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Revised: 00/00/00

Subject: Levacetylleucin (Aqneursa) Oral Suspension

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Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Niemann-Pick disease type C (NPC) is a rare, progressive autosomal recessive lysosomal storage disorder which results in the accumulation of cholesterol and other fatty substances within various tissues of the body, including brain tissue. The clinical presentation of NPC varies based on age and may include visceral, neurologic, and psychiatric symptoms. Children with NPC 2 years of age and younger are classified as perinatal and early-infantile disease and present with liver disease and prolonged neonatal jaundice, hepatosplenomegaly, and developmental delay. Children with NPC aged 2 years to early adolescence are classified as late-infantile or juvenile-onset disease and present with neurological manifestations (e.g., clumsiness, progressive ataxia, dysarthria, dystonia), hepatomegaly or splenomegaly, and vertical supranuclear gaze palsy, which is considered the clinical hallmark of the disorder. Lastly, adolescents greater than 15 years old and adults are classified as adolescent/adult-onset disease and present with atypical psychotic disorder, progressive neurologic symptoms (e.g., ataxia, dystonia, dysarthria) and vertical supranuclear gaze palsy. Unfortunately, diagnosis may be delayed due to the variable age of onset and various symptoms.

Genetic testing is used to confirm the diagnosis through the *NPC1* gene (NPC type 1C) or *NPC2* gene (NPC type 2C) sequencing, two genes that are known to cause NPC. Biallelic variants in either of the two genes result in the same clinical disease. If two known or likely pathogenic alleles are present, then the diagnosis is confirmed. If sequencing shows two pathogenic alleles with 1 or 2 potential variants of unknown significance, then disease is possible and a filipin test is conducted. If the filipin test is highly positive with 'classical' staining or moderately positive with 'variant' staining, then NPC is considered confirmed, and if “mildly” stained, then it is likely not NPC but may be possible NPC heterozygote. Until recently, treatment options were limited and included miglustat (Yargesa, Zavesca) at 100 – 200 mg by mouth once to three times per day along with symptomatic management and the patient’s needs (e.g.,

physical and speech therapy). On September 24, 2024, the FDA approved levacetylleucin (Aqneursa) oral suspension for the treatment of neurological manifestations of NPC in adults and pediatric patients weighing greater than or equal to 15 kg.

The safety and effectiveness of levacetylleucin (Aqneursa) was evaluated in a randomized, double-blind, placebo-controlled, crossover study in 60 patients. Enrollment criteria included patients aged 4 years or older with a confirmed diagnosis of NPC. Patients were required to have at least mild disease-related neurological symptoms. Patients were assessed over a 2-week baseline period. Patients were then randomized in a 1:1 ratio to one of the two treatment sequences: Treatment Sequence 1 (N=30) with levacetylleucin treatment in Period I then crossover to placebo in Period II or Treatment Sequence 2 (N=30) with placebo in Period I then crossover to levacetylleucin treatment in Period II. Levacetylleucin (Aqneursa) and placebo were administered orally with or without food for 12 weeks in each crossover period. Patients aged ≥13 years received 4 gram per day (as 2 gram morning dose, 1 gram afternoon dose, and 1 gram evening dose), and those less than 13 years were dosed based on body weight. Fifty-nine patients (98%) completed the study and received both placebo and active treatment. One patient withdrew based on healthcare provider decision during levacetylleucin (Aqneursa) treatment. Of the 60 randomized patients (37 adults and 23 pediatric patients), 27 were female and 33 were male. The median age at treatment initiation was 25 years (range: 5 to 67 years). Ninety percent of the patients were Caucasian, 3% Asian, and 7% other. The majority of the patients (n=51, 85%) received miglustat treatment prior to randomization and during the trial. The primary efficacy outcome 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 fSARA score was assessed at baseline, 6 weeks, 12 weeks (the end of Period I), 18 weeks, and 24 weeks (end of Period II). The estimated mean fSARA total score was 5.1 when patients were treated with levacetylleucin (Aqneursa) and 5.6 when patients were treated with placebo. The estimated treatment difference for the fSARA total score was -0.4 (95% CI: -0.7, -0.2) (Table 1).

Table 1: Summary of fSARA Efficacy Results

Variable	**fSARA Total Score**	
	Treatment Sequence 1: Levacetylleucin - Placebo	Treatment Sequence 2: Placebo - Levacetylleucin
Baseline	N=30	N=30
➢ Mean (SD)	5.2 (3.0)	6.3 (3.3)
Period I	N=29	N=30
➢ Mean (SD)	4.5 (2.6)	6.0 (3.4)
Period II	N=28*	N=30
➢ Mean (SD)	5.1 (2.8)	5.6 (3.1)
Estimated Mean fSARA Score (SE) by Treatment		
Levacetylleucin (Aqneursa)	5.1 (0.1)	
Placebo	5.6 (0.1)	

Treatment Difference (95% CI)	-0.4 (-0.7, -0.2)**

CI = confidence interval; SD = standard deviation; SE = standard error.
* Two patients did not have an assessment at the end of Period II (week 24).
** Two-sided p-value <0.001

The most common adverse reactions with levacetylleucin (Aqneursa) (incidence ≥5% and greater than placebo) are abdominal pain, dysphagia, upper respiratory tract infections, and vomiting.

POSITION STATEMENT:

Comparative Effectiveness

The Food and Drug Administration has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of levacetylleucin (Aqneursa) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is at least 15 kg body weight with a diagnosis of Niemann-Pick disease type C (NPC)
2. One of the following ("a" or "b"): - Laboratory documentation of the genetic testing results must be submitted
    a. Genetic test demonstrating biallelic known or likely pathogenic variants in the *NPC1* or *NPC2* gene
    b. Both of the following ("i" and "ii"):
        i. Genetic test demonstrating two pathogenic alleles with 1 or 2 potential variants of unknown significance in the *NPC1* or *NPC2* gene
        ii. Filipin test is highly positive with 'classical' staining or moderately positive with 'variant' staining
3. **NOT** being administered in combination with arimoclomol (Miplyffa)
4. Negative pregnancy test prior to therapy initiation (only for women of reproductive potential)
5. Prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.
6. Dose does not exceed 4 grams daily

Approval duration: 6 months

Levacetylleucin (Aqneursa) is considered experimental or investigational for any other indications due to insufficient evidence in the peer-reviewed medical literature to support safety, efficacy, and net health outcome.

Continuation of levacetylleucin (Aqneursa) **meets the definition of medical necessity** for members meeting the following criteria:

1. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met ALL indication-specific initiation criteria.
2. Member has a clinical meaningful response (e.g., improvement, stabilization, and/or slowed decline in gait, sitting, stance, and speech disturbance) with no significant adverse drug reactions (e.g., severe hypersensitivity reactions) necessitating discontinuation of therapy.
3. **NOT** being administered in combination with arimoclomol (Miplyffa)
4. Recent negative pregnancy test (only for women of reproductive potential)
5. Prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.
6. Dose does not exceed 4 grams daily

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Levacetylleucin (Aqneursa) is indicated for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥15 kg.
- The recommended oral dosage is based on the patient's actual body weight:

Patient Body Weight	Morning Dose	Afternoon Dose	Evening Dose
15 to <25 kg	1 gram	No dose	1 gram
25 to <35 kg	1 gram	1 gram	1 gram
35 kg or more	2 grams	1 gram	1 gram

- For females of reproductive potential, verify that the patient is not pregnant.
- For oral administration, obtain the required number of levacetylleucin (Aqneursa) packets for the prescribed dose. Open and empty the entire contents of each packet into a container with 40 mL of water, orange juice, or almond milk. Do not use hot liquid. Stir to form a suspension, and then swallow the suspension immediately (within 30 minutes). Discard any unused if not administered within 30 minutes.
- For gastrostomy tube (G-Tube) (French size 18 or larger) administration, obtain the required number of levacetylleucin (Aqneursa) packets for the prescribed dose. Open and empty the entire contents

of each packet into a container with 40 mL of water ONLY. Do not use hot liquid. Stir to form a suspension. Draw up the suspension into a catheter tip syringe and administer the suspension immediately through the G-tube. Flush any residual suspension in the catheter tip syringe with an additional 20 mL of water. Flush the G-tube again, as needed, until no residual suspension is left in the syringe or feeding tube. Discard unused suspension if not administered immediately.

- Avoid concomitant use of levacetylleucin (Aqneursa) with N-acetyl-DL-leucine and N-acetyl-D-leucine. The D-enantiomer, N-acetyl-D-leucine, competes with levacetylleucine for monocarboxylate transporter uptake, which may reduce the levacetylleucine efficacy.

Dose Adjustments

- No dosage adjustments are required for patients with renal or hepatic impairment.

Drug Availability

- Levacetylleucine (Aqneursa) is an oral suspension supplied as white to off-white granules in a unit dose multi-layer aluminum/polyethylene packet. Each packet contains 1.7 gram white to off-white granules, equivalent to 1 gram levacetylleucine, and each carton contains 28 unit-dose packets (NDC 83853-101-01).
- Levacetylleucine (Aqneursa) should be stored at room temperature between 20°C to 25°C (68°F to 77°F); excursion permitted between 15°C to 30°C (59°F to 86°F).

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Embryo-Fetal Toxicity:** Based on findings from animal reproduction studies, levacetylleucine (Aqneursa) may cause embryo-fetal harm when administered during pregnancy. Administration of levacetylleucine to pregnant rats and rabbits during the period of organogenesis caused an increase in embryo-fetal death (post implantation loss/resorption) and skeletal malformations at a dose that was approximately 1.4-fold and 6-fold, respectively, the maximum recommended human dose (MRHD) of 4 g/day of levacetylleucine (based on body surface area). The decision to continue or discontinue levacetylleucine (Aqneursa) treatment during pregnancy should consider the female's need for levacetylleucine (Aqneursa), the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal disease. For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment with levacetylleucine (Aqneursa). Advise females of reproductive potential to use effective contraception during treatment and for 7 days after the last dose if levacetylleucine (Aqneursa) is discontinued.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

E75.242	Niemann-Pick disease type C

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: The following National Coverage Determination (NCD) was reviewed on the last guideline revised date: Self-administered Drug List (A54770). No Local Coverage Determination (LCD) was found at the time of the last guideline revised date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

None

REFERENCES:

1. Aqneursa (levacetylleucin) [package insert]. Austin, TX: IntraBio Inc.; September 2024.
2. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 9/29/24.
3. DRUGDEX System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2024 Sept 29].
4. DynaMed [database online]. Ipswich, MA: EBSCO Information Services.; 2024. URL http://www.dynamed.com. Accessed 9/29/24.

5. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Sept 29]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/09/24.

GUIDELINE UPDATE INFORMATION:

01/01/25	New Medical Coverage Guideline: Levacetylleucin (Aqneursa) oral suspension for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥15 kg.