PHARMACY COVERAGE GUIDELINE

Medications for Niemann-Pick Disease type C: AQNEURSA™ (levacetylleucine) oral suspension MIPLYFFA™ (arimoclomol) capsules Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

AQNEURSA (levacetylleucine)

➢ **Criteria for initial therapy:** Aqneursa (levacetylleucine) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Pediatrician

2. Individual is 4 years of age weighing at least 15 kg

3. Individual has a confirmed diagnosis of neurological manifestations of Niemann-Pick disease type C (NPC)

4. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate
    a. Has clinical signs and symptoms of at least one neurological manifestations of Niemann-Pick disease type C (e.g., but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia)
    b. **ONE** of the following:
        i. Genetic confirmation of a pathogenic variants/mutation involving **both** alleles of *NPC1* or *NPC2*
        ii. Genetic confirmation of a pathogenic variants/mutation involving **one** allele of *NPC1* or *NPC2* plus **either**:
            1. Abnormal biomarker screening for oxysterols (e.g., cholestane triol assay, C-triol bile acid derivative)
            2. Skin biopsy with fibroblast culture and filipin staining
    c. There is documentation of a negative pregnancy test in a woman of childbearing potential

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual is not currently taking other drugs that may cause a severe adverse reaction or a significant drug interactions that may require discontinuation such as:
    a. N-acetyl-DL-leucine
    b. N-acetyl-D-leucine

7. Aqneursa (levacetylleucine) will not be used concurrently with Miplyffa (arimoclomol)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Aqneursa (levacetylleucine) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Pediatrician

2. Individual has a confirmed diagnosis of neurological manifestations of Niemann-Pick disease type C (NPC)

3. Individual's condition has responded while on therapy with response defined as improvements or stabilization in ambulation, fine motor skills, swallowing, cognition, and speech

4. Individual has been adherent with the medication

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Individual is not currently taking other drugs that may cause a severe adverse reaction or a significant drug interactions that may require discontinuation such as:
   a. N-acetyl-DL-leucine
   b. N-acetyl-D-leucine

7. Aqneursa (levacetylleucine) will not be used concurrently with Miplyffa (arimoclomol)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

MIPLYFFA (arimoclomol)

- **Criteria for initial therapy:** Miplyffa (arimoclomol) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Pediatrician

2. Individual is 2 years of age or older

3. Individual has a confirmed diagnosis of neurological manifestations of Niemann-Pick disease type C (NPC)

4. Requested agent will be used in combination with miglustat

5. Individual has received and completed **ALL** the following **baseline tests** before initiation of treatment and with continued monitoring of the individual as clinically appropriate
   a. Has clinical signs and symptoms of at least one neurological manifestations of Niemann-Pick disease type C (e.g., but not limited to, hearing loss, vertical supranuclear gaze palsy, ataxia, dementia, dystonia, seizures, dysarthria, or dysphagia)
   b. **ONE** of the following:

i. Genetic confirmation of a pathogenic variants/mutation involving **both** alleles of *NPC1* or *NPC2*
ii. Genetic confirmation of a pathogenic variants/mutation involving **one** allele of *NPC1* or *NPC2* plus **either**:
    1. Abnormal biomarker screening for oxysterols (e.g., cholestane triol assay, C-triol bile acid derivative)
    2. Skin biopsy with fibroblast culture and filipin staining

6. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

7. Miplyffa (arimoclomol) will not be used concurrently with Aqneursa (levacetylleucine)

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Miplyffa (arimoclomol) and/or generic equivalent (if available) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Neurologist, Pediatrician

2. Individual has a confirmed diagnosis of neurological manifestations of Niemann-Pick disease type C (NPC)

3. Individual's condition has responded while on therapy with response defined as improvements or stabilization in ambulation, fine motor skills, swallowing, cognition, and speech

4. Individual has been adherent with the medication

5. **If available:** Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Miplyffa (arimoclomol) will not be used concurrently with Aqneursa (levacetylleucine)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

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Medications for Niemann-Pick Disease type C: AQNEURSA™ (levacetylleucine) oral suspension MIPLYFFA™ (arimoclomol) capsules Generic Equivalent (if available)

2. **Off-Label Use of Cancer Medications**

Description:

Miplyffa (arimoclomol) is indicated for use in combination with miglustat for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older. The mechanism(s) by which arimoclomol exerts its clinical effects in patients with NPC is unknown.

Aqneursa (levacetylleucine) is indicated for the treatment of neurological manifestations of Niemann-Pick disease type C (NPD-C) in adults and pediatric individuals weighing ≥15 kg. Levacetylleucine, a modified amino acid, is also known as N-acetyl-l-leucine (NALL) the L-enantiomer of N-acetyl-dl-leucine. The distinct molecular target for levacetylleucine in the treatment of NPD-C is unknown. A relationship was not observed between increasing levacetylleucine exposure and clinical efficacy. The time course of pharmacodynamic response is unknown. Levacetylleucine is metabolized into acetate and L-leucine by ubiquitously expressed enzymes, which are used endogenously in catabolic and metabolic pathways. Cytochrome P450 enzymes are not involved in the metabolism of levacetylleucine.

Niemann-Pick disease (NPD) is a group of autosomal recessive disorders associated with splenomegaly, variable neurologic deficits, and the storage of lipids including sphingomyelin and cholesterol. NPD is also known as sphingomyelin-cholesterol lipidosis. There are three types of NPD: Niemann-Pick disease type A (NPD-A), Niemann-Pick disease type B (NPD-B), and Niemann-Pick disease type C (NPD-C).

NPD-C is caused by pathogenic variants of the *NPC1* and *NPC2* genes that result in impaired cellular processing and transport of low-density lipoprotein (LDL) cholesterol and other macromolecules, including glycosphingolipids. The diagnosis of NPD-C is suspected based upon the clinical features and biomarker screening for oxysterols; it is confirmed when genetic testing identifies both disease-causing alleles in *NPC1* or *NPC2*. *NPC1* and *NPC2* proteins are involved in cholesterol efflux from late lysosomal and endosomal compartments and regulate cholesterol content within membranes.

NPD-C has a wide phenotypic spectrum. Onset can range from *in utero*, infancy, childhood, or adulthood. Prenatal cases present with fetal ascites. Neonatal onset occurs with severe hepatic disease and/or respiratory failure. Neonates may have hypotonia and developmental delay with little or no hepatic and pulmonary involvement. Most cases of NPD-C have an onset in middle to late childhood after normal early development. Neurologic manifestations include cerebellar involvement (clumsiness, gait problems, eventual frank ataxia), vertical supranuclear ophthalmoplegia, and slowly progressive cognitive deterioration. Dystonia, dysarthria, dysphagia and seizures are common. Death typically occurs from aspiration pneumonia in the second or third decade of life. Adult onset is usually similar to juvenile/childhood cases but with slower progression. Adult cases may also present with cognitive dysfunction or psychiatric disturbances.

Safety and effectiveness of Miplyffa (arimoclomol) was assessed in a randomized, double- blind, placebo controlled, 12-month trial in individuals 2 to 19 years of age who had a molecularly confirmed diagnosis of NPC (NCT02612129). Fifty patients were randomized 2:1 to treatment with weight-adjusted Miplyffa (arimoclomol) (31 to 124 mg) or placebo orally three times per day. The randomization was stratified by miglustat use status at

baseline. In the trial, 76% and 81% of individuals in the Miplyffa (arimoclomol) and placebo groups, respectively, received miglustat six months or longer prior to the time of enrollment.

Efficacy assessment of Miplyffa (arimoclomol) included the rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score, which was performed at baseline and every 3 months until 12 months of treatment. The R4DNPCCSS is a measure of NPC disease progression that consists of the four items assessing ambulation, speech, swallow, and fine motor skills that individuals with NPD-C and their caregivers and physicians have identified as most relevant with higher scores representing greater severity of disease. The fifth domain of NPCCSS cognition was not assessed. The mean baseline R4DNPCCSS score was higher in the Miplyffa (arimoclomol) group (n=26; mean=8.9) than the placebo group (n=13; mean=7), with an overall mean R4DNPCCSS score of 8.3. The change from baseline to month 12 was in the arimoclomol group was -0.2 and the change in the placebo group was 1.9 resulting in a placebo-subtracted difference of -2.2. There were insufficient data to determine the effectiveness of the use of Miplyffa (arimoclomol) without miglustat for the treatment of neurological manifestations in patients with NPD-C.

The safety and efficacy of Aqneursa (levacetylleucine) for the treatment of NPD-C were evaluated in a randomized, double-blind, placebo-controlled, two-period crossover study (NCT05163288) that evaluated the efficacy of Aqneursa (levacetylleucine) in 60 individuals (37 adults and 23 pediatric individuals weighing ≥ 15 kg). To be eligible for the study, individuals had to be aged 4 years or older with a confirmed diagnosis of NPD-C. The median age at treatment was 25 years (range: 5 to 67 years). Individuals were required to have at least mild disease-related neurological symptoms.

The primary efficacy outcome of levacetylleucine was assessed using a modified version of the Scale for Assessment and Rating of Ataxia (SARA), referred to as the functional SARA (fSARA). The SARA is a clinical assessment tool that assesses gait, stability, speech, and upper and lower limb coordination across 8 individual domains. The fSARA consists only of gait, sitting, stance, and speech disturbance domains of the original SARA with modifications to the scoring responses. Each domain was rescored from 0 to 4, where 0 is the best neurological status and 4 the worst, with a total score ranging from 0 to 16. The estimated treatment difference for the fSARA total score was -0.4 (95% CI: -0.7, -0.2). At 12 weeks, treatment with levacetylleucine led to a greater decrease in the SARA total score compared with placebo (least-squares mean difference -1.28; 95% CI -1.91 to -0.65); a difference of more than 1 point on the SARA total score is considered clinically meaningful.

Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

5-domain Niemann-Pick type C Clinical Severity Scale (NPCCSS)		
Domain	**Scoring**	**Minimum-Maximum Score**
Ambulation	0 = Normal 1 = Clumsy 2 = Ataxic unassisted gait or not walking by 18 months 4 = Assisted ambulation or not walking by 24 months	0-5

	5 = Wheelchair dependent	
Fine Motor Skills	0 = Normal 1 = Slight dysmetria/dystonia (independent manipulation) 2 = Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty) 4 = Moderate dysmetria/dystonia (limited fine motor skills, difficulty feeding self) 5 = Severe dysmetria/Dystonia (gross motor limitation, requires assistance for selfcare activities)	0-5
Swallow	0 = Normal, no dysphagia 1 = Cough while eating Intermittent dysphagia* + 1 = w/Liquids + 1 = w/Solids Dysphagia* + 2 = w/Liquids + 2 = w/Solids 4 = Nasogastric tube or gastric tube for supplemental feeding 5 = Nasogastric tube or gastric tube feeding only	0-5
Cognition	0 = Normal 1 = Mild learning delay, grade appropriate for age 2 = 3 = Moderate learning delay, individualized curriculum or modified work setting 4 = Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function 5 = Minimal cognitive function	0-5
Speech	0 = Normal 1 = Mild dysarthria (easily understood) 2 = Severe dysarthria (difficult to understand) 3 = Non-verbal/functional communication skills for needs 5 = Minimal communication	0-5
5-domain NPCCSS score	Sum of all scores from the 5-domains above	0-25 (higher score = more severe clinical impairment)
* Score is additive (to the “cough while eating”-score of 1) within the two subsections of intermittent dysphagia and dysphagia (example: for intermittent dysphagia with solids and dysphagia with liquids a score of 4 applies (1 + 1 + 2))		

Scale for the Assessment and Rating of Ataxia (SARA)

SARA is a clinical scale which assesses a range of different impairments in cerebellar ataxia. The SARA is a tool for assessing ataxia. It has eight categories with accumulative score ranging from 0 (no ataxia) to 40 (most severe ataxia). When completing the outcome measure each category is assessed and scored accordingly. Scores for the eight items range as follows:

1. Gait (0-8 points)
2. Stance (0-6 points)
3. Sitting (0-4 points)
4. Speech disturbance (0-6 points)
5. Finger chase (0-4 points)

6. Nose-finger test (0-4 points)
7. Fast alternating hand movement (0-4 points)
8. Heel-shin slide (0-4 points)

Once each of the 8 categories have been assessed, the total is calculated to determine the severity of ataxia. For motor activities of the four extremities (items 5-8), assessments are performed bilaterally, and the mean values are used to obtain the total score.

Resources:

Miplyffa (arimoclomol) capsules product information, revised by Acer Therapeutics, Inc. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 23, 2024

Aqneursa (levacetylleucine) oral suspension product information, revised by IntraBio, Inc. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed October 23, 2024.

Schiffmann R. Overview of Niemann-Pick Disease. In: UpToDate, Nordli DR, Dashe JF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through September 2024. Topic last updated March 12, 2024. Accessed October 23, 2024.

Mengel E, Bembi B, del Toro M, et al.: Clinical disease progression and biomarkers in Niemann-Pick disease type C: A prospective cohort study. Orphanet J Rare Dis (2020) 15:328. https://doi.org/10.1186/s13023-020-01616-0. Accessed October 23, 2024.

Patterson MC, Lloyd-Price L, Guldberg C, et al.: Validation of the 5-domain Niemann-Pick type C Clinical Severity Scale. Orphanet J Rare Dis (2021) 16:79. https://doi.org/10.1186/s13023-021-01719-2. Accessed October 23, 2024.

Mengek E, Patterson MC, Da Riol RM, et al.: Efficacy and safety of arimoclomol in Niemann-Pick disease type C: Results from a double-blinded, randomized, placebo-controlled, multinational phase 2/3 trial of a novel treatment. J Inherit Metab Dis. 2021; 44:1463–1480. Accessed October 23, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT02612129: Arimoclomol Prospective Double-blind, Randomized, Placebo-controlled Study in Patients Diagnosed With Niemann-Pick Disease Type C. Available from: http://clinicaltrials.gov. Last update posted May 13, 2024. Last verified May 2024. Accessed October 23, 2024.

Bremova-Ertl T, Claassen J, Foltan T, et al. Efficacy and safety of N-acetyl-L-leucine in Niemann-Pick disease type C. J Neurol 2022; 269:1651-1652. Accessed October 23, 2024.

Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N-Acetyl-l-Leucine in Niemann-Pick Disease Type C. NEJM 2024 Feb 1; 390 (5):421-431. Accessed October 23, 2024.

ClinicalTrials.gov Bethesda (MD): National Library of Medicine (US). Identifier NCT05163288: Effects of N-Acetyl-L-Leucine on Niemann-Pick Disease Type C (NPC): A Phase III, Randomized, Placebo-controlled, Double-blind, Crossover Study. Available from: http://clinicaltrials.gov. Last update posted September 13, 2023. Last verified September 2023. Accessed October 23, 2024.