Report AQNEURSA® - L-Acetylleucine

Product & Mechanism of action

Substance: L-Acetylleucine

Brand Name: Aqneursa

Originator/licensee: Intrabio Ireland Limited

Classification: NCE

ATC code: Not yet assigned

Orphan Status:
Eu: Yes
Us: Yes

Mechanism of action: The active substance is levacetylleucine, a modified form of the amino acid leucine that targets underlying processes of neurological dysfunction. While the mechanism of action of levacetylleucine is not yet fully understood, non-clinical studies have demonstrated that it corrects energy metabolism, including improved production of adenosine triphosphate, the main source of energy for cerebellar tissues and cells [1].

Authorized indications Licensing status

Authorized Indication:
EMA: L-Acetylleucine is indicated for the treatment of neurological manifestations of NPC disease, in combination with miglustat, or as a monotherapy in pts. where miglustat is not tolerated, in adults and children aged ≥6 years and weighing ≥ 20 kg [1].

FDA: L-Acetylleucine is indicated for the treatment of neurological manifestations of NPC in adults and paediatric pts. weighing ≥15 kg [2].

Route of administration: OS

Licensing status
EU CHMP P.O. date: 24/07/2025
FDA M.A. date: 24/09/2024

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
AE: Adverse Event
CHMP: Committee for Medicinal Products for Human Use
CI: Confidential Interval
M.A.: Marketing Authorization
NPC: Niemann-Pick type C
OS: Oral administration
PFS: Progression-Free Survival
P.O.: Positive Opinion
PS: Performance Status
Pts: Patients
SAE: Serious adverse events
SARA: Scale for the Assessment and Rating of Ataxia
SD: Standard deviation
TRAE: Treatment related AEs
WHO: World Health Organization

Essential therapeutic features

Summary of clinical EFFICACY:
NCT05163288 was a double-blind, placebo-controlled, crossover, phase III trial to evaluate the safety and efficacy of L-acetylleucine for the treatment of NPC.
Eligible pts. were ≥4 years of age with a confirmed diagnosis of NPC. Pts. had to have mild to severe symptoms (SARA score between 7 and 34).
Pts. (n=60) were randomly assigned in a 1:1 ratio to receive L-acetylleucine for 12 weeks followed by placebo for 12 weeks (n=30), or placebo for 12 weeks followed by L-acetylleucine (n=30).
L-acetylleucine or matching placebo was administered orally two to three times per day. Pts. aged ≥13 years and weighing ≥15 Kg received 4 gr. per day. The dosage in paediatrics was based on pt.'s body weight (0.1 g/Kg of body weight per day; total of two to four g per day).

The primary endpoint was the total score on the SARA scale (mSARA in the US).
The mean (±SD) baseline SARA total scores that were used in the primary analysis were 15.88±7.50 before receipt of the first dose of L-Acetylleucine and 15.68±7.39 before receipt of the first dose of placebo.

The mean change from baseline in the total score and the least-squares mean difference on the SARA and mSARA are represented in table 1 [3].

Table 1. Primary endpoint

	L-acetylleucine (			Placebo			
	No. of pts. Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	No. of pts. Assessed at End of Treatment Period	Score at End of Treatment Period	Change from Baseline	Least-squares mean difference
SARA	59	13.71±7.68	−1.97±2.43	58	15.2±7.27	−0.60±2.39	−1.28 points; 95% CI, −1.91 to −0.65; P<0.001
mSARA	59	11.37±5.81	−1.66±1.97	58	12.47±5.34	−0.67±1.74	*

*the analysis of mSARA total score was considered to be ancillary, and the results are reported without a P value for the between-group differences.

Summary of clinical SAFETY:
A total of 79 AEs occurred in 36 pts. when they were receiving L-Acetylleucine, and 75 events occurred in 30 pts, when they were receiving placebo. No AEs led to premature discontinuation of the trial. The incidence of upper respiratory tract infection was higher in pts. receiving L-Acetylleucine (10%) vs. those receiving placebo (5%).
The incidence of falls was lower in pts. receiving L-Acetylleucine (7%) than in those receiving placebo (15%). No SAEs were considered by investigators to be related to L-Acetylleucine or placebo. One death occurred but it was not related to trial treatment [3].

Ongoing studies:
- ***For the same indication:*** Yes
- ***For other indications:*** Yes

Discontinued studies (for the same indication): No

References:
[1] https://www.ema.europa.eu/en/medicines/human/EPAR/aqneursa
[2] https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/219132s000lbl.pdf
[3] https://www.nejm.org/doi/full/10.1056/NEJMoa2310151
[4] https://www.orpha.net/en/disease/detail/646
[5] https://www.sciencedirect.com/science/article/abs/pii/S1071909121000073

NHS impact

Cost of therapy:
Not yet available.

Epidemiology:
Prevalence at birth of Niemann-Pick disease type C ranges between 1/45,000-286,000 worldwide [4].

POSSIBLE PLACE IN THERAPY:
At present, drug treatment options for pts. with NPC are limited. Symptom management can be addressed through supportive measures. Miglustat, a glycosphingolipid synthesis inhibitor, is the only drug approved in the EU and in >40 countries worldwide but not the US [5].

L-Acetylleucine could represent a new opportunity for these pts.

OTHER INDICATIONS IN DEVELOPMENT: Ataxia-Telangiectasia (NCT03759678); Tay-Sachs and Sandhoff Disease (NCT03759665).

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT: -
OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:
Tanespimycin (NCT00514371);
Aplidin (NCT01102426);
Venetoclax (NCT02755597)

*Service reorganization: No
*Possible off label use: Yes