arimoclomol (Miplyffa™) and levacetylleucine (Aqneursa™)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO318

Description
Arimoclomol (Miplyffa) is a synthetic pyridine derivative that is not currently identified within a specific drug class. Levacetylleucine (Aqneursa) is a is a modified amino acid (N-acetyl-L-leucine; NALL) that uses monocarboxylate transporters to cross the blood-brain barrier and reach the central nervous system.

Length of Authorization
- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
arimoclomol (Miplyffa)	Treat neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older	47 mg capsule	90 capsules/30 days
		62 mg capsule	
		93 mg capsule	
		124 mg capsule	
levacetylleucine (Aqneursa)	Treat neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients weighing ≥15 kg	1 g unit dose packet	112 unit-dose packets/28 days

Initial Evaluation

I. **Arimoclomol (Miplyffa) or levacetylleucine (Aqneursa)** may be considered medically necessary when the following criteria below are met:
   A. The medication is prescribed by, or in consultation with, a neurologist, endocrinologist, metabolic disorder specialist, or a physician specializing in the treatment of Niemann-Pick disease type C; **AND**
   B. Member has a diagnosis of **Niemann-Pick disease type C (NPC)** when the following are met:
      1. Presence of a genetically confirmed mutation in both alleles of NPC1 or NPC2; **OR**
         i. Mutation in only one allele of NPC1 or NPC2 plus either positive filipin staining or elevated cholestane-triol/oxysterols level (i.e., greater than two times the upper limit of normal); **AND**
      2. Member has one or more neurological symptom(s) of Niemann-Pick disease type C (e.g., loss of motor function, difficulty swallowing, speech and cognitive impairment, etc.); **AND**
      3. Member can walk independently or with assistance; **AND**

C. The request is for:
    1. Levacetylleucine (Aqneursa); **AND**
        i. Member is 4 years of age or older; **AND**
        ii. Member weighs 15 kg or more; **AND**
        iii. Levacetylleucine (Aqneursa) will not be used in combination with arimoclomol (Miplyffa); **OR**
    2. Arimoclomol (Miplyffa); **AND**
        i. Member is 2 years of age or older; **AND**
        ii. Member weighs 8 kg or more; **AND**
        iii. The medication will be taken in combination with miglustat*; **AND**
        iv. Arimoclomol (Miplyffa) will not be used in combination with levacetylleucine (Aqneursa)

*Please note: medications notated with an asterisk may require additional review.

II. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) are considered investigational or not medically necessary when used for all other conditions, including but not limited to:
    A. Amyotrophic Lateral Sclerosis
    B. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) used in combination with each other for any indication, including Niemann-Pick disease type C (NPC)
    C. Gaucher Disease
    D. Myositis

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Member's weight is documented; **AND**
IV. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) will not be used in combination with each other; **AND**
V. Member has experienced benefit from treatment defined as disease stabilization or slowed disease progression and treatment provides clinical benefit to the member (e.g., improvement in gait, sitting, stance, speech, fine motor skills, etc.); **AND**
VI. If the request is for arimoclomol (Miplyffa), arimoclomol (Miplyffa) will be used in combination with miglustat*

*Please note: medications notated with an asterisk may require additional review.

Supporting Evidence

I. Niemann-Pick disease type C (NPC) is a rare, inherited lysosomal storage disorder characterized by the abnormal accumulation of cholesterol and other lipids in the cells. These genetic mutations impair the intracellular trafficking of lipids, leading to progressive neurological and hepatic dysfunction. Biomarker profile genetic testing identifying two alleles with known disease-causing mutations in either NPC1 or NPC2 gene confirms the diagnosis of NPC, and is the most reliable way to confirm the diagnosis of NPC. As a neurodegenerative disease with a very heterogeneous presentation, symptoms typically appear in childhood and can include developmental delay, ataxia, seizures, and progressive liver enlargement, with later stages often involving cognitive decline, motor impairment, and difficulty swallowing. The age of onset of neurological symptoms predicts the severity of the disease and determines life expectancy. The prevalence of NPC is estimated to be approximately 1 in 100,000 to 150,000 live births, and it is estimated that there are 900 people in the United States with NPC. The spectrum of NPC ranges from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease. The late-infantile and juvenile-onset forms account for the majority of NPC cases. Across all phenotypes, the median age of death is 13 years (range, 0.1 to 69 years), most often due to respiratory failure.

II. Therapeutic management of NPC primarily focuses on symptom management and slowing disease progression, as there is no cure. Supportive therapies, such as physical and occupational therapy, anti-seizure medications, and interventions to manage liver complications, are often recommended to address specific symptoms. Early diagnosis and intervention are crucial for improving the quality of life and prolonging survival, but the overall prognosis remains poor, particularly in later stages of the disease. Regular monitoring and a multidisciplinary care approach are essential to optimize treatment and manage complications.

III. Miglustat (Opfolda, Yargesa, Zavesca) has been approved in the European Union, Canada, and Japan and is considered a standard of care for treating progressive neurological complications in NPC internationally. Niemann-Pick Type C Guidelines Working Group and the International Niemann-Pick Disease Alliance 2018 consensus clinical management recommend miglustat as an effective and recommended treatment option in the management of existing neurologic manifestations of NPC in children and adults who exhibit symptoms of neurological decline (Strength of recommendation: 2; Level of evidence: C). Clinical evidence suggests that miglustat can help slow the progression of the disease particularly in patients with moderate symptoms or in the early stages of the disease, with effects noted on motor and cognitive functions. Data from a randomized, controlled trial and a retrospective, observational cohort study support the use of miglustat in the treatment of NPC disease in adults and children 12 years and older. Administered orally, miglustat's dosage depends on the patient's age and weight, with treatment often beginning in early childhood for those with signs of neurological involvement. However, common side effects, including gastrointestinal issues such as diarrhea, nausea, and weight loss require careful monitoring. Dose adjustments are often necessary to manage these side effects. Despite miglustat's position as a standard of care, there has been no significant change in the survival of patients with NPC.

IV. From the 2018 International NPC guidelines, "miglustat therapy is not appropriate for patients who have profound neurological disease, which, in the opinion of the attending physician, would make it difficult to assess for any improvements with therapy. Such symptoms may include but are not limited to:

a. Profound dementia resulting in the need for 24 h care
b. Inability to ambulate without a wheelchair
c. Complete lack of verbal communication
d. Swallowing difficulties profound enough to require tube feeding through a per-cutaneous gastrostomy..."

Additionally, the guidelines do not recommend miglustat therapy in the following situations: patients who are pre-symptomatic or only have spleen/liver enlargement, patients with another life-threatening illness with estimated life span less than 1 year (Strength of recommendation: 2; Level of evidence: C).

Arimoclomol (Miplyffa)

V. As of September 2024, there are two FDA-approved therapies for NPC: arimoclomol (Miplyffa) and levacetylleucine (Aqneursa). Arimoclomol (Miplyffa) is an orally administered capsule that is indicated for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients two years of age and older and weigh ≥8kg. The approval of arimoclomol (Miplyffa) was based on data from a Phase 3, randomized, double-blind, placebo-controlled, 12-month trial in patients aged two to 18 years with NPC1 or NPC2. Fifty patients were randomized 2:1 to treatment with weight-adjusted arimoclomol (Miplyffa) (31 to 124 mg) or placebo orally three times per day. Inclusion criteria included participants with at least one neurological sign of NPC, ability to walk independently or with assistance, and on stable dose of miglustat for at least 6 continuous months. Among these 50 patients, 39 (78%) received miglustat as background treatment in the trial. The primary endpoint evaluated a rescored 4-domain NPC Clinical Severity Scale (R4DNPCCSS) score in the patients who used miglustat as their background treatment at 12 months. The R4DNPCCSS is a measure of NPC disease progression that looks at four items that patients with NPC, their caregivers and physicians have identified as most relevant including ambulation, speech, swallow and fine motor skills. Higher scores signify a greater severity of the disease. A 0.2-point decrease on the R4DNPCCSS was observed in patients who received arimoclomol (Miplyffa) in combination with miglustat, compared with an increase of 1.9 points in patients who received placebo with miglustat. Secondary endpoints (change from baseline in CGI-I, R4DNPCCSS, 17-domain NPCCSS, NPC-cdb, EQ-5D-y, 9HPT, SARA) were assessed and found to be not statistically significant. While the primary outcome was assessed via a validated assessment tool, the quality of evidence is considered low as there are several uncertainties that remain including lack of additional well-designed confirmatory trials, lack of a well-established MOA, unknown effectiveness without miglustat, and a small population size that could impact the interpretability of the rescored R4NPCCSS which limit the durability of results. Although arimoclomol (Miplyffa) showed a

statistically significant difference in the modified R4DNPCCSS score, the effect of treatment was relatively small. The most common adverse reactions in arimoclomol (Miplyffa)-treated patients (≥15%) were upper respiratory tract infection, diarrhea, and decreased weight. Serious adverse reactions reported in arimoclomol (Miplyffa)-treated patients were three hypersensitivity reactions including urticaria and angioedema. Three (6%) of the arimoclomol (Miplyffa)-treated patients had the following adverse reactions that led to withdrawal: increased serum creatinine (one patient), and progressive urticaria and angioedema (two patients). One patient in the arimoclomol group died, assessed as related to NPC progression. There are no specific contraindications to using arimoclomol (Miplyffa); however, warnings and precautions include: hypersensitivity reactions, embryofetal toxicity, and increase creatinine.

VI. Arimoclomol (Miplyffa) is administered orally three times daily, with or without food, and is dosed based on patient body weight (see appendix for dosing). Arimoclomol (Miplyffa) must be administered with miglustat. There are limited data to determine the efficacy of arimoclomol (Miplyffa) without miglustat at this time.

Levacetylleucine (Aqneursa)

VII. Levacetylleucine (Aqneursa) is available as orally dosed unit packets given three times daily to treat neurological manifestations of NPC in adults and pediatric patients weighing ≥15 kg. The approval of levacetylleucine (Aqneursa) was based on data from a Phase 3, randomized, double-blind, placebo-controlled, two-period crossover study, which evaluated 12 weeks of levacetylleucine (Aqneursa) therapy in two groups. Patients were randomized in a 1:1 ratio to one of the two treatment sequences:

- Treatment Sequence 1 (N=30): levacetylleucine (Aqneursa) in Treatment Period I, followed by immediate crossover to placebo in Treatment Period II
- Treatment Sequence 2 (N=30): placebo in Treatment Period I, followed by immediate crossover to levacetylleucine (Aqneursa) in Treatment Period II

Most participants continued to receive background miglustat throughout the trial. Although the FDA label does not mandate the concurrent administration of miglustat with levacetylleucine (Aqneursa), it is probable that healthcare providers will choose to continue miglustat therapy when prescribing levacetylleucine (Aqneursa) as a majority of participants in the pivotal clinical trial were on concomitant miglustat (85%). Key inclusion criteria included patients aged four years or older, weighing >15kg, with a confirmed diagnosis of NPC, and at least mild disease-related neurological symptoms (SARA score between 7 – 34). The primary outcome was the functional Scale for the Assessment and Rating of Ataxia (fSARA). The estimated mean fSARA total score was 5.1 when patients were treated with Aqneursa and 5.6 when treated with placebo with an estimated treatment difference for the fSARA total score at −0.4 (95% CI (−0.7, −0.2); p<0.001). Most common adverse reactions (incidence ≥5%) in levacetylleucine (Aqneursa)-treated patients were abdominal pain, dysphagia, upper respiratory tract infections, and vomiting. Three patients had transient adverse events that were judged to be related to treatment (anal incontinence, restless-leg, rosacea). No serious adverse events occurred that

were considered by an investigator to be related to levacetylleucine (Aqneursa) or placebo. One death was due to aspiration pneumonia after a preplanned placement of a percutaneous endoscopic gastrostomy tube and therefore was not related to trial treatment. There are no specific contraindications, but embryo-fetal toxicity is listed as a warning and precaution to using levacetylleucine (Aqneursa).

VIII. Although levacetylleucine (Aqneursa) showed a statistically significant difference in fSARA score, the clinical significance of these results are of low confidence. Considering NPC is a neurodegenerative disease with a very heterogeneous presentation, the short trial duration is a limitation of the study as a 12-week duration may not have been enough to be able to demonstrate benefit in a patient who is not progressing quickly and may explain why the treatment effect was small, albeit statistically significant. While the observed average treatment effect in fSARA is -0.45, at least a 1-point improvement in any of the four fSARA domains were seen more often when subjects received levacetylleucine (Aqneursa) than received placebo. As improvements in neurological symptoms would not be expected given the known natural history of NPC, this change is considered to be clinically meaningful. Furthermore, the two treatment sequences had significantly different baseline fSARA scores and the primary outcome analysis averaged the levacetylleucine (Aqneursa) response in each sequence. Extended follow-up data up to 12 months was presented at the European Academy of Neurology Congress in 2024 that evaluated 54 patients on levacetylleucine (Aqneursa). At 12 months, the mean change from baseline on the 5-domain Niemann-Pick disease type C Clinical Severity Scale (NPCCSS) was −0.115 in the levacetylleucine (Aqneursa) arm and 1.5 ± 3.1 in the historical cohort (mean difference 1.56; 95% CI, 0.31–2.92; P < 0.017). Given the limited data available, it is difficult to reliably determine whether there was a further decrease in fSARA as time on therapy increased. Longer-term data will help to ascertain treatment benefits.

IX. Due to differences in trial design, a formal cross-trial comparison of the pivotal trials for levacetylleucine (Aqneursa) and arimoclomol (Miplyffa) is not possible. Both treatments are backed by a single small, relatively short randomized clinical trial, with each demonstrating a statistically significant but modest difference in the primary outcome. However, even a 1- to 2-point difference on each scale can lead to a meaningful improvement in a patient's quality of life.

Investigational or Not Medically Necessary Uses

I. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Amyotrophic Lateral Sclerosis
   B. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) used in combination with each other for any indication, including Niemann-Pick disease type C (NPC)
      i. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) have distinct mechanisms of action, although the exact ways in which they produce clinical effects in NPC

are not fully understood. Sequential or combined use of Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) has not been studied in clinical trials, there is currently no evidence to support a synergistic effect, additive benefits, or assess safety when arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) are used combination.

C. Gaucher Disease
D. Myositis

Appendix

I. Arimoclomol (Miplyffa) dosing recommendation

Table 1. Recommended Dosage of Arimoclomol (Miplyffa) Based on Body Weight (kg)	
Patient Body Weight	Recommended Dosage
8 - 15 kg	47 mg three times a day
>15 - 30 kg	62 mg three times a day
>30 - 55 kg	93 mg three times a day
>55 kg	124 mg three times a day

a. Miplyffa capsules may be swallowed whole or the contents of the capsule can be added to a suitable beverage, soft food, or added to water to allow administration via a feeding tube
b. For patients with an eGFR 15 to < 50 mL/minute, the recommended oral dosage of arimoclomol (Miplyffa) in combination with miglustat is based on actual body weight and given twice daily.

II. Levacetylleucine (Aqneursa) recommended dosage: supplied in unit dose packets, each containing 1 g of levacetylleucine as granules for oral suspension

Table 2. Recommended Dosage of Levacetylleucine Based on Body Weight (kg)				
Body Weight (kg)	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose
15 to <25 kg	1g	No dose	1g	2g
25 to <35 kg	1g	1g	1g	3g
35 kg or more	2g	1g	1g	4g

a. Aqneursa packets can be added to water, orange juice, or almond milk. Contents can be administered via gastronomy tube (G-tube) by mixing with water.

III. While not FDA-approved, miglustat dosing is based on the doses studied in clinical trials/compendia and dose approved in the European Union for NPC. Miglustat use requires careful monitoring for side effects and regular treatment adjustments to optimize patient outcomes. Some forms of miglustat (Opfolda) are available in 65-mg capsules, therefore certain treatment regimens may not allow for exact dosing. *Please refer to updated clinical compendia for dosing recommendations. Generic miglustat along with brand (Opfolda, Yargesa, Zavesca) may require additional clinical review and prior authorization criteria to be met.*

Table 3. Off-label dosing for miglustat based on clinical compendia		
Patient population	BSA	Miglustat dose
<12 years of age	BSA ≤0.47 m^2	100 mg once daily
	BSA >0.47 to 0.73 m^2	100 mg 2 times daily
	BSA >0.73 to 0.88 m^2	100 mg 3 times daily
	BSA >0.88 to 1.25 m^2	200 mg 2 times daily
	BSA >1.25 m^2	200 mg 3 times daily
≥12 years of age and older	-	200 mg 3 times daily

IV. BSA (m^2) = $\sqrt{\frac{\text{height (cm) x weight (kg)}}{3600}}$

References

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2. AQNEURSA. Package Insert. IntraBio Inc.; September 2024.
3. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis*. 2018;13(1):50.
4. Burton BK, 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.
5. Cortina-Borja M, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. *Orphanet J Rare Dis*. 2018;13(1):143.
6. Mengel E, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: results from a double-blind, randomized, placebo-controlled, multinational phase 2/3 trial of a novel treatment. *J Inheri Metab Dis.* 2021;44(6):1463–1480.
7. Patterson MC, et al. Validation of the 5-domain Niemann-Pick type C clinical severity scale. *Orphanet J Rare Dis.* 2021;16(79):1–9.
8. 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;390(5):421-431.
9. Martakis K, et al. Long-term findings of N-acetyl-L-leucine for Niemann-Pick disease type C. *Neuropediatrics*. 2024;55(S01):S1–S25.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
miglustat (Opfolda, Yargesa, Zavesca) and eliglustat (Cerdelga) Policy	Niemann-Pick disease type C *(off-label)*

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	02/2025