Pharmacy Policy Bulletin: J-1423 Niemann Pick Disease Type C – Commercial and Healthcare Reform	
Number: J-1423	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.):** **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-1423-001	**Original Date:** 12/04/2024
Effective Date: 12/20/2024	**Review Date:** 12/04/2024

Drugs Product(s):	• Aqneursa (levacetylleucine) • Miplyffa (arimoclomal)
FDA-Approved Indication(s):	Aqneursa • Treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥ 15 kg. Miplyffa • Treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric 2 years of age and older, in combination with miglustat.

Background:	• The exact mechanism of action for Aqneursa is unknown. It is thought that Aqneursa is taken up by monocarboxylate transporters, correcting metabolic dysfunction and improving adenosine triphosphate energy production. This may then normalize lysosomal dysfunctions. • Miplyffa acts by increasing activation of transcription factor EB (TFEB) and transcription factor E3 (TFE3), upregulating the coordinated lysosomal expression and regulation (*CLEAR*) genes. • Niemann-Pick disease type C is a slowly progressive lysosomal disorder whose significant manifestations are age-dependent. In the perinatal and infancy periods, presentation is predominantly visceral with hepatosplenomegaly, jaundice, and pulmonary infiltrates. From late infancy onward, NPC primarily presents through neurologic manifestations such as ataxia, dysarthria, dysphagia, cognitive impairment, and seizures. Individuals with NPC in childhood experience motor dysfunction and progressive cognitive impairment, which may be mistaken for learning impairment. • NPC is rare; it is estimated that 2.9 in 1 million patients in the U.S. during had the disease between 2015 and 2020. However, it is associated with significant mortality with an average life expectancy of 13 years. • NPC is caused by a mutation in either the NPC1 gene (~95% of cases) or the NPC2 gene (~5%); both genes encode for proteins regulating cellular cholesterol homeostasis. Mutations in either NPC1 or NPC2 proteins impairs cholesterol

	movement from the lysosome, resulting in accumulation of unesterified cholesterol in lysosomes, and subsequent dysregulation of cholesterol homeostasis. However, the connection between dysfunction of cholesterol homeostasis and neurodegeneration is not entirely understood.
	• There is no evidence supporting the efficacy of, or investigating the safety of, concurrent use of Aqneursa and Miplyffa.
	• Prescribing Considerations:
	  ○ Neurological manifestations of NPC may include ataxia, dysarthria, dysphagia, cognitive impairment, and seizures.
	  ○ Aqneursa may cause embryo-fetal toxicity. Advise females of reproductive potential to use effective contraception during treatment and for 7 days after the last dose of Aqneursa if discontinued. Females of reproductive potential should verify that they are not pregnant prior to initiating Aqneursa.
	  ○ For patients with an eGFR ≥ 15 to < 50 mL/minute, Miplyffa, in combination with miglustat, is given twice daily rather than the normal dosing of three times daily.

Approval Criteria

I. Initial Authorization

A. Aqneursa

When a benefit, coverage of Aqneursa may be approved when all of the following criteria are met **(1. through 3.)**:

1. The member has a diagnosis of Neimann-Pick Disease Type C (ICD 10: E75.242), confirmed by the following **(a.)**:
  a. Mutations in the NPC1 or NPC2 genes
2. The member has neurological symptoms of Neimann-Pick Disease Type C (e.g., ataxia, dysarthria, dysphagia, cognitive impairment, seizures).
3. The member weights at least 15 kg.

B. Miplyffa

When a benefit, coverage of Miplyffa may be approved when all of the following criteria are met **(1. through 4.)**:

1. The member has a diagnosis of Neimann-Pick Disease Type C (ICD 10: E75.242), confirmed by the following **(a.)**:
  a. Mutations in the NPC1 or NPC2 genes
2. The member has neurological symptoms of Neimann-Pick Disease Type C (e.g., ataxia, dysarthria, dysphagia, cognitive impairment, seizures).
3. The member is 2 years of age or older.
4. The medication will be used in combination with miglustat.

II. Reauthorization

When a benefit, reauthorization of Aqneursa and Miplyffa may be approved when the following criterion is met **(A.)**:

A. The prescriber attests that the member has experienced positive clinical response to therapy.

III. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Aqneursa and Miplyffa should not be used in combination with each other.
II. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.
III. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy.

Authorization Duration

- Commercial and HCR Plans: If approved, up to a 12 month authorization may be granted.

Automatic Approval Criteria

None

References:

1. Aqneursa [package insert]. Austin, TX: IntraBio; September 2024.
2. Niemann-Pick Disease Type C. GeneReviews. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1296/. Accessed September 30, 2024.
3. Jiang X, Ory DS. Advancing diagnosis and treatment of Niemann-Pick C disease through Biomarker Discovery. *Explor Neuroprotective Ther*. 2021 Dec 9:146-158.
4. Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of *N*-Acetyl-l-Leucine in Niemann-Pick Disease Type C. *N Engl J Med*. 2024 Feb 1;390(5):421-431.
5. Burton BK, Ellis AG, Orr B, et al. Estimating the prevalence of Niemann-Pick Disease Type C (NPC) in the United States. *Mol Genet Metab*. 2021;134(1-2):182-187.
6. Miplyffa [package insert]. Celebration, FL: Zevra Therapeutics; September 2024.
7. DRUGDEX System (Micromedex 2.0). Greenwood Village, CO: Truven Health Analytics; 2024.
8. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2018 Apr 6;13(1):50.