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New Drug Evaluations: Miplyffa™ (arimoclomol) capsules, Aqneursa™ (levacetylleucine) oral suspension
Medications for Niemann-Pick Disease Type C

Date of Review: December 2025
Generic Name: arimoclomol
Generic Name: levacetylleucine

End Date of Literature Search: 10/08/25
Brand Name (Manufacturer): Miplyffa (Zevra Therapeutics)
Brand Name (Manufacturer): Aqneursa (IntraBio)

Dossier Received: MIPLYFFA (yes); AQNEURSA (no)

Plain Language Summary:

- Niemann-Pick Disease type C is a rare condition passed down in families that causes many different symptoms. Many people have trouble walking due to loss of muscle control, or other problems such as seizures or dementia. Symptoms can start anytime from infancy to adulthood and get worse over time. There is no cure.
- The Food and Drug Administration has approved 2 medicines to treat Niemann-Pick disease type C. These medicines have been studied in a small number of people. Most had the diagnosis confirmed with genetic testing.
    - Arimoclomol is a medicine that people take 3 times a day by mouth or feeding tube. After 12 months, people taking arimoclomol with another medicine called miglustat had a small improvement in symptoms compared to people taking placebo with miglustat. Arimoclomol was only studied in people who developed symptoms as babies or during childhood.
    - Levacetylleucine is a medicine that people take 2 to 3 times a day by mouth or feeding tube. After 12 weeks, people taking levacetylleucine had a small improvement in some symptoms compared to people who took a placebo. The survey doctors used to evaluate symptoms was different from the survey people took with arimoclomol. Most people were also taking miglustat.
- There is not enough information to determine if one medicine is better than another or if arimoclomol and levacetylleucine work better or are safe to take at the same time.
- These medicines have not been studied in very many people, and their long-term safety beyond 12 months compared to placebo is unknown.
- We recommend that the Oregon Health Authority pay for arimoclomol and levacetylleucine when the provider documents why someone needs these medicines. This process is called prior authorization.

Research Questions:

1. What is the evidence for efficacy and safety for medications for Niemann-Pick disease type C (NPC)?
2. Are there any differences in efficacy and harms for the medications for NPC for certain demographic subtypes (e.g., age of onset, concomitant miglustat, symptom types, or other demographic differences)?

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Conclusions:

- Evidence for arimoclomol and levacetylleucine safety and efficacy in patients with NPC was evaluated in one phase II/III trial and one phase III trial. Arimoclomol is approved by the Food and Drug Administration (FDA) in combination with miglustat for neurological manifestations of NPC in patients 2 years of age and older. Levacetylleucine is FDA-approved for neurological manifestations of NPC in adult and pediatric patients weighing at least 15 kg.[1,2]
- Miglustat is an off-label therapy for NPC that has some evidence for improving symptoms and is recommended for many patients with NPC by experts.[3,4]
- There is low-certainty evidence from one 12-month, double-blind, phase II/III, randomized controlled trial (RCT) of patients age 2 to 19 years (n=50) that, when combined treatment with miglustat, arimoclomol improves symptoms of NPC compared to placebo combined with miglustat.[5] There was a statistically significant difference in the baseline to 12-month change in 4-domain NPC Clinical Severity Scale (NPCCSS; range 0 to 20, higher scores indicate more severe impairment) in those taking baseline miglustat and arimoclomol (change -0.2) compared to patients taking placebo and miglustat (1.9; difference -2.2, 95% confidence interval [CI] -3.8 to -0.6).[5] The FDA determined the subgroup without miglustat had insufficient evidence to support use of arimoclomol monotherapy for NPC.[6] This trial had methodological concerns with the endpoint which underwent alteration by the FDA as well as concerns with the standardization of procedures across trial sites which may reduce reliability of the results.[6,7]
- There is low-certainty evidence from one randomized, double-blind, phase III, crossover trial that levacetylleucine improves ataxia symptoms over 12 weeks in patients 4 years of age and older with NPC (n=60) weighing at least 15 kg.[8] Using the Scale for the Assessment and Rating of Ataxia (SARA; range 0 to 40, with lower scores indicating better neurologic status), mean change from baseline in the SARA total score was −1.97 points after 12 weeks of levacetylleucine and −0.60 points after 12 weeks of receiving placebo (least-squares mean (LSM) difference, −1.28 points; 95% CI, −1.91 to −0.65; P<0.001).[8] Using the functional SARA (fSARA) as an alternative, FDA requested endpoint, mean fSARA score was statistically significantly lower for levacetylleucine (fSARA 5.1) compared to placebo (fSARA 5.6; difference -0.4, 95% CI -0.7 to -0.2; P<0.001), though it is unclear if this is clinically meaningful.[8] This trial had methodological concerns with the endpoint which underwent alteration at FDA request and is of short duration for assessment of a chronic progressive condition.[4]
- There is no comparative data between treatments of arimoclomol with miglustat versus levacetylleucine.
- There is insufficient evidence of the efficacy and safety of combination therapy of arimoclomol used with levacetylleucine.
- There is insufficient evidence arimoclomol with miglustat is effective for adolescent- or adult-onset NPC. It is unclear if there are differences in efficacy and safety of either drug for other subtypes of NPC based on age of onset or specific mutation.
- There were no significant safety signals with either medication, but data is limited by small sample sizes and short study durations of placebo control. Both are thought to be embryo-fetal toxic and should be avoided in patients who may become pregnant.[1,2]

Recommendations:

- Make arimoclomol and levacetylleucine non-preferred on the Oregon Health Plan (OHP) Preferred Drug list (PDL).
- Implement prior authorization (PA) for high cost treatments for Niemann-Pick disease type C.
- Implement separate miglustat PA for 100 mg formulation with corresponding updates to PA criteria for Pompe Disease and Gaucher disease.
- After evaluation of costs in executive session, miglustat (Zavesca®) brand was made preferred.

Background:

Niemann-Pick disease is an autosomal recessive disease with three distinct pathologies of type A, B, and C. Type A and B are acid sphingomyelinase deficiencies caused by mutations on the SMPD1 gene.[9] Type C affects roughly 1 in 100,000 to 150,000 people, though it may be underrecognized.[3,9] It is a neurological disorder which results from mutations on NPC1 and NPC2 genes with the C1 subtype affecting more than 90% of those with NPC.[10] It is most common in

populations from Nova Scotia.[10] Different types of mutations are possible, including missense, splicing, frameshift, or premature stop mutations.[5] Presence of stop mutations on both alleles is associated with severe disease progression and early onset, while other genotype/phenotype relationships have not been consistently described.[5] These mutations result in abnormal cholesterol trafficking and esterification. Toxic cholesterol accumulates in the lysosome and results in cell damage.[10] There is no cure for NPC. The disease symptoms vary by type and age of onset. Those developing symptoms as infants often have more aggressive disease than those presenting later in life as adolescents or adults.[5]

NPC may present anytime between the neonatal period and adulthood, and patients with later onset may live up to 70 years.[9] It is associated with a number of signs and symptoms. Common symptoms include inability to look up and down, difficulty walking, difficulty swallowing, and progressive loss of vision and hearing.[10] Liver involvement is common and may include neonatal cholestasis, hepatosplenomegaly, acute liver failure, cirrhosis, and hepatocellular carcinoma.[10] Neurologic involvement with neurodegeneration results in cerebellar ataxia, dysarthria, dysphagia, and progressive dementia.[9] Patients may have seizures, cataplexy, narcolepsy, and dystonia. Adult-onset patients may be misdiagnosed with other hereditary ataxic disorders.[9] Other organs may also be affected including bone marrow and lungs, though direct lung involvement is more common with other types of Niemann-Pick disease.[9] Aspiration pneumonia is a problematic complication as the disease progresses.

Patients can be divided into four phenotypic forms: fetal and early infantile, late infantile, juvenile, and adolescent/adult-onset.[9] The fetal and early infantile form often presents with fetal hydrops and ascites and is usually fatal within 5 years. The late infantile form usually presents with seizures and other neurological manifestations; lifespan is generally 7 to 12 years. The juvenile form of mid to late childhood is most common and may begin with school difficulties, ataxia, and loss of motor abilities. Seizures and dementia develop later, and splenomegaly is common. Prognosis ranges from late teen years to 30 years old, sometimes longer. Those with the adolescent/adult-onset form typically have a gradual onset of disease. Patients may have psychosis, mild ataxia, dystonia, dysarthria, cognitive dysfunction. Epilepsy is possible but rare in adult-onset patients.[9] Diagnosis can be difficult due to the varying presentations and similarities with other conditions (e.g., Huntington disease, Wilson disease, Friedreich ataxia, etc.). Biomarkers can be used to aid with diagnosis, which should be confirmed with genetic testing and possibly a filipin test.[3]

Miglustat is approved as treatment for neurological manifestations of NPC in Europe, Japan, and Canada.[4,5] It works as a substrate reduction treatment to reduce accumulation of glycosphingolipid in the lysosome.[9] Miglustat has United States (US) approval for some forms of Gaucher disease in adults (100 mg formulation) and in certain patients with Pompe disease (65 mg formulation).[11] It is considered off-label in the US for NPC.[5] Miglustat has been studied in several trials in people with NPC, including RCTs and multiyear long-term longitudinal cohorts. Efficacy may be improved in those with juvenile and adult-onset NPC compared to infantile onset.[9] Guidelines from 2018 developed by NPC experts from Europe, Australia, and North America made a weak recommendation that all NPC patients be considered for miglustat therapy based on low-quality evidence.[3] There was significant disagreement amongst the experts making this recommendation.[3] There was more uniformity among experts that pre-symptomatic patients or those who only have spleen/liver enlargement should not be offered miglustat (weak recommendation, low-quality evidence), that it should not be started in those with advanced neurological disease/dementia (weak recommendation, low-quality evidence), and that it should not be started in NPC patients with another life threatening illness with estimated life span of less than 1 year (weak recommendation, low-quality evidence).[3] The FDA has stated miglustat is considered standard of care in adult and pediatric patients with NPC by experts.[4] Dosing ranges from 100 mg daily to 200 mg given three times daily, based on age and body surface area.[11] Most other options are supportive in nature such as mobility aids and rehabilitation for strength and balance, or medications to treat symptoms such as spasticity, hypersalivation, epilepsy, and cataplexy.[9] Epilepsy should be treated by a specialist as some medications, including carbamazepine and vigabatrin, may aggravate the disease.[3]

There are several scales used globally for NPC clinical care. The NPCCSS is a clinician-reported outcome measure which was based on a 4-domain NPC specific disability scale. It was broadened to a 17-domain severity scale to characterize and quantify disease severity and progression for ongoing patient monitoring and was validated for clinical assessment of disease over a one year time period NPC patients (range 0 to 54).[6,8] It includes 9 major domains (ambulation, cognition, eye movement, fine motor, hearing, memory, seizures, speech, and swallowing) and 8 minor domains (auditory brainstem response, behavior, gelastic cataplexy, hyperreflexia, incontinence, narcolepsy, psychiatric, and respiratory problems). Major domains include a clinically reported 0 to 5 ordinal scale; minor domains have a 0 to 2 response scale. Higher numbers indicate greater clinical severity. The FDA has noted several concerns with this instrument.[6] The cognition domain response options may be dependent on a patient's educational and employment services, and the overlapping clinical presentations cannot be interpreted as distinct states of cognitive function.[6] The FDA does not consider the cognition score fit-for-purpose for use in regulatory decision making.[6] Additionally, the response categories may not be fully linear with several domains having no response category for certain values. For example, a score of 3 for ambulation is not a possible response option (**Appendix 3**).[6]

The Scale for the Assessment and Rating of Ataxia (SARA) is an 8-domain rating scale (range 0-40) reported to be reliable and valid with high internal consistency when used for patients with cerebellar ataxias but has not been validated in NPC. It measures symptom and ataxia severity where higher numbers correspond to worsening disease. SARA domains include gait, speech disturbance, finger chase, nose-finger test, fast alternating hand movement, heel-shin slide, stance, and sitting.[12] Different domains account for different total points (e.g., gait has 9 points, speech has 7 points).[4] The modified SARA (mSARA; range 0-30) omits the stance and sitting domains. During clinical trials for levacetylleucine, the FDA requested rescoring of categories to allow all domains to have equal points, and recommended use of the functional SARA (fSARA, range 0 to 16) as a trial endpoint.[2,4] The fSARA includes only the domains of gait, stance, sitting, and speech.[4] A minimally clinically important difference (MCID) for NPCCSS was not identified, a 1 point difference in SARA may be clinically significant.[8] Modified versions of this assessment tool (mSARA and fSARA) are not validated.

Beginning in January 2026, the Oregon Health Authority is proposing that high cost medications for rare conditions be carved out of Coordinated Care Organization (CCO) payments and billed directly to fee-for-service (FFS). Medications can be included in this carve-out if they meet the following criteria:

1. Estimated acquisition cost of more than $500,000 per member over a 12-month period
2. Are indicated for rare conditions, and
3. Have few alternatives, as determined by the Oregon Health Authority

Both arimoclomol and levacetylleucine are currently included in the list of medications proposed to be carved-out of CCO budgets. Over a 1 year period from 4/1/24 to 3/31/25, there were 8 Oregon Health Plan members with a diagnosis indicating NPC in their medical claims.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations. Pharmacology and Pharmacokinetic Properties are listed in **Appendix 2**.

Clinical Efficacy:

<u>Arimoclomol</u>

Arimoclomol is FDA-approved in combination with miglustat for the treatment of neurological manifestations of NPC in patients 2 years of age and older.[1] It is a small molecule given orally that is able to cross the blood brain barrier with detectable levels in the cerebrospinal fluid.[5] While the mechanism of action is not fully understood,[1] it is thought to affect the heat shock response and prevent misfolding of proteins which may preserve cellular function and prevent cell death in cells with lysosomal stress.[5]

Arimoclomol originally received a complete response letter (i.e., denial of approval) from the FDA in June 2021.[6] This denial was based on questions about the inclusion and validity of the cognition domain in the primary efficacy endpoint, change in NPCCSS, of the pivotal trial.[6] Additionally, there were scoring concerns around the swallow domain ("*whether the response options overlapped, were ordered to reflect increasing disease severity, and allowed for comprehensive assessment of swallowing, including silent aspiration*"), standardization of procedures used to administer the NPCCSS, and the concerns regarding if scoring of speech, fine motor, and ambulation domains were non-linear with overlapping scoring of adjacent responses.[6] The application was resubmitted in December 2023, where it was approved based on additional information provided and a public advisory committee (i.e., Genetic Metabolic Diseases Advisory Committee) meeting.[6] In the resubmission, the cognitive domain was excluded from the primary efficacy endpoint and swallow scoring was revised.[6,7] The FDA noted that lack of standardized procedures for this symptom assessments reduces confidence in reliability of results and scoring consistency between clinicians and within the same clinician over time.[6] The speech, fine motor, and ambulation domains were accepted in the resubmission, though it was noted that the NPCCSS would be improved by creating linear severity scoring with non-overlapping options.[6]

The trial used for both FDA approval submissions (NCT02612129) was a 12-month, randomized, placebo-controlled, double-blind, phase 2/3 trial using the 5-domain NPCCSS score as the primary endpoint.[5] As described above, a 4-domain version was used in the revised submission leading to FDA approval after omission of the cognitive domain (range 0 to 20, higher scores indication more severe impairment).[6] The full 17-domain NPCCSS was administered during trial visits.[5] Clinical Global Impression-Improvement scale (CGI-I) scores were used to assess overall health.[5] After stratification by baseline miglustat use, patients were randomized to weight-adjusted arimoclomol (n=34) or matching placebo (n=16) given orally three times a daily, in addition to routine clinical care.[5] Just over half of the patients (n=27) were previously enrolled in an observational study of natural disease course.[5] Patients attended 6 trial visits over 12-months.[5] Most patients (n=41) then opted to enroll in the open-label extension study through month 36.[5] Sample size and trial duration were informed by feasibility rather than sample size calculation.[5]

Predefined subgroup analyses were included for those above or below 4 years old, and those with or without baseline miglustat.[5] There was a statistically significant difference in the baseline to 12-month change in 4-domain NPCCSS in those taking baseline miglustat and arimoclomol (change -0.2), while the placebo group on miglustat score worsened (1.9; difference -2.2, 95% CI -3.8 to -0.6).[5] The FDA determined the subgroup without miglustat had insufficient evidence to support use of arimoclomol monotherapy for NPC.[6] The 5-domain NPCCSS in the original protocol showed similar results to the 4-domain NPCCSS for the full treatment population (**Table 3**), while the CGI-I responder rate showed no difference.[5]

In addition to the concerns raised by the FDA review regarding the NPCCSS tool and assessment procedures, other bias was noted (**Table 3**). Attrition was different between groups (arimoclomol 20.6% vs. 6.3% placebo) and there was an "early escape clause" allowing unblinding of patients with rapid progression.[5] Two arimoclomol patients were unblinded and further evaluations at study visits were not included in the analysis.[5] Missing data imputation was not done for the primary efficacy analysis.[5] There were some baseline differences in the initial NPCCSS score with higher scores in the arimoclomol group in all 5 domains.[5] There were no patients with adolescent-adult onset disease included in the study.[5]

<u>Levacetylleucine (N-acetyl-L-leucine)</u>

Levacetylleucine has an FDA indication for treatment of neurological manifestations of NPC in adults and pediatric patients weighing at least 15 kg.[2] It is the L-enantiomer of an acetylated amino acid and is the prodrug of leucine, an essential amino acid.[12] While the mechanism of action is unknown,[2] it crosses the blood-brain barrier and is thought to enter enzyme-controlled pathways that correct metabolic dysfunction and improve energy production of adenosine triphosphate.[8] This may improve lysosomal dysfunction and potentially reduce storage of unesterified cholesterol and sphingolipids.[8]

Approval was primarily based on a 12-week, double-blind, placebo-controlled, randomized, crossover trial in patients 4 years and older with NPC.[8,12] The trial was originally designed to assess total score on the SARA (range 0 to 40) where lower scores indicate better neurological status.[8,12] The authors report a modified SARA (mSARA) score was requested by the FDA, excluding sitting and stance domains and including the remaining 6 domains (range 0 to 30).[8,12] However, the FDA review reports that the tool modification request for was the fSARA (range 0-16) to be used, including the domains of gait, stance, sitting, and speech and rescored for each domain to include the same score weight.[2,4] The Agency stated that the excluded "*neurological exam findings do not directly assess the patient's ability to function, nor do they reflect clinically meaningful change in a patient's ability to perform daily functions, making them unsuitable for inclusion in a primary efficacy endpoint to convey clinical benefit."*[4] The Agency responded by rescoring the desired response categories *"to create the same number of response categories across each domain… to ensure equal representation of each domain in the total score and interpretability of a 1-point change as clinically meaningful".*[4] The trial was powered at 80% to detect a 1.0 point difference in total SARA score.[8] Most patients opted to continue in the open-label extension study after completion of the initial trial.[8]

A total of 60 total patients with NPC and baseline SARA scores of 7 to 34 were randomized to each treatment sequence with immediate crossover at 12 weeks.[8] Patients ranged from 5 to 67 years of age and weighed at least 15 kg.[8] The LSM difference from baseline was improved after 12 weeks for the levacetylleucine period (Change -1.97) compared to the placebo period (Change -0.6; LSM difference -1.28, 95% CI -1.91 to -0.65).[8] The mean fSARA score was also improved for levacetylleucine (fSARA 5.1) compared to placebo (fSARA 5.6) with a small difference between groups (LSM difference -0.4, 95% CI -0.7 to -0.2; P<0.001).[8] The NPCCSS was included as an exploratory endpoint and showed no statistically significant difference in score change (Levacetylleucine -0.3, Placebo 0.1; difference -0.5, 95% CI -1.2 t 0.2), though NPCCSS is validated for changes over a 1-year period rather than 12 weeks.[8] The FDA subgroup analysis of patients based on miglustat at baseline did not identify a statistical difference in fSARA compared to those not on baseline miglustat. However, the patient group was extremely small (n=4 first trial period, n=5 second trial period after crossover) and the study was not powered to show differences between subgroups.[8]

It is unclear if the crossover design, with no washout between crossover, is most appropriate for a progressive disease. Trial duration was short in setting of a long-term, progressive condition. While statistically significant, it is unclear if the less than 1.0 point difference in the fSARA between treatment groups is clinically significant.

Clinical Safety:

Arimoclomol

Three patients withdrew due to adverse events (urticaria, angioedema, increased serum creatinine).[5] One death occurred in the active treatment group.[5] One placebo treated patient withdrew due to worsening epilepsy, which was considered part of disease progression.[5] Six arimoclomol treated patients had serum creatinine increases of more than 1.5-fold, with 2 patients with levels more than double the baseline value.[5] Arimoclomol is known to cause a reversible rise in serum creatinine by inhibiting a transporter and reducing creatinine secretion into the kidneys.[5] While there are no listed contraindications, there are warnings about hypersensitivity reactions (e.g., urticaria, angioedema), risk for embryo-fetal toxicity due to high anticipated fetal exposure and increased rates of post-implantation loss noted in animal studies, and risk for increased creatinine without effect on glomerular function (mean increase 10-20% above baseline).[1]

Adverse events occurring more often than placebo in the subgroup receiving both arimoclomol and miglustat are found in **Table 1**. The study population was limited to 19 years and younger, any differences in safety in the adult population are unknown.

Table 1. Adverse Events Occurring in at Least 8% of Patients on Arimoclomol and Miglustat[1]

Adverse event	**Arimoclomol and miglustat N=26 n (%)**	**Placebo and miglustat N=13 n (%)**
Upper respiratory tract infection	8 (31)	2 (15)
Diarrhea	6 (23)	3 (23)
Decreased weight	4 (15)	0
Decreased appetite	3 (12)	0
Tremor	3 (12)	0
Urticaria (with or without angioedema)	3 (12)	0
Headache	3 (12)	1 (8)
Lower respiratory tract infection	3 (12)	1 (8)
Seizure	3 (12)	1 (8)

Levacetylleucine (N-acetyl-L-leucine)

One patient withdrawal and death occurred after complications of gastrostomy tube placement followed by aspiration pneumonia, unrelated to treatment.[8] Four patients experienced thrombocytopenia during the trial.[8] All were on concomitant miglustat and 2 had thrombocytopenia present at baseline. One patient experienced an exacerbation of rosacea during therapy that responded to treatment.[8] The composite rate of infections and infestations was more than 5% higher for levacetylleucine (16/60, 26.7%) than placebo (12/59, 20.3%).[8] Concomitant use with the racemic mixture or isolated D-enantiomer (e.g., N-acetyl-D-leucine or N-acetyl-DL-leucine) would compete for binding sites and be expected to reduce efficacy.[2] Levacetylleucine is a p-glycoprotein inhibitor; concomitant use of p-glycoprotein transport substrates may also cause altered drug levels and increased risk for adverse reactions.[2]

The crossover design without washout and small overall trial size limits interpretation of some safety data. **Table 2** presents adverse events from the first trial period before crossover. There are no labeled contraindications, and labeling includes a warning regarding risk of embryo-fetal toxicity based on higher rates of embryo-fetal death and skeletal malformations in animal studies.[2]

Table 2. Adverse Events Occurring in at Least 5% of Patients on Levacetylleucine During the First Half of The Trial[2]

Adverse event	**Levacetylleucine N=30 n (%)**	**Placebo N=30 n (%)**
Upper respiratory tract infection	5 (17%)	1 (3%)
Abdominal pain	2 (7%)	0 (0%)
Dysphagia	2 (7%)	0 (0%)
Vomiting	2 (7%)	0 (0%)

Look-alike / Sound-alike Error Risk Potential: N-acetyl-D-leucine or N-acetyl-DL-leucine; Migalastat

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Mortality
2) Quality of Life
3) Functional status
4) Neurologic function
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Change in NPCCSS 4- or 5- domain scale over time
2) Change in SARA or fSARA scale over time

Table 3. Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Mengel et al. NCT02612129[5,6] DB, PC, RCT, MC Phase 2/3 2:1 randomization Stratified by miglustat use at baseline	1. Arimoclomol weight adjusted orally/feeding tube three times daily (16 mg, 31 mg, 62 mg capsules; dose 93 to 372 mg/day) 2. Placebo orally/feeding tube 3 times daily 12 m duration	Demographics: -Female: 52% -NPC1 mutation on both alleles: 100% -Miglustat use at baseline: 78% -Mean age: 11.1 y (range 2-19) -White: 90% -Age at first neurologic symptoms ◊ Prenatal: 2% ◊ Early-infantile: 16% ◊ Late-infantile: 48% ◊ Juvenile: 34% ◊ Adolescent/Adult: 0% -H/O Seizure: 28% Key Inclusion Criteria: -NPC diagnosis (molecularly confirmed) -2 to 19 years old -stable miglustat dosing x 6m (if prescribed) -Minimum 1 neurologic sign of disease -Walk independently or with assistance Key Exclusion Criteria: -Other trial participation (exception: non-interventional registries) -Severe liver or renal insufficiency -Other investigational product within 4 weeks -Severe, uncontrolled epileptic seizures -Neurologically asymptomatic	ITT: 1. 34 2. 16 PP: 1. 27 2. 15 Attrition: 1. 7 (20.6%) 2. 1 (6.3%) Miglustat subgroup: 1. 22 2. 12	Primary Endpoint: 4-domain NPCCSS from baseline at 12 m in miglustat subgroup (FDA) 1. -0.2 2. 1.9 Difference -2.2 (95% CI -3.8 to –0.6) 5-domain NPCCSS change from baseline at 12 m (original protocol) 1. 0.76 (95% CI, -0.05 to 1.56) 2. 2.15 (95% CI, 1.05 to 3.25) Difference -1.4 (95% CI, -2.76 to -0.03) p-value=0.046 Secondary Endpoint: CGI-I at 12 m responder (stable or improved) 1. 20/34 (58.8%) 2. 9/16 (56.3%) Difference 2.6% (95% CI, -26.8 to 32.0) P=1.000	NA	Any TEAE: 1. 30/34 (88.2%) 2. 12/16 (75.0%) Serious TEAE*: 1. 5/34 (14.7%) 2. 5/16 (31.3%) Vomiting: 1. 8/34 (23.5%) 2. 4/16 (25.0%) Withdraw due to AE 1. 3 2. 1 Death 1. 1 (NPC progression) 2. 0	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Randomized via interactive response technology stratified by age and baseline miglustat use.. Some unbalance in baseline NPCCSS score with higher scores in the active drug group (NPCCSS full scale median difference 6 points, median difference 5-domain NPCCSS score 3.5 points. Performance Bias: (Low) Placebo capsules matched composition, texture, appearance, solubility, smell, and flavor of active drug. Unblinded DSMB allowed for "early escape clause" for rapid disease progression and use of "rescue" arimoclomol treatment initiation with exclusion from future efficacy assessment. Serum creatinine reviewed by independent expert to avoid accidental unblinding as arimoclomol causes reversible increase in SCr due to transport inhibition. Detection Bias: (High) Clinicians provided with NPCCSS scoring manual and training. Caregivers were not trained but caregiver reports were often used to provide assessments. Caregivers did not have daily diaries. There were no instructions on the order of assessments of NPCCSS and SARA assessments and certain NPCCSS domains were notably higher on visits when SARA was also given. Most (84%) baseline CGI-I scores were completed retrospectively. Sample size and trial duration informed by feasibility rather than sample size calculation. Attrition Bias: (High) Uneven attrition. Option for "early escape clause" unblinding used for 2 arimoclomol patients with rapid progression. Missing data not imputed for primary analysis but included in sensitivity analysis. Reporting Bias: (Unclear) Unclear given outcome changes after trial initiation and data lock, though varying NPCCSS versions generally had similar findings Other Bias: (Unclear) Funding by Orphazyme A/S (original manufacturer) **Applicability**: Patient: No adolescent-adult onset patients (who typically have slower disease progression) included. All patients had preexisting neurological signs of disease. Most on miglustat at baseline and all were ambulatory. Roughly half of study population recruited from preceding observational study of disease progression, potentially indicating they had NPC forms with slower overall disease progression than overall infantile and juvenile NPC population.

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Date: December 2025

								Intervention: Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Miglustat dosing not reported. Comparator: Placebo appropriate with allowance of miglustat co-administration. Outcomes: Significant concerns around appropriateness of endpoint voiced by FDA and modifications mandated. MCID unclear. Setting: 14 sites in 9 countries (Europe and US) from June 2016 to June 2018
2. Bremova-Ertl et al. NCT05163288[4,8,12] DB, PC, crossover, RCT, MC Phase 3 1:1 randomization	1. N-acetyl-L-leucine then crossover to placebo 2. Placebo then crossover to N-acetyl-L-leucine Weight based dosing: - ≥ 13 y or 4 to 12 y and ≥35 kg: 2g AM, 1g afternoon, 1g PM - 4 to 12y and 25 to < 53 kg: 1g AM, 1 g afternoon, 1g PM - 4 to 12y and 15 to 25 kg: 1 g AM, 1g PM Granules for oral suspension in a sachet suspended in 40 mL water, orange juice, or almond milk given using study provided measuring cup.	Demographics: -Age Range 5 to 67 y -Age < 18 y: 38% -Female 45% -White 90% -Age at diagnosis: <2y 15% 2 to <6y 23% 6 to <15y 38% ≥ 15y 23% -Mean NPC duration 171 months -Miglustat Use 85% -Baseline SARA 1. 15.88 2. 15.68 Key Inclusion Criteria: -NPC diagnosis (US: confirmed with genetic testing. Non-US: Clinical features plus genetic test, or positive biomarker screen and/or filipin test without genetic test, or positive biomarker screen and/or filipin test with genetic test identifying only one NPC mutation.) -Age 4 y or more -performed washout of other agents x 42 d (miglustat allowed) -SARA score 7 to 34 (out of 40) PLUS EITHER	N=60, crossover design ITT: 1. 60 2. 59 ITT with score at end of treatment period: 1. 59 2. 58	Primary Endpoint: SARA at end of each 12-week period Mean (SD) 1. -1.97±2.43 2. -0.6±2.39 LSM difference -1.28 (95% CI, -1.91 to -0.65) P<0.001 Mean fSARA at end of each 12-week period 1. 5.1 2. 5.6 Difference -0.45 (95% CI, -0.7 to -0.19) P<0.001		TEAE: 1. 36 (60.0%) 2. 30 (50.8%) Withdrawal/ Death 1 patient during first half of trial (PEG tube placement complication with aspiration pneumonia)		**Risk of Bias (low/high/unclear)**: Selection Bias: (Low) Centrally randomized with Medpace ClinTrack Interactive Response Technology web-based system with permuted block design. Baseline demographics by treatment order not reported. Performance Bias: (Low) Matching placebo granules for oral suspension. Double-blind assignment maintained until database lock. Compliance assessed with review of unused sachets returned by patients. Detection Bias: (High) Crossover design may not be appropriate for progressive disease, though overall treatment period was short and progression may be minimal. No washout period occurred between different treatment periods of trial which could affect results from second half of trial. Modifications to primary endpoint after data collection. Attrition Bias: (Low) Mixed-effects model with 'missing at random' assumption used for missing data. Reporting Bias: (Unclear) Protocol published. Differing information regarding requests for endpoint adjustment between FDA and trial authors/manufacturer. Other Bias: (Unclear) Funded by IntraBio (trial design, drug supply, contracted out data analyses [Cetara]) **Applicability**: Patient: Subtype by age mixed, unclear if treatment more effective in any specific subtype of NPC. Baseline scores ~15-16 on 40 point scale Intervention: Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Comparator: Placebo appropriate with allowance of miglustat. Dosing appropriate based on prior studies. Product acceptable for administration via feeding tube. Outcomes: Significant concerns around appropriateness of endpoint voiced by FDA and modifications mandated. The clinical significance of a 0.45 improvement on n fSARA is unclear. Setting: 13 sites (Australia, Europe, US)

	12-week duration for each treatment then crossover	2-7 of SARA gait subtest OR able to perform 9HPT-D in 20 to 150 seconds (SCAFI subtest) -Weight ≥ 15 kg -If childbearing/siring potential, using defined effective birth control. <u>Key Exclusion Criteria</u>: -Allergy to Acetyl-leucine or derivatives or known excipients used in research product. -Participation in other medication research trial within 42 days -Severe, uncorrectable vision, hearing impairment, arthritis, or other musculoskeletal disorder which interferes with assessments						

<u>Abbreviations</u>: AE = adverse event; AM = morning; ARR = absolute risk reduction; CGI-I = Clinical Global Impression-Improvement scale; CI = confidence interval; DSMB = data safety monitory board; FDA = Food and Drug Administration; fSARA = functional Scale for Assessment and Rating of Ataxia; H/O = history of; ITT = intention to treat; LSM = least squared mean; m= month; MCID = minimum clinically important difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NPC = Niemann- Pick disease type C; NPCCSS = 5-domain NPC clinical severity scale; PEG = percutaneous endoscopic gastrostomy; PM = evening; PP = per protocol; R4DNPCCSS = rescored 4-domain NPC Clinical Severity Scale; SARA = Scale for Assessment and Rating of Ataxia; SCAFI = Spinocerebellar Ataxia Functional Index; SCr = serum creatinine; SD = standard deviation; TEAE = treatment emergent adverse events; US = United States; y=year; 9HPT-D = 9-Hole Peg Test with dominant hand.
*All considered related to NPC except those leading to discontinuation

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Appendix 1: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use MIPLYFFA™ safely and effectively. See full prescribing information for MIPLYFFA.

MIPLYFFA (arimoclomol) capsules, for oral use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
MIPLYFFA 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. (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended MIPLYFFA oral dosage, in combination with miglustat, for patients with actual body weight of (2.1):
  - 8 kg to 15 kg, is 47 mg three times a day
  - > 15 kg to 30 kg, is 62 mg three times a day
  - > 30 kg to 55 kg, is 93 mg three times a day
  - > 55 kg, is 124 mg three times a day
- Administer with or without food. (2.1)
- See full prescribing information for recommended dosage in patients with an eGFR ≥ 15 to < 50 mL/minute. (2.2)
- See full prescribing information for instructions on preparation and administration. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Capsules: 47 mg, 62 mg, 93 mg and 124 mg of arimoclomol. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypersensitivity Reactions*: Urticaria and angioedema have been reported. Discontinue MIPLYFFA in patients who develop these adverse reactions. (5.1)
- *Embryofetal Toxicity*: May cause fetal harm. Advise pregnant females of the potential risk to the fetus and consider pregnancy planning and prevention. (5.2)
- *Increased Creatinine without Affecting Glomerular Function:* Mean increases in serum creatinine of 10-20% have been reported. Use alternative measures to assess renal function which are not based on creatinine. (5.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (≥15%) are: Upper respiratory tract infection, diarrhea, and decreased weight. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Zevra Therapeutics, Inc. at toll-free phone 1-844-600-2237 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *Substrates of the Organic Cationic Transporter 2 (OCT2 substrates)*: Monitor for adverse reactions and reduce the dosage of the OCT2 substrate. (7.1)

----------USE IN SPECIFIC POPULATIONS----------
- *Females and Males of Reproductive Potential*: Based on animal findings, MIPLYFFA may impair fertility. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 9/2024

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use AQNEURSA safely and effectively. See full prescribing information for AQNEURSA.

AQNEURSA™ (levacetylleucine) for oral suspension
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------
AQNEURSA is indicated for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adults and pediatric patients weighing ≥15 kg. (1)

----------DOSAGE AND ADMINISTRATION----------
- For females of reproductive potential, verify that the patient is not pregnant prior to initiating treatment. (2.1)
- Recommended dosage (2.2)

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

- See the full prescribing information for administration instructions. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
For oral suspension: 1 gram levacetylleucine in a unit-dose packet. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
Embryo-Fetal Toxicity: May cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 days after the last dose if AQNEURSA is discontinued. (5.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and greater than placebo) are abdominal pain, dysphagia, upper respiratory tract infections, and vomiting. (6)

To report SUSPECTED ADVERSE REACTIONS, contact IntraBio Inc. at 1-833-306-9677 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- *N-acetyl-DL-leucine or N-acetyl-D-leucine*: Avoid concomitant use with AQNEURSA. (7.1)
- *P-glycoprotein (P-gp) Transporter Substrates*: Monitor for adverse reactions if used with AQNEURSA. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2024

Appendix 2. Pharmacology and Pharmacokinetic Properties.

Parameter	Arimoclomol	Levacetylleucine
Mechanism of Action	unknown	unknown
Oral Bioavailability	Not determined; Tmax ~ 0.5 hours	NR
Distribution	Mean apparent volume of distribution of arimoclomol at steady state in healthy adult subjects is 211 L	Apparent (oral) volume of distribution is 253 L
Protein Binding	10%	NR
Elimination	Mean apparent clearance of arimoclomol at steady state is 34 L/hr in healthy adult subjects. 12% of the dose was recovered in feces and 77.5% in urine (42% unchanged)	Apparent (oral) clearance is 139 L/h
Half-Life	4 hours	Estimated half-life is around 1 hour
Metabolism	Arimoclomol is predominantly metabolized through glutathionation, O-glucuronidation and NO-oxime cleavage	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.

Abbreviations: h = hour; L = liter; NR = not reported.

Appendix 3: NPCCSS assessment for Ambulation, Speech, Swallowing, Fine Motor, and Cognition from NCT02612129[6]

Ambulation	Score =
Normal	0
Clumsy	1
Ataxic unassisted gait or not walking by 18 months	2
Assisted ambulation or not walking by 24 months	4
Wheelchair dependent	5
Speech	**Score =**
Normal speech	0
Mild dysarthria (easily understood)	1
Severe dysarthria (difficult to understand)	2
Non-verbal/functional communication skills for needs	3
Minimal communication	5
Swallow	**Score =**
Normal, no dysphagia	0
Cough while eating	1
Intermittent dysphagia with liquids*	(+1)
Intermittent dysphagia with solids*	(+1)
Dysphagia with liquids*	(+2)
Dysphagia with solids*	(+2)
Nasogastric tube or gastric tube for supplemental feeding	4
Nasogastric tube or gastric tube feeding only	5
Fine Motor Skills	**Score =**
Normal	0
Slight dysmetria/dystonia (independent manipulation)	1
Mild dysmetria/Dystonia (requires little to no assistance, able to feed self without difficulty)	2
Moderate dysmetria/Dystonia (limited fine motor skills, difficulty feeding self)	4
Severe dysmetria/Dystonia (gross motor limitation, requires assistance for self-care activities)	5
Cognition	**Score =**
Normal	0
Mild learning delay, grade appropriate for age	1
Moderate learning delay, individualized curriculum or modified work setting	3
Severe delay/plateau, no longer in school or no longer able to work, some loss of cognitive function	4
Minimal cognitive function	5

Appendix 4: Proposed Prior Authorization Criteria

Medications for Niemann-Pick disease Type C

Goal(s):
- Ensure medically appropriate use of medications for Niemann-Pick disease Type C
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Miplyffa™ (arimoclomol)
- Aqneursa™ (levacetylleucine)

Covered populations: FFS and CCO patients beginning 1/1/26

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request for arimoclomol or levacetylleucine in a patient already taking the other agent (i.e., combination therapy without documentation of planned therapeutic switch)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Has the diagnosis of Niemann-Pick disease type C been confirmed by genetic testing or a filipin test?	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
5. Is the request being made by or in consultation with an expert in metabolic or genetic disease or experienced in treating Niemann-Pick disease type C?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is there documentation that the patient has developed at least one neurological manifestation of disease?	**Yes**: Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Has baseline severity been documented using NPCCSS, SARA, or some other appropriate tool for assessing Niemann-Pick disease type C? Examples: • Niemann-Pick Disease Type C Clinical Severity Scale (NPCCSS) • Scale for the Assessment and Rating of Ataxia (SARA)	**Yes**: Go to #8 Record tool and value:_____	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Go to #11
9. Is the patient pregnant or actively trying to conceive?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #10
10. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness.
11. Has the provider documented patient-specific goals for this therapy over the next 6 to 12 months? Note: Goals of therapy can vary from intent to cure, disease burden reduction, disease stabilization and control of symptoms.	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
12. Has the provider defined objective criteria to evaluate unsuccessful treatment or lack of response based on individual patient goals and current symptoms (i.e., when would the provider consider discontinuing therapy)? To qualify for treatment coverage, the patient and provider must have a documented discussion about when risks of the therapy outweigh the benefits and a knowledge of the realistic expectations of treatment efficacy. Care must always take place in the context of the patient's support systems, overall heath, and core values.	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
13. Is the request for arimoclomol in a patient who is at least 2 years old and ambulatory (with or without assistance)?	**Yes**: Go to #14	**No:** Go to #15
14. Is patient taking concomitant miglustat or starting miglustat therapy with arimoclomol initiation?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness Arimoclomol is only approved for use in combination with miglustat.
15. Is the request for levacetylleucine in a patient weighing at least 15 kg?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient been adherent to current therapy?	**Yes:** Go to #2	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
2. Is there documentation that the patient's goals of therapy established prior to treatment have been met?	**Yes**: Approve for 12 months	**No:** Go to #3
3. Is there documentation that pre-established criteria for unsuccessful treatment or lack of response have been met?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. Have the patient and provider had a documented discussion about when benefits of the therapy outweigh the potential risks?	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 12/25 (SF)
Implementation: 1/1/26

Miglustat 100 mg capsule (Zavesca, Yargesa, generic)

Goal(s):
- Ensure medically appropriate use of miglustat for Niemann-Pick disease Type C and Gaucher disease.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:
- Up to 12 months

Requires PA:
- Miglustat (ZAVESCA, YARGESA, generic 100 mg capsules). For OPFOLDA see Pompe disease criteria.

Covered Populations: FFS and CCO patients beginning 1/1/26

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for a patient with a prior FFS approval for the requested drug?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #3
3. Is the drug prescribed by made or in consultation with an expert in metabolic or genetic disease or experienced in treating Niemann-Pick disease type C or Gaucher disease?	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the drug being prescribed for Niemann-Pick disease type C?	**Yes**: Go to #5	**No:** Go to #7
5. Is that patient at least 2 years old?	**Yes**: Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the drug being prescribed for mild to moderate type 1 Gaucher disease in an adult (18 years or older)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count b. Low hemoglobin and hematocrit levels c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly?	**Yes:** Go to #8 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Does the patient have a documented contraindication, intolerance, inadequate response, or inability to access or adhere to enzyme replacement therapy?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product?	**Yes**: Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Go to #11
11. Does the patient have either: • A documented failure (either therapeutic or due to adverse events) with the preferred version of this product OR • Documentation of inability to access product to due to national/regional shortage?	**Yes**: Approve therapy for up to 6 months.	**No:** Pass to RPh. Deny; cost effectiveness.

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to miglustat?	**Yes**: Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient been adherent to current therapy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness

Gaucher Disease

Goal(s):
- Ensure medically appropriate use of drugs for Gaucher disease

Length of Authorization:
- Up to 12 months

Requires PA:
- Drugs for Gaucher disease (pharmacy and provider administered claims)

  Note: See Agents for Pompe Disease criteria if miglustat is being prescribed for Pompe Disease

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. FDA-Approved Minimum Ages

Drug	Age
Eliglustat	18
Imiglucerase	2
Taliglucerase alfa	4
Velaglucerase alfa	4

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #3
3. Is the request from a provider experienced in the treatment of Gaucher disease?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness .
4. Is the request for treatment of Type 1 Gaucher Disease? Note: Type 1 disease is characterized predominately by bone involvement without CNS symptoms.	**Yes**: Go to #6	**No:** Go to #5
5. Is the request for treatment of Type 3 Gaucher Disease? Note: Drugs are not FDA-approved for Type 2 or 3 Gaucher disease. Type 3 disease is characterized by both bone involvement and CNS symptoms.	**Yes:** Refer requests to the medical director for review. Provide relevant chart notes and literature documenting medical necessity.	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for an FDA-approved age in Table 1?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
7. Does the patient have current symptoms characteristic of bone involvement such as: a. Low platelet count b. Low hemoglobin and hematocrit levels c. Radiologic bone disease, T-score less than -2.5 or bone pain d. Delayed growth in children (<10th percentile for age) OR e. Splenomegaly or hepatomegaly?	**Yes:** Go to #8 Document baseline labs and symptoms	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for combination treatment with more than one targeted therapy for Gaucher disease?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #9
9. Is the request for enzyme replacement therapy?	**Yes:** Go to #10	**No:** Go to #11
10. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy & Therapeutics Committee.	**Yes:** Inform prescriber of covered alternatives in class. Approve preferred therapy for up to 6 months.	**No:** Approve for up to 6 months
11. Does the patient have a documented contraindication, intolerance, inadequate response, or inability to access or adhere to enzyme replacement therapy?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness
12. Is the request for eliglustat?	**Yes:** Go to #13	**No:** Approve for up to 6 months
13. Does the patient have cardiac disease, long-QT syndrome, or is currently taking a Class IA or Class III antiarrhythmic medication?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #14

Approval Criteria		
14. Does the patient have moderate to severe hepatic impairment?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #15
15. Does testing for CYP2D6 metabolizer status indicate extensive, intermediate or poor CYP2D6 metabolism?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Is the dose consistent with FDA labeling based on CYP2D6 metabolism and use of concomitant CYP inhibitors (see FDA labeling for full details)?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation based on chart notes that the patient experienced a significant adverse reaction related to treatment for Gaucher disease?	**Yes**: Go to #2	**No:** Go to #3
2. Has the adverse event been reported to the FDA Adverse Event Reporting System?	**Yes:** Go to #3 Document provider attestation	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient been adherent to current therapy?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is there objective documentation of benefit based on improved labs or patient symptoms?	**Yes:** Approve for up to 12 months Document labs and patient symptoms	**No:** Pass to RPh. Deny; medical appropriateness

Implementation: 1/1/26 1/1/2020

Pompe Disease Agents

Goal(s):
- Ensure medically appropriate use of approved agents for the treatment of Pompe disease

Length of Authorization:
- Up to 12 months

Requires PA:
- Alglucosidase alfa (pharmacy and provider administered claims)
- Avalglucosidase alfa (pharmacy and provider administered claims)
- Cipaglucosidase alfa (pharmacy and provider administered claims)
- Miglustat (OPFOLDA) (pharmacy and provider administered claims)

Covered Populations:
- Opfolda (miglustat): FFS and CCO patients beginning 1/1/26
- All others: FFS only

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1: FDA-approved Dosage and Administration

Agent	Indication	Age Minimum	Dosing Regimen
Alglucosidase alfa	Early Onset Pompe Disease (EOPD) Late Onset Pompe Disease (LOPD)	None	20 mg/kg IV once every 2 weeks
Avalglucosidase alfa	Late Onset Pompe Disease (LOPD)	≥ 1 year	< 30 kg: 40 mg/kg IV once every 2 weeks ≥ 30 kg: 20 mg/kg IV once every 2 weeks
Cipaglucosidase alfa*	Late Onset Pompe Disease (LOPD)	18 years or older	<40 kg: not indicated ≥40 kg: 20 mg/kg IV once every 2 weeks

			-plus- Miglustat 260 mg orally (≥ 50 kg) -or- 195 mg orally (≥40 kg to <50 kg) (administer 1 hour before cipaglucosidase infusion)

*must be administered with miglustat according to FDA labeled dosing parameters

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the requested agent for an approved indication and dosed appropriately based on age and weight taken within the past month? (**see Table 1**)	**Yes:** Document patient weight and go to #3. Weight: _____	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is there documentation that the provider has assessed the patient for signs or susceptibility to the following? • Fluid volume overload • Acute underlying respiratory illness • Compromised cardiac or respiratory function necessitating fluid restriction	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the treatment for the diagnosis of Pompe disease confirmed by either DNA testing or enzyme assay (e.g. acid alpha-glucosidase activity test)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
6. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for treatment of late-onset Pompe disease (LOPD)?	**Yes:** Go to #11	**No:** Go to #8
8. Has the provider documented a baseline value for ALL the following assessments? • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)? • Cardiac imaging (e.g. chest x-ray, echocardiography)? • CRIM status?	**Yes:** Document baseline results and go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the patient CRIM-negative?	**Yes:** Go to #10	**No:** Approve for 3 months If approved, a referral will be made to case management by the OHA.
10. Is there documentation that concomitant immune tolerance induction (ITI) therapy will be initiated with enzyme replacement therapy (ERT)?	**Yes:** Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the request for cipaglucosidase alfa or miglustat for Pompe Disease?	**Yes:** Go to #12	**No:** Go to #13

Approval Criteria		
12. Does the provider plan to order combination treatment as outlined in Table 1?	**Yes:** Approve miglustat as combination treatment. Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
13. Is the patient 5 years of age or older?	**Yes:** Go to #14	**No:** Go to #15
14. Is there a baseline documentation for both of the following? • Pulmonary function test (PFT) with spirometry including baseline percent predicted forced vital capacity (FVC) • Demonstration of completed 6-minute walk test (6MWT) -OR- Muscle weakness in the lower extremities?	**Yes:** Approve for 6 months Document baseline results. If approved, a referral will be made to case management by the OHA.	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the provider documented a baseline value for both of the following assessments: • Muscle weakness/Motor function? (e.g. AIMS, PDMS-2, Pompe PEDI, etc) • Respiratory status (e.g. FEV, FVC, or other age-appropriate test of pulmonary function)?	**Yes:** Approve for 3 months Document baseline results. If approved, a referral will be made to case management by OHA.	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documented evidence of adherence and tolerance to the approved infusion therapy regimen through claims history and/or provider assessment?	**Yes:** Go to #2	**No:** Pass to RPh, Deny; medical appropriateness
2. Is this a request for **al**glucosidase alfa?	**Yes:** Go to #3	**No:** Go to #5

Renewal Criteria		
3. Is this the first renewal for **al**glucosidase alfa?	**Yes:** Go to #4	**No:** Go to #5
4. Is there documentation that the patient has recently been tested* for IgG antibody formation? ** Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter per manufacturer labeling.*	**Yes**: Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Compared to baseline measurements, is there documented evidence of improvement or stabilization in muscle, motor, and/or respiratory function?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is patient under 5 years old? Note: Approve therapy per Table 1 (including miglustat if appropriate)	**Yes:** Approve for 3 months	**No:** Go to #7
7. Has the patient received the requested therapy for at least 6 months? Note: Approve therapy per Table 1 (including miglustat if appropriate)	**Yes:** Approve for 12 months	**No:** Approve for 3 months

P&T/DUR Review: 12/25; 6/24 (DE); 2/22; 4/21;
Implementation: 1/1/26; 7/1/24; 4/1/22; 5/1/21