PRIOR AUTHORIZATION POLICY

POLICY: Niemann-Pick Disease Type C – Aqneursa Prior Authorization Policy
- Aqneursa™ (levacetylleucine for oral suspension – IntraBio)

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OVERVIEW

Aqneursa, a modified amino acid, is indicated for the treatment of neurological manifestations of **Niemann Pick disease type C** (NPC) in patients weighing ≥ 15 kg.[1]

Disease Overview

NPC is an autosomal recessive, progressive lysosomal storage disorder.[5] NPC is considered an ultra-rare disease with an estimated incidence of 1 in 100,000 live births; however, this is thought to underestimate individuals with later onset disease.[4-6] NPC is caused by mutations in NPC1 (90% to 95%) or NPC2 (5%) that yield deficient function of the corresponding proteins that normally bind and transport cholesterol.[6] The lysosomal dysfunction in NPC leads to an accumulation of lipids in the brain, liver, and spleen.

The presentation of NPC is heterogeneous characterized by visceral, neurological, or psychiatric symptoms that may present at any age with variable rates of progression.[4] Patients have difficulties with walking, swallowing, speaking, concentration, and/or memory. The age of onset of neurological symptoms predicts the severity of the disease and determines life expectancy; NPC is classified according to the age of onset of neurological manifestations. Three forms of NPC are described: 1) visceral-neurodegenerative (< 2 years [early infantile]); 2) neurodegenerative (2 to 6 years [late infantile] and 6 to 15 years [juvenile]; and 3) psychiatric-neurodegenerative (> 15 years [adults]). Patients with the adolescent/adult-onset neurological form are estimated to represent ≥ 20% of cases of NPC, and due to longer survival, likely make up the largest patient group in terms of disease prevalence. The spectrum of NPC ranges from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease. In addition, atypical presentations (fatal systemic perinatal form and initial systemic disease) constitute a small, but significant, proportion of cases.

Clinical Efficacy

The efficacy of Aqneursa was established in one Phase III, randomized, double-blind, placebo-controlled, crossover, multicenter, pivotal study in patients ≥ 4 years of age and ≥ 15 kg with at least mild disease-related neurologic symptoms and a confirmed diagnosis of NPC (n = 60).[1-3] In the US, it was required that patients had genetically confirmed NPC as evidenced by either a positive genetic test for mutations in both copies of NPC1 or a positive genetic test for mutations in both copies of NPC2.[2] Patients were randomized to one of two treatment sequences: Sequence 1 (n = 30), Aqneursa in Period 1 (12 weeks), followed by immediate crossover to placebo in Period 2 (12 weeks); or Sequence 2 (n = 30), placebo in Period 1 (12 weeks), followed by immediate crossover to Aqneursa in Period 2 (12 weeks). Concurrent use of miglustat (Zavesca®, generic) was allowed; 85% of patients were taking miglustat. Most patients were ≥ 18 years of age (62%; age range 5 to 67 years). Disease severity ranged from mild to moderate. The largest group of patients had juvenile-onset NPC, around one-quarter of patients had late infantile-onset NPC, and another one-quarter had adolescent- or adult-onset NPC; a small number had early infantile NPC.

The primary efficacy endpoint outside of the US was the total score on the Scale for Assessment and Rating of Ataxia (SARA) assessed after 12 weeks of treatment with Aqneursa; in the US, the primary endpoint was the modified SARA (mSARA) score.[2] The SARA is an eight-item clinical rating scale (gait, stance, sitting, speech disturbance, finger-chase test, nose-to-finger test, fast-alternating-hand-movements test, and

heel-along-shin slide); scores range from 0 to 40 with lower scores indicating better neurological status. The mSARA excludes sitting and stance domains from the SARA and scores range from 0 to 30, with lower scores indicating better neurologic status. A 1-point change in the SARA total score is considered a clinically meaningful transition, reflecting gain or loss of complex function (e.g., clinically meaningful improvement at ≥ -1 point, or a clinically meaningful worsening of ≥ +1 point).[10] The mean baseline SARA score was 15.88 points and the mean baseline mSARA score was 13.20 points.

At Week 12 (end of Period 1), the mean change from baseline in the SARA total score was significantly greater with Aqneursa vs. placebo -1.97 points vs. -0.60 points, respectively (least squares [LS] mean difference -1.28 points; 95% confidence interval [CI]: -1.91, -0.65; P < 0.001).[2] The mean change in mSARA was similar to the mean change in the SARA total score. For patients taking miglustat (n = 50), the difference in change from baseline SARA total score favored Aqneursa vs. placebo (LS mean difference -1.47 points; 95% CI: -2.16, -0.78). For patients not taking miglustat (n = 9), the 95% CI for the mean difference in change from baseline SARA total score crossed the threshold for unity (difference -0.61 points; 95% CI: -1.88, 0.66), but directionally favored Aqneursa. In patients assigned to Sequence 1, neurologic symptoms progressed when Aqneursa was stopped; the mean change in SARA total score from the end of Period 1 to the end of Period 2 was +1.55 points.

Limited extended follow-up data (12 months) are available from an open-label extension phase of the pivotal trial (n = 54).[11] The primary endpoint was the modified 5-domain Niemann-Pick disease type C Severity Scale (NPCCSS) [5-domains include ambulation, speech, fine motor skills, swallow, and cognition; scores range from 0 to 25 with lower scores representing better neurological status]. After 12 months, the mean change from baseline on the 5-domain NPCCSS significantly favored Aqneursa vs. the natural historical cohort (-0.155 points vs. +1.5 points; mean difference 1.56 points; 95% CI: 0.31, 2.92; P < 0.017), corresponding to a 108% reduction in annual disease progression. The results of the 17-domain NPCCSS were supportive of the primary analysis and improvements in neurological status observed in the pivotal trials' primary endpoint (SARA) were sustained during the long-term follow-up.

Guidelines

Consensus clinical management guidelines for NPC have been developed by the International Niemann-Pick Disease Registry (INPDR) project (2018).[4] Disease-modifying therapy is discussed; however, Aqneursa is not addressed. Optimal disease management includes a multidisciplinary team (e.g., primary care physician, metabolic disease specialist, neurologist, psychiatrist, anesthesiologist, neuro-ophthalmologist, neuropsychologist, speech and language therapist, occupational and physical therapists, nutritionist, gastroenterologist, social worker, genetic counselor) based in a specialty care center. The mainstay of therapy is symptom management with disease-modifying agents when available. Patients should be assessed for growth and developmental delay, mobility, swallowing and diet, speech, spasticity, bowel and bladder dysfunction, cataplexy, mental well-being, hypersalivation/drooling, and hearing.

Regarding disease-modifying therapies, all patients with a confirmed diagnosis of NPC should be considered for miglustat (strength of recommendation: 2; level of evidence C; 13% of experts completely agree, 38% mostly agree, 13% partially agree, 25% mostly disagree, and 13% completely disagree).[4] However, there are several instances in which miglustat is not recommended: patients who are pre-symptomatic or have only spleen or liver enlargement, those with advanced neurological disease (e.g., inability to ambulate without a wheelchair, complete lack of verbal communication, swallowing difficulties profound enough to require tube feeding through a percutaneous gastrostomy) or dementia (e.g., need for 24-hour care), and patients with another life-threatening illness with estimated lifespan < 1 year (noted not to be based on evidence). Note: In the US, miglustat is indicated as monotherapy for the treatment of adults with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a

therapeutic option.[8] However, in other countries, it is approved for the management of neurologic manifestations of NPC.[5]

Treatment goals should be established at diagnosis and reviewed regularly (generally every 6 to 12 months) and aimed at improving or maintaining the physical and psychosocial well-being of the patient.[4]

NPC Diagnosis

When NPC is clinically suspected, diagnosis can be confirmed by the combination of biochemical and molecular genetic studies.[4] In any individual in whom the diagnosis of NPC is considered based on their clinical manifestations and/or abnormal biomarker profile genetic testing for NPC genes should be conducted to confirm the diagnosis. Mutation analysis of NPC1 and NPC2 genes is mandatory to confirm the diagnosis of NPC. It is also the only reliable method to diagnose NPC carriers within a family and the highly preferred strategy for prenatal diagnosis. The identification of two alleles with known disease-causing mutations in either NPC1 or NPC2 gene confirms the diagnosis of NPC. Approximately 700 NPC1 variants have been reported among which around 420 are considered pathogenic, with only a limited number being common (p.I1061T, pP1007A) or recurrent mutations. Interpretation of new missense and splicing mutations should be undertaken with caution and their pathogenicity must be verified. The presence of very severe mutations (frameshift, nonsense, large deletion) in both alleles often results in early-infantile neurological disease (with a higher risk of severe, possibly fatal, systemic disease). Approximately 26 pathogenic NPC2 mutations have been described. Most are frameshift of nonsense as well as large deletion variants that leads to a severe clinical phenotype. Among the missense mutations in NPC2, two variants (p.V39 M and p.P120S) have been associated with the juvenile or adult forms of the disease. More patients from North Africa, Italy, and Turkey have been identified with NPC2 mutations.

The filipin test is no longer considered a first-line test for the diagnosis of NPC; however, it remains a very useful diagnostic tool in uncertain cases where biomarkers and/or molecular analysis provide inconclusive results and to assess the pathogenicity of novel genetic variants. This assay needs to be performed on cultured fibroblasts from skin biopsies; it is invasive and has a long turnaround time. Furthermore, the assay is technically challenging, labor intensive, and is only performed in specialized laboratories. If only one pathogenic mutation is identified by molecular analysis of NPC1 and NPC2, filipin testing should be performed.

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Aqneursa. All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Aqneursa as well as the monitoring required for adverse events and long-term efficacy, approval requires Aqneursa to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Aqneursa is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Niemann-Pick disease type C.** Approve for the duration noted if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy: Approve for 6 months if the patient meets ALL of the following (i, ii, iii, iv, and v):
     - **i.** Patient is ≥ 4 years of age; AND
     - **ii.** Patient weighs ≥ 15 kg; AND
     - **iii.** Patient has one or more neurologic symptom(s) of Niemann-Pick disease type C; AND
       Note: Examples of neurologic symptoms of Niemann-Pick disease type C are loss of motor function, difficulty swallowing, and speech and cognitive impairment.
     - **iv.** The diagnosis is established by a genetic test showing biallelic pathogenic variants in either the NPC1 gene or NPC2 gene; AND
     - **v.** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, neurologist, or a physician who specializes in the treatment of Niemann-Pick disease type C or related disorders.
   - **B)** Patient is Currently Receiving Aqneursa. Approve for 1 year if the patient meets BOTH of the following (i and ii):
     - **i.** According to the prescriber, patient has derived benefit from treatment defined as disease stabilization, slowed progression, or improvement; AND
     - **ii.** The medication is prescribed by or in consultation with a geneticist, endocrinologist, metabolic disorder subspecialist, neurologist, or a physician who specializes in the treatment of Niemann-Pick disease type C or related disorders.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Aqneursa is not recommended in the following situations:

1. **Ataxia-Telangiectasia.** A multinational, multicenter, open-label, rater-blinded prospective Phase II study is underway to assess the safety and efficacy of levacetylleucine for the treatment of Ataxia-Telangiectasia.[7,9] The primary completion date is anticipated in December 2024. Results are not yet available.

2. **Combination use with Miplyffa (arimoclomol capsules).** Miplyffa, in combination with miglustat is indicated for the treatment of neurologic manifestations of Niemann-Pick disease type C in patients ≥ 2 years of age.[13] There are no data available regarding combination use of Miplyffa and Aqneursa.

3. **GM2 Gangliosidoses**. GM2 gangliosidoses (Tay-Sachs and Sandhoff diseases) are rare, autosomal recessive, neurodegenerative diseases. Levacetylleucine (4 g per day in patients ≥ 13 years of age and weight-based doses for patients 6 to 12 years of age) was evaluated in a Phase IIb multinational, open-label, rater-blinded study in patients ≥ 6 years of age with a genetically confirmed diagnosis of GM2 gangliosidoses (n = 30).[7,8] The study met its Clinical Impression of Change in Severity primary endpoint, as well as secondary measures of ataxia and global impression. Additional study is needed.

4. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Aqneursa™ granules [prescribing information]. Austin, TX: IntraBio; September 2024.
2. Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N-acetyl-L-leucine in Niemann-Pick type C. *N Engl J Med.* 2024;390(5):421-431.
3. Fields T, Bremova-Ertl TM, Billington I, et al. N-acetyl-L leucine for Niemann-Pick type C: a multinational double-blind randomized placebo-controlled crossover study. *Trials*. 2023;24:361.
4. Geberhiwot T, Moro A, Dardis A, et al; on behalf of the International Niemann-Pick Disease Registry (INPDR). Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2018;13:50
5. Patterson M. Niemann-Pick Disease Type C. 2000 Jan 26 [updated 2020 Dec 10]. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
6. Berry-Kravis E. Nieman-Pick disease type C: diagnosis, management and disease-targeted therapies in development. *Semin Pediatric Neurol.* 2021;31:100879.
7. Fields T, Patterson M, Bremova-Ertl T, et al. A master protocol to investigate a novel therapy acetyl-L-leucine for three ultra-rare neurodegenerative diseases: Niemann-Pick type C, the GM2 ganliosidoses, and ataxia telangiectasia. *Trials*. 2021;22:84.
8. Martakis K, Claassen J, Gascon-Bayari J, et al. Efficacy and safety of N-acetyl-L-leucine in children and adults with GM2 gangliosidoses. *Neurology*. 2023;100(10):e1072-e1083.
9. IntraBio. N-Acetyl-L-Leucine for ataxia-telangiectasia. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2024 Sept 25]. Available at: https://clinicaltrials.gov/study/NCT03759678?intr=IB1001&rank=5. NLM Identifier: NCT03759678.
10. Park J, Bremova-Ertl T, Brands M, et al. Assessment of the reliability, responsiveness, and meaningfulness of the scale for the assessment and rating of ataxia (SARA) for lysosomal storage disorders. *J Neurol.* 2024;271(10):6888-6902..
11. Bremova-Ertl T, Ramaswami U, Rohrback M, et al. Long-term findings of N-acetyl-L-leucine for Niemann-Pick disease type C [oral presentation]. Presented at: the 10th Congress of the European Academy of Neurology; Helsinki, Finland; June 29 to July 2, 2024.
12. Data on file. IntraBio. September 26, 2024.
13. Miplyffa™ capsules [prescribing information]. Frederiksberg, Denmark/Celebration, FL: Zevra Denmark A/S/Zevra Therapeutics; September 2024.