

- 2) Phase 3 clinical trial in NPC: Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N-acetyl-L-leucine in Niemann-Pick Disease type C. *NEJM* 2024; 390(5):421-431.
- 3) Phase 2 clinical trial in GM2 gangliosidosis: Martakis K, Claassen J, Gascon-Bayari J, et al. Efficacy and safety of N-acetyl-L-leucine in children and adults with GM2 gangliosidoses. *Neurol* 2023; 100(10):e1072-e1083.
- 4) Information on P-gp transporter substrates:
<https://www.uptodate.com/contents/image?imageKey=DRUG%2F73326>