Use of Aqneursa in GM1 and GM2 Gangliosidoses

<u>The following guidance is for individuals and families living with GM1 or GM2 gangliosidosis who are considering off-label use of Aqneursa. This information is designed for 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.</u>

- Background
    - Aqneursa (levacetylleucine or N-acetyl-L-leucine; NALL) is a chemically altered form of an amino acid found in our bodies, L-leucine
    - The modification is believed to enhance transport across the blood brain barrier, leading to improved energy production, reduced lysosomal volume, and reduced neuroinflammation
    - Aqneursa was approved for use in a lysosomal storage disorder called 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 similar features impacting brain function
    - NALL has been shown to improve motor function and lifespan in mouse models of both NPC and GM2
    - NALL is a version of N-acetyl-DL-leucine (brand name Tanganil), which is approved for vertigo in France and has been used by many in the NTSAD community
- Approved uses
    - Aqneursa was approved for use in Niemann-Pick C disease (NPC) in patients weighing more than 15kg (33 pounds) in September 2024. Aqneursa is made by IntraBio. It was previously referred to as IB1001.
    - This approval was based on a double-blind, placebo-controlled, crossover trial where 60 patients aged 5 to 67 years were randomized to receive NALL for 12 weeks followed by placebo for 12 weeks or vice versa (i.e. they crossed over the treatment they were given)
    - When looking at the primary endpoint, the Scale for the Assessment and Rating of Ataxia (SARA, a clinical measure of ataxia severity), mean SARA scores improved when taking NALL (a smaller improvement was also seen in patients while taking the placebo)
- Available data in GM2 gangliosidoses
    - Aqneursa was studied in an open-label (all participants knew they were on drug, without a placebo), rater-blinded study where 30 patients at least years old received NALL for 6 weeks followed by a 6-week washout period;

performance in the study was recorded and scored by a reviewer who did not know if the patients were taking Aqneursa when assessing either being on drug or washout (off drug)
    - Patients were scored on either an 8-meter walk test or a 9-hole peg test for each subject based on their abilities; patients showed small improvements while taking Aqneursa and a small worsening when off of Aqneursa
    - IntraBio has applied to the FDA for approval for Aqneursa for GM2 gangliosidoses via Supplemental Drug Application and is currently appealing the FDAs request for a placebo-controlled study
- 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
- Safety profile
    - Side effects in the NPC trial that occurred in ≥5% of patients and more common in those taking NALL compared to placebo include upper respiratory infections (URI), abdominal pain, difficulty swallowing, and vomiting
- Known drug interactions/Contraindications
    - NALL should not be taken with N-acetyl-DL-leucine (Tanganil) or N-acetyl-D-leucine as these may reduce the efficacy of NALL

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

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.

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