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Drug Class Update with New Drug Evaluation: Drugs for Pompe Disease

Date of Review: June 2024

Date of Last Review: February 2022
Dates of Literature Search: 01/01/2022 - 04/01/2024
Brand Name (Manufacturer): -POMBILITI (Amicus Therapeutics US, LLC)
-OPFOLDA (Amicus Therapeutics US, LLC)

Generic Name: -cipaglucosidase alfa-atga
-miglustat

Dossier Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The purpose of this class update is to evaluate new literature published since the last review and evaluate the efficacy and safety of cipaglucosidase alfa-atga, a new formulation of recombinant human acid alfa glucosidase (GAA), which is prescribed in combination with miglustat to enhance stability.

Plain Language Summary:

- People who have Pompe disease are not able to make enough of an enzyme called lysosomal acid alfa glucosidase (GAA). Enzymes are proteins that help speed up chemical reactions in the body. Without enough GAA, cells are not able to properly break down chemicals. This results in buildup of waste products in skeletal muscle, the heart, lungs, and other body tissues. People living with Pompe disease havereduceds muscle strength which eventually makes walking, breathing, and other activities much more difficult.
- Some medicines are designed to partially replace the missing GAA enzyme in people with Pompe disease. This process is called enzyme replacement therapy (ERT).
- Although ERT may be used early childhood to help patients with certain types of Pompe disease live longer, avoid serious breathing problems, and help muscle function, the amount of benefit they give over time is not clear. ERT may have many side effects so medical specialists and patients must decide together if ERT should be started, what to watch for, and if it should be stopped because it is not working or is unsafe to continue therapy.
- Cipaglucosidase alfa-atga is an ERT medicine that the United States Food and Drug Administration approved to treat Pompe disease in adults aged 18 years and older who weigh more than 40 kg and who are not improving on their current medicine. Cipaglucosidase alfa is given by a provider in combination with another medicine called miglustat that helps cipaglucosidase alfa work longer in the body and allows it to get into the cells to do its job.
- Cipaglucosidase alfa plus miglustat may not improve walking distance , but may slightly improve ability to breathe when compared to alglucosidase alfa plus placebo. Treatment may make no difference to quality of life, the risk of allergic reactions, or the number of side effects compared with alglucosidase treatment.

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- Before Oregon fee-for-service (FFS) Medicaid will pay for ERT for people with Pompe disease, the provider must send in additional information to the Oregon Health Authority. This process is called prior authorization (PA).
- We recommend that cipaglucosidase alfa-atga (POMBILITI) plus miglustat (OPFOLDA) be non-preferred, and that providers explain why someone needs one of these complement inhibitors before Medicaid will pay for it. This process is called prior authorization.

Research Questions:

1. What is the efficacy and effectiveness of cipaglucosidase alfa-atga plus miglustat in improving mobility, muscle or pulmonary function, quality of life, or disease progression in patients with Pompe disease?
2. What are the harms of cipaglucosidase alfa-atga plus miglustat treatment in Pompe disease patients?
3. Are there specific subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) for which cipaglucosidase alfa-atga plus miglustat is better tolerated or more effective than other available lysosomal storage disorder agents when used for the treatment of Pompe disease?

Conclusions:

- This class update includes information from one randomized controlled trial (RCT) and one open label extension.[1-5]
- Cipaglucosidase alfa-atga (POMBILITI™) is a recombinant human acid alfa glucosidase (GAA) approved for use in patients with LOPD.[1,4]
- Miglustat (OPFOLDA) is only indicaed for use in combination with cipaglucosidase alfa.[3]
- There is low-quality evidence from one phase 3 trial that cipaglucosidase alfa in combination with miglustat resulted in no statistically significant difference in the distance walked in 6 minutes from baseline to week 52 compared to placebo (cipaglucosidase alfa +21.3 meters vs. +7.1 meters for the alglucosidase alfa/placebo; difference 14.2 meters [95% confidence interval [CI] -2.6 to 31.0]) in patients with late onset Pompe disease.[1,4] A minimum clinically important difference (MCID) is not established for a 6-minute walk distance (6MWD) in people with Pompe disease, though experts have stated a difference of at least 30 meters in patients with chronic respiratory disease would be considered clinically meaningful.[6]
- There is low-quality evidence from one phase 3 trial that patients treated with cipaglucosidase-miglustat had less of a decline in lung function from baseline to week 52 based on % predicted forced vital capacity (FVC) while sitting compared to those treated with alglucosidase-placebo (-1.6% and -4%, respectively), with a mean difference of 2.3% [95% CI 0.2 to 4.6%]).[1,4] A minimum clinically important difference (MCID) is not established for this endpoint in people with Pompe disease. However, in lung diseases like chronic obstructive pulmonary disease (COPD), a change of at least a 15% over a year has been considered clinically meaningful.[7]
- There is insufficient long-term evidence on safety of cipaglucosidase-miglustat. In the pooled safety population of 3 clinical trials, 41 (27%) patients treated with cipaglucosidase alfa-atga plus miglustat experienced hypersensitivity reactions, including 4 (3%) patients who reported severe hypersensitivity reactions and 4 (3%) more patients who experienced anaphylaxis.[1] The most common adverse reactions reported in ≥5% of patients were headache, diarrhea, fatigue, nausea, abdominal pain, and pyrexia.[1]
- Cipaglucosidase alfa-atga in combination with miglustat is contraindicated in pregnancy.[2,3] There is also a FDA boxed warning for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions and risk of acute cardiorespiratory failure in patients susceptible to fluid volume overload with cipaglucosidase alfa-atga infusions.[2]
- More long-term data is necessary to determine efficacy of cipaglucosidase alfa beyond 12 months. Somep people treated with alglucosidase alfa experience a decline in effectiveness over time, and there is insufficient long-term evidence to evaluate treatment persistence with cipaglucosideas alfa.

Recommendations:

- Implement prior authorization (PA) criteria for cipaglucosidase alfa and miglustat combination therapy PA criteria as proposed in Appendix 6.
- Evaluate costs in executive session.

Summary of Prior Reviews and Current Policy

Pharmacotherapy for Pompe disease was last reviewed by the Pharmacy and Therapeutics (P & T) Committee meeting in February 2022. At that time, avalglucosidase alfa was added to the Lysosomal Storage Disorders PDL class along with alglucosidase alfa. Both remain non-preferred. Prior authorization (PA) criteria was implemented for avalglucosidase alfa to ensure medically appropriate use. PA criteria evaluate safe and appropriate utilization of avalglucosidase alfa including a risk assessment related to FDA boxed warning for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs) and risk of acute cardiorespiratory failure in susceptible patients.

Background:

Pompe disease is a rare inherited, degenerative disease caused a deficiency of the lysosomal alpha glucosidase (GAA).[8] Normally, GAA facilitates the breakdown of glycogen to glucose in cell lysosomes throughout the body. In Pompe disease, deficiencies of GAA leads to accumulation of glycogen stored in skeletal and cardiac muscle as well as other tissues.[8,9] Excess glycogen due to GAA deficiency results in a spectrum of disease that ranges from mild progressive myopathy to profound muscle weakness, impaired mobility, and respiratory distress.[8,9] Pompe disease affects an estimated 1 per 40,000 people worldwide. In the United States, prevalence of Pompe is estimated between 1 in 21,979 and 1 in 9,625 births. Compared to other racial groups, prevelance may be higher in people identifying as African Americans (1 per 14,000 people).[10-12] Risk factors for development of Pompe disease include family history of glycogen storage disease (Type 2) where, at conception, siblings of a patient have a 25% chance of disease development.[12]

There are two types of Pompe disease characterized by the age of onset, type of organs involved, progression rate, and severity.[13-15] Infantile-onset Pompe disease (IOPD) comprises about one-quarter of Pompe disease cases with symptoms that generally present before 12 months of age.[13] IOPD is generally associated with rapid progression and decline of motor function with more hypotonia and severe cardiac involvement.[13] In many cases, IOPD symptoms include cardiomyopathy and respiratory insufficiency which, if left untreated, typically results in death from cardiorespiratory failure by the second year of life.[8,9,13] Late-onset Pompe disease (LOPD) is a less severe form which generally presents after 12 months of age with less pronounced symptoms and slower overall muscle decline.[14,15] Even with partial loss of GAA activity, individuals with LOPD still experience significant muscle weakness and fatigue that may eventually require use of a wheelchair or other assistive devices.[14,15] As in IOPD, respiratory failure is a common cause of mortality in patients with LOPD.[14,15] Male gender and an earlier age of onset may predict a more rapid disease course.[14,15]

The GAA gene influences the production of GAA protein which is necessary for hydrolyzation of glycogen to glucose in the lysosome.[16] The gene is located on chromosome 17q25 and hundreds of variations have been identified.[12,17] The clinical course of Pompe disease depends upon the type of mutation and subsequent residual GAA activity.[18] There are at least two known variants (c.1726G>A and c.2065G>A) that cause a pseudodeficiency where low levels of GAA activity are found with no evidence of clinical disease.[19-21] Typically, diagnosis of Pompe is accomplished by an acid alpha-glucosidase activity test obtained from dried blood spots and may be confirmed by a second test or by observance of 2 disease-causing GAA alleles via gene mutation analysis.[14,15] Less than 1% of normal GAA gene activity, or complete deficiency, is consistent with classic IOPD while partial deficiency (2%-40% of normal activity) is characteristic of non-classic IOPD and LOPD.[14,15]

Treatment for Pompe disease includes a variety of strategies which depend upon patient age, stage, genetic factors, and clinical manifestations.[14,15,17,22] Management usually requires a multidisciplinary approach with expertise in cardiology, pulmonology, metabolic disease, neurology, rehabilitation services, and nutrition support. [14,15,17] Respiratory, motor, and nutritional assessments are needed at regular intervals to track disease activity and monitor progress. [14,15,17] Some studies suggest that enhanced nutrition and exercise may help slow muscle function decline in LOPD patients.[14,15,17] A cardiology evaluation with chest X-rays and echocardiography may be of value to monitor left ventricular mass index (LMVI) and risk of sudden cardiac death.[14,15,17,23] Respiratory surveillance is accomplished through regular pulmonary function tests (PFTs) to ensure airway integrity.[14,15,17] For those patients with a need for respiratory support, supplemental oxygen or non-invasive ventilatory support may be warranted.[14,15,17] Assessment of musculoskeletal changes and function via magnetic resonance imaging (MRI), periodic scoliosis tests, and bone mineral density scans are also suggested.[14,15,17] Annual hearing evaluations and renal function studies, as well as periodic nutritional/feeding assessments are a crucial component in the effective management of patients with Pompe disease.[14,15,17]

Enzyme replacement therapy (ERT) has been studied for many clinical outcomes in Pompe disease including mortality, respiratory function, ventilator dependence, and walking distance, but efficacy depends on types and stages of disease.[24] In IOPD, ERT is typically started upon diagnosis or once symptomatic Pompe disease is recognized.[14,15,17] Although evidence shows that ERT may prolong survival in patients with IOPD, it is not a cure. Treatment can be associated with severe infusion-related reactions and/or extremely high antibody titers that diminish treatment efficacy.[24] The benefit of ERT in LOPD patients is less clear and may be dependent upon clinical signs, symptoms and rate of progression.[14,15,17] There is conflicting evidence and opinions on the optimal time to initiate ERT and whether treatment should be started in pre- or asymptomatic individuals.[15,30]

There have been a number of enzyme replacement therapies developed to treat Pompe disease.[25] Most of the available therapies are bimonthly intravenous infusions administered alone or in combination with a stabilizing agent.[2,3,25] Alglucosidase alfa is approved for use in both IOPD and LOPD.[26-28] Low-quality evidence from clinical trials demonstrated treatment with alglucosidase alfa over 52 weeks may reduce risk of death and requirement for ventilation support in patients with IOPD.[26-30] Alglucosidase alfa treatment over 78 weeks may also improve walking distance and respiratory function compared to placebo in patients with LOPD.[31] Differences compared to placebo in walking difference and respiratory function were generally small.[31] Treatment with avalglucosidase alfa may result in similar improvements in respiratory function compared to alglucosidase alfa in adults with LOPD based on one non-inferiority trial.[32] The new recombinant human GAA, cipaglucosidase alfa, has a similar mechanism of action to alglucosidase alfa but contains higher amounts of mannose 6-phosphate to increase binding properties.[4] Cipaglucosidase alfa is given in combination with the pharmacological chaperone miglustat which is thought to stabilize the enzyme, increase its uptake, and improve enzyme activity.[25] The safety and efficacy of cipaglucosidase alfa plus miglustat was recently assessed by the FDA and approved for treatment of adult patients weighing more than 40 kg with LOPD.[1-3] Some limitations of all ERT include a short duration of action that necessitate frequent hospital infusions, autoimmune responses or anaphylactic reactions to therapy, and limited long-term efficacy data.[1-3,27-31]

Clinically important outcomes for Pompe disease include morbidity, mortality, disease progression, ventilator use, and improvements in motor, pulmonary, or cardiac function.[32] Pulmonary function assessments in people with Pompe disease are often obtained by measurement of FVC and maximal inspiratory and expiratory muscle pressures (MIP and MEP, respectively).[27,29,33] A predicted FVC value of >80% is considered to be in the normal range.[36] When a patient's FVC reaches roughly 50% of predicted, non-invasive ventilation with positive airway pressure support is typically advised.[7,33] In chronic diseases such as chronic obstructive pulmonary disease (COPD), at least a 15% change in FVC over a year has been considered clinically meaningful.[7,33] The six-minute walk test (6MWT) has been used to measure gross motor function and functional exercise level for daily physical activities in patients with Pompe disease.[25,27] Normal values for the 6MWT vary based on age, and can range from roughly 500 meters in health adults to 700 meters in healthy adolescents.[25,27] The 6MWT has been extensively used to measure response to treatment in patients with chronic disease such as COPD, heart failure, and multiple sclerosis.[6] One study of 112 patients with COPD found the 6MWD would need to differ by 54 meters (95% CI 37 to 71 m), or a relative change of 15%, for patients to notice a difference in walking ability

from "about the same" to "a little bit better."[6,36] The manual muscle test (MMT) is a measure of skeletal muscle strength in the shoulder, elbow, hip, and knee.[4] The total score ranges from 0-80 with lower scores indicative of lower muscle strength.[4] The minimal clinically important difference (MCID) on the MMT is unknown. The Patient-Reported Outcomes Measurement Information System (PROMIS) scale for physical function evaluates patient response with a series of questions each scored on a scale from 1 to 5 based of difficulty (lower score indicates less ability to perform a task).[4] The PROMIS fatigue form has a similar scoring system (questions scored on a scale from 1 to 5) with higher scores indicative of a higher level of fatigue.[4]

The Gait, Stairs, Gower's maneuver, Chair (GSGC) total score is the sum of the component scores from 4 functional tests and ranges from a score of 4 (normal performance) to 27 (worst performance).[4] The GSGC total score includes performances for four assessments (G=Gait by walking for 10 meters, S=climbing 4 steps on a Stair, G=Gower's maneuver, C=rising from a Chair) and a qualitative global assessment of the manner in which it was accomplished (e.g. "waddling" or "climbs while clinging to railing with both hands" or "not possible" etc.).[4] The minimal clinically important difference (MCID) on the MMT, PROMIS form, and GSGC is unknown. Although the 6MWT, FVC, have been utilized to assess progress for many chronic conditions, the significance of these outcomes and their respective minimal clinically important differences have generally not been validated in Pompe disease.[36] A summary of selected outcome measures used in clinical trials of adults with Pompe disease is presented in **Table 1**.

Table 1. Selected Outcome Measures used in Clinical trials of Adult Patients with Pompe Disease

Test	Measure	Range	MCID
6MWD	Functional endurance	About 400 – 700 meters in healthy adults	About 7-9% change from baseline (roughly 30 meters)
FVC	Respiratory muscle strength	3 and 5 liters in adults	10-15% change from baseline
MMT (Lower, Upper, Total)	Skeletal muscle strength	Range: 0-80 with lower scores indicative of lower muscle strength 0=no contractile ability; 5=full range motion (maximal resistance)	Unknown
PROMIS – physical function PROMIS - fatigue	Self-reported, health-related quality of life	Physical – Questions or statements regarding capability -Range of responses: no problems to severe dysfunction -T-score 50 = average -Lower scores worse Fatigue – Questions or statements regarding symptoms -Range of responses: Mild feelings of tiredness to an overwhelming, debilitating, feeling of exhaustion -T-score 50 = average -Higher scores worse	Unknown
GSGC total score	Skeletal muscle strength	Ranges from 4 (normal performance) to 27 (worst performance):	Unknown

Key: 6MWT=Six-minute walk test; FVC=forced vital capacity; GSGC=Gait, Stairs, Gower's maneuver, Chair; MCID=minimal clinically important difference; MMT= manual muscle test; PROMIS=Patient-Reported Outcomes Measurement Information System

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Scottish Intercollegiate Guidelines Network (SIGN) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
After review, 3 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:
No new high-quality guidelines were identified since the last review.

New Formulations or Indications:
A new formulation of miglustat (OPFOLDA) was FDA approved in September 2023.[2] OPFOLDA is used as an enzyme stabilizer and is intended to be taken with cipaglucosidase alfa for the treatment of Pompe disease.[2] OPFOLDA is supplied as a 65 mg oral capsule, and the suggested dose is based on actual body weight (260 mg for patients weighing ≥50 kg and 195 mg for patients weighing ≥40 kg to <50 kg) which is administered every other week approximately 1 hour before intravenous administration of cipaglucosidase alfa.[2] Miglustat binds with, stabilizes, and reduces inactivation of cipaglucosidase alfa-atga in the blood after infusion.[2] Miglustat dissociates from cipaglucosidase alfa-atga after it is internalized and transported into lysosomes.[2] Miglustat alone has no pharmacological activity in cleaving glycogen.[2]

New FDA Safety Alerts:

Table 2. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change	Addition or Change and Mitigation Principles (if applicable)
Alglucosidase alfa[28]	Lumizyme	March 2024	Warnings and Precautions	5.1 – Hypersensitivity Reactions Including Anaphylaxis *…consider pretreating with antihistamines, antipyretics, and/or corticosteroids* *Appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when LUMIZYME is administered*

				5.2 – Infusion Associated Reactions *…pyrexia, chills, flu-like illness, myalgia, arthralgia, pain, fatigue, urticaria, rash, pruritus, erythema, dyspnea, tachycardia, flushing, nausea, headache and syncope have been observed.*
Avalglucosidase alfa[37]	Nexviazyme	September 2023	Warnings and Precautions	5.1 Hypersensitivity Reactions Including Anaphylaxis *Life-threatening hypersensitivity reactions, including anaphylaxis, have been reported.* 5.2 Infusion-Associated Reactions *Prior to administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids.*

Randomized Controlled Trials:
A total of 204 citations were manually reviewed from the initial literature search. After further review, all citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

NEW DRUG EVALUATION:
See **Appendix 3** 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.

Clinical Efficacy:
Cipaglucosidase alfa-atga (POMBILITI™) is a recombinant human acid alfa glucosidase (GAA) approved for use in patients with LOPD.[1,4] Cipaglucosidase alfa is administered as an intravenous infusion at a dose of 20 mg/kg once every 2 weeks and must be administered one hour after premedication with miglustat (OPFOLDA).[1-3] Miglustat is used to stabilize cipaglucosidase and helps increase ERT uptake and minimize loss of enzyme activity during infusion.[1-3] The recommended dose of miglustat is based on actual body weight.[1-3] For patients weighing ≥50 kg: the recommended dosage is 260 mg orally every other week, and for patients ≥40 kg to <50 kg the recommended dosage is 195 mg orally every other week.[1-3] In 2023, the FDA approved cipaglucosidase alfa-atga in combination with miglustat for the treatment of adult patients with LOPD weighing ≥40 kg and who are not improving on their current ERT.[1-3]

Safety and efficacy of cipaglucosidase alfa/miglustat was assessed in one phase 3, randomized, double-blind, multicenter superiority trial in ERT-experienced and ERT-naïve LOPD patients (PROPEL; ATB200-03; NCT#03729362; **Table 5**).[1-4] Patients (n=123) were randomly allocated in a 2:1 ratio to either cipaglucosidase alfa 20 mg/kg IV plus miglustat 195/260 mg oral (n=85) every 2 weeks or a non-U.S.-approved alglucosidase alfa productal glucosidase alfa at 20 mg/kg plus oral placebo every two weeks (n=38) for 52 weeks.[1,4] The study enrolled patients aged 18 years or older with genetically confirmed GAA enzyme deficiency who weighed 40 kg or more at screening.[1,4] Patients were required to have a sitting FVC of at least 30% of the predicted value for healthy adults at screening and be able to perform two 6-minute walk tests . For both tests, participants were required to have a 6MWD between 75 m and 90% of the predicted distance value for healthy adults (inclusive).[1,4] In addition, the lower value of the 6MWD had to be within 20% of the higher value of the 6MWD.[1,4] Patients were excluded if they had current use of miglitol, miglustat, acarbose, or voglibose, previous therapy or pharmacological treatment for Pompe disease (other than alglucosidase alfa)

within prior 30 days, or treatment with gene therapy for Pompe disease.[1,4] Any patients who were dependent on invasive or noninvasive ventilation support for more than 6 hours per day while awake were also excluded.[1,4]

The trial used adequate methods for randomization and allocation concealment and overall baseline demographics were generally similar between groups. The mean age of enrolled patients was 47 years. Roughly 77% of patients were treatment-experienced (had received alglucosidase alfa at the recommended dose and regimen of 20 mg/kg once every 2 weeks for at least 2 years) and 23% were treatment naïve.[1,4] People reandomized to cipaglucosidase alfa/miglustat were more commonly female (58% vs. 48%) and had slightly longer 6MWDs (358 meters vs. 350 meters), but the impact of these differences is unknown.[1,4] In treatment-experienced patients, there was a higher mean 6MWD at baseline in the cipaglucosidase alfa/miglustat group compared to patients receiving alglucosidase alfa (347 m vs. 335 m, respectively), but mean percent predicted FVC were comparable for both groups.[1,4] For ERT naïve patients, mean 6MWD results were lower in the cipaglucosidase alfa/miglustat group compared with the alglucosidase alfa group (394 m vs. 408.3 m, respectively).[1,4] Almost all subjects had protocol deviations with many (54%) reportedly due to the COVID-19 pandemic (55% in the cipaglucosidase alfa/miglustat and 50% in the alg-pbo group).[1,4]

The primary efficacy endpoint was the change in ambulatory function based on the 6MWT from baseline to Week 52 in patients treated with cipaglucosidase alfa/miglustat compared to alglucosidase alfa.[1,4] Key secondary endpoints included change in FVC (based on % predicted in the sitting position at Week 52); lower manual muscle test (MMT) score; PROMIS-physical function total score; PROMIS-fatigue total score; 6MWD at week 26; and the total GSGC score at week 52.[1,4] In addition, a prespecified analysis was performed on subgroups randomized by previous ERT status (ERT-experienced or ERT-naive).[1,4] The subgroups were compared for the primary and key secondary endpoints, as well as for treatment-emergent adverse events.[1,4] At 52 weeks, the mean change in 6MWD from baseline to week 52 was 21.3 meters (95% CI 12.1 to 30.5) for the cipaglucosidase alfa/miglustat group compared to 7.1 meters (95% CI -6.9 to 21.1) for the alglucosidase alfa/placebo group. Although the mean difference of 14.2 meters (95% CI -2.6 to 31.0) favored cipaglucosidase/miglustat, the result was not statistically significant.[1,4] Patients receiving cipaglucosidase alfa/miglustat had a slower decline from baseline in FVC% predicted (while sitting) compared to alglucosidase alfa (-1.6% and -4%, respectively) at week 52 for a least squares mean difference of 2.3% [95% CI 0.02 to 4.6; p=0.0484]) in favor of cipaglucosidase alfa/miglustat.[1] The GSGC total score also favored cipaglucosidase alfa/miglustat over alglucosidase alfa (MD -1.5; 95% CI -2.4 to -0.6), but there was no difference between groups for other secondary outcome measures.[1,4] When results were stratified by ERT history, the results were mixed. The ERT-experienced patients demonstrated a statistically significant difference in sitting FVC (% predicted) for those treated with cipaglucosidase alfa/miglustat compared to alglucosidase alfa (MD 4.08%; 95% CI 1.62 to 6.54), but the differenced were not significant for the ERT naïve subgroup.[1,4]

There are several limitations to this study. Despite being powered to detect differences, the study failed to identify a statistically significant difference between groups in the primary outcome measure. Both groups reported declines in the percent predicted FVC (with slower decline in patients treated with cipaglucosidase alfa/miglustat). Previous trials evaluating alglucosidase alfa have reported mean improvements of 3.4% in percent predicted FVC compared to placebo although trials may not be directly comparable.[31] Some studies have shown that many patients that initially benefitted from ERT treatment experience a secondary decline in ambulation, muscle strength, and pulmonary function over time.[38] More long-term data is necessary to determine efficacy of cipaglucosidase alfa beyond 12 months.

Clinical Safety:

There were 151 patients in the cipaglucosidase alfa /miglustat combined safety population, all of whom were age 18 years or older with LOPD.[1,2] Of those patients, 37 received the comparator in the ATB200-03 (“PROPEL”) trial and were switched to cipaglucosidase alfa/miglustat in the follow up trial ATB200-07.[1,2,5]

In these trials, the most common serious adverse events (SAEs) reported were anaphylaxis and urticaria.[1,2] There were 41 (27%) patients who received cipaglucosidase alfa-atga plus miglustat and experienced hypersensitivity reactions, including 4 (3%) patients who reported severe hypersensitivity reactions and 4 (3%) patients who experienced anaphylaxis.[1,2] Five patients permanently discontinued cipaglucosidase alfa/miglustat because of an adverse reaction (AE).[1,2] Other AEs reported in >5% of the pooled safety population included abdominal pain, diarrhea, fatigue, headache, nausea, and pyrexia.[1,2]

In the comparative efficacy trial (ATB200-03), 85 patients with LOPD received cipaglucosidase alfa 20 mg/kg along with miglustat 260 mg every other week, and 38 patients with LOPD received alglucosidase alfa 20 mg/kg with placebo every other week for 52 weeks.[1,2,4] The alglucosidase alfa product used in the study had not been approved for use in the United States.[1,2,4] Serious adverse events were reported in eight (9%) of patients treated with cipaglucosidase alfa/miglustat compared to 1 (3%) in the comparator group, but none were life-threatening and there were no deaths.[1,2,4] Most AEs in the cipaglucosidase alfa/miglustat and comparator groups were reported as either mild (42% both groups) or moderate (44% vs. 50%, respectively).[1,2,4] Three patients in the cipaglucosidase alfa/miglustat group had an AE that led to discontinuation versus 1 in the comparator group.[1,2,4] The most common AEs reported in >5% of the cipaglucosidase alfa/miglustat group were headache and diarrhea. The AEs reported during ATB200-03 are summarized in **Table 3.**[1,2,4]

Table 3. Adverse events occurring in more than 5% of patients in ATB200-03[1,2,4]

Adverse reaction	Cipaglucosidase alfa-atga plus miglustat (n=85)	Alglucosidase alfa plus placebo (n=38)
Headache	8%	8%
Diarrhea	6%	5%
Dizziness	5%	5%
Abdominal distention	4%	5%
Abdominal pain	2%	11%
Nausea	2%	13%
Pruritis	2%	5%

Cipaglucosidase alfa plus miglustat is currently under investigation in an open-label extension trial of PROPEL.[5] There were 118 patients included in the safety population.[5] Patients who were on cipaglucosidase alfa/miglustat in the original PROPEL study continued their treatment while the patients who initially received alglucosidase were switched to cipaglucosidase alfa/miglustat.[5] At the time of data cutoff almost 92% of patients in the cipaglucosidase alfa/miglustat group had received more than 24 months of cipaglucosidase alfa/miglustat treatment and 92% of the patients switched over to cipaglucosidase alfa/miglustat had at least 12 months of cipaglucosidase alfa/miglustat treatment.[5] Baseline characteristics of both groups remained generally similar.[5] No new safety issues were identified during the open-label extension trial.[5] The safety profile of patients switched from alglucosidase alfa plus placebo to cipaglucosidase alfa/miglustat was similar to those patients who continued cipaglucosidase alfa/miglustat treatment throughout PROPEL.[5]

Cipaglucosidase alfa/miglustat is contraindicated in pregnancy.[2,3] There is also a boxed warning in the FDA labeling for the possibility of life-threatening hypersensitivity reactions including anaphylaxis, infusion-associated reactions (IARs), and risk of acute cardiorespiratory failure in susceptible patients who received cipaglucosidase alfa infusions.[2,3] Patients with advanced Pompe disease may have compromised cardiac and respiratory function which may increase risk of severe complications from IARs.[2,3] Also, patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised

cardiac or respiratory function for whom fluid restriction is indicated may be at increased risk of serious exacerbation of their cardiac or respiratory status during cipaglucosidase alfa-atga infusion.[2,3] Patients with an acute underlying illness at the time of cipaglucosidase alfa-atga infusion may be at greater risk for IARs.[2,3] The FDA labeling suggests more frequent monitoring of vital signs during infusion in patients with increased risk, and in the event of a severe IAR, therapy should be immediately discontinued, and appropriate medical treatment initiated.[2,3] If the clinical benefit outweighs risks, a re-challenge with cipaglucosidase alfa-atga (plus miglustat) may be considered but at a lower infusion rate and only if tolerated.[2,3]

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Functional ability or symptom improvement (motor, pulmonary, or cardiovascular)
2) Disease progression
3) Quality of life
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Motor function as assessed by change from baseline to Week 52 in 6MWD

Table 4. Pharmacology and Pharmacokinetic Properties.[1-3]

Parameter	Cipaglucosidase alfa	Miglustat
Mechanism of Action	Recombinant human GAA enriched with bis-M6P N-glycans to mediate binding to M6P receptors on the cell surface with high affinity. After CI-MPR binding, it is internalized and transported into lysosomes where it undergoes proteolytic cleavage and N-glycans trimming which are both required to yield the most mature and active form of GAA. Cipaglucosidase alfa-atga then exerts enzymatic activity in cleaving glycogen.	Competitive and reversible inhibitor of glucosylceramide synthase which reduces glycosphingolipid biosynthesis and the amount of glycosphingolipid build-up in tissues. Does not have any direct therapeutic efficacy.
Oral Bioavailability	N/A – administered via intravenous infusion	Bioavailability 97% (decreased 36% when administered with food)
Distribution and Protein Binding	Vd: 2.0–4.7 L	Vd: 83-105 L
Half-Life	2.1 hours	6-7 hours
Metabolism/Excretion	The metabolic pathway has not been characterized but expected to be metabolized into small peptides and amino acid via catabolic pathways.	Renal excretion; 67% unchanged in urine

Abbreviations: bis-M6P= bis-phosphorylated; CI-MPR= cation-independent mannose-6-phosphate receptor; GAA=alpha glucosidase; L= liters; M6P= mannose 6-phosphate; N/A= not applicable; Vd= volume of distribution

Table 5. 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. Schoser B, et al;[4] ATB200-03 (PROPEL)[1] Phase 3, PG, DB, RCT NCT03729362	1. Cipaglucosidase alfa-atga/miglustat: cipaglucosidase alfa-atga 20 mg IV + 260 mg oral miglustat every 2 wks (or 195 mg for patients weighing 40 to <50 kg) Vs. 2. Alglucosidase alfa 20 mg/kg IV + oral placebo every 2 wks Duration: 52 weeks	Demographics: -Mean Age: 1. 47.6 yrs 2. 45.1 yrs -Female: 1. 58% 2. 47% Race/Ethnic groups: White persons 1. 87% 2. 79% Asian or Asian American persons 1. 4% 2. 3% Black, African and African American persons 1. 0% 2. 3% Japanese: 1. 2% 2. 11% Other 1. 6% 2. 3% -ERT-experienced: 77% -ERT treatment duration (mean): 7.4 yrs -Use walking aid: 1. 20% 2. 29% -6MWT (mean): 1. 358 m 2. 350 m -Sitting FVC, % predicted (mean): 1. 71 2. 70	ITT: 1. 85 2. 38 PP: 1. 80 2. 37 Attrition: 1. 5 (6%) 2. 1 (3%)	Primary Endpoint: Change from baseline in 6MWD at week 52 1. 20.8 m 2. 7.2 m MD = 13.7 (95% CI -1.2 to 28.5); p=0.071 Secondary Endpoints: Change from baseline in sitting FVC, % predicted 1. -0.9% 2. -4% MD = 2.7% (95% CI 0.4 to 5.0) Change in MMT lower extremity MD = 1.0 (95% CI -0.5 to 2.4) Change in PROMIS physical function MD = 1.9 (95% CI -1.5 to 5.3) Change in PROMIS fatigue MD = 0.0 (95% CI -2.1 to 2.2) Change in GSGC MD = -1.4 (95% CI -2.5 to -0.4)	NS NA NS NS NS NA	Serious AE 1. 8 (9%) 2. 1 (3%) Treatment Emergent AE 1. 95% 2. 97% Discontinuations due to AE 1. 3 (4%) 2. 1 (3%) 95% CI and p-values not reported	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Adequate randomization and allocation concealment methods used via proprietary interactive response technology software. Centralized block randomization procedure used and were stratified by 6MWT and ERT status. Performance Bias: Low. Study investigators at sites accessed the IRT system via web or phone call to enroll and randomize patients. Treatment assignment only accessible to an unblinded pharmacist at the site who handled and prepared study drug and was not involved in any other aspect of the trial. Identical appearance of study drug and comparator. Detection Bias: Unclear. Double blinded but method of blinding assessors was not reported. Attrition Bias: Low. 130 individuals were screened for eligibility; 125 were enrolled and randomly assigned to treatment; 2 people in the alglucosidase alfa + placebo group did not receive any dose due to absence of genotype confirmation and were excluded from the intention-to-treat population; 117 completed study. Overall dropout rate 4.9%. Reporting Bias: Low. Efficacy results on ITT population. Statistical analyses for all secondary outcomes were reported. Other Bias: Unclear. The manufacturer designed the study in collaboration with the authors; manufacturer was responsible for trial monitoring, data collection, and statistical analysis; and funded third-party medical writing assistance for the manuscript. **Applicability**: Patient: LOPD patients 18 years or older; mostly treatment experienced population, people with ventilator dependence were excluded; pearticipants had to complete 2 6MWT which may limit applicability in more

		Key Inclusion Criteria: -Adults aged ≥18 years -Weight ≥40 kg -Confirmed diagnosis of LOPD -6MWD ≥75 m and ≤90% of predicted value for healthy adults -Sitting FVC ≥30% of the predicted value for healthy adults Key Exclusion Criteria: -Received investigational or pharmacological treatment for LOPD -Ventilation support for >6 hours while awake -Current use of miglitol, miglustat, acarbose, or voglibose						severe disease. Underepresentation of Black, African and African American persons and possibly Hispanic or Latino, Latina or Latinx persons may limit applicability to Oregon Medicaid population. Intervention: Cipaglucosidase alfa/miglustat Comparator: Alglucosidase alfa in combination with placebo. Alglucosidase formulation used in this study is not FDA approved. Avalglucosidase may have been more appropriate AC based on indication. Outcomes: Outcomes (6 MWT and FVC) represent clinically relevant outcomes for patients. The minimum clinically important difference in these outcomes for people with Pompe disease has not been established. Setting: 62 neuromuscular and metabolic medical centers in 24 countries including United States and Canada.

Abbreviations: 6MWD =Six-minute walk distance; AC = active comparator; AE = adverse event; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; FVC = forced vital capacity; GSGC = Gait, Stairs, Gower's maneuver, Chair; ITT = intention to treat; IV = intravenous; LOPD = late-onset Pompe Disease; m = meters; MD = mean difference; mITT = modified intention to treat; MMT= manual muscle test; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PG = parallel group; PP = per protocol; PROMIS=Patient-Reported Outcomes Measurement Information System; RCT = randomized controlled trial

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Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
alglucosidase alfa	LUMIZYME	VIAL	N
avalglucosidase alfa-ngpt	NEXVIAZYME	VIAL	N
cipaglucosidase alfa-atga	POMBILITI	VIAL	N
miglustat	MIGLUSTAT	CAPSULE	N
miglustat	OPFOLDA	CAPSULE	N
miglustat	YARGESA	CAPSULE	N
miglustat	ZAVESCA	CAPSULE	N

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to April 01, 2024

1 pompe disease.mp. or Glycogen Storage Disease Type II/2586
2 cipaglucosidase.mp./9
3 alglucosidase.mp./207
4 avalglucosidase.mp./28
5 2 or 3 or 4/219
6 1 and 5/204

Appendix 3: Prescribing Information Highlights

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use POMBILITI™ safely and effectively. See full prescribing information for POMBILITI.

POMBILITI (cipaglucosidase alfa-atga) for injection, for intravenous use
Initial U.S. Approval: 2023

WARNING: SEVERE HYPERSENSITIVITY REACTIONS, INFUSION-ASSOCIATED REACTIONS, and RISK OF ACUTE CARDIORESPIRATORY FAILURE IN SUSCEPTIBLE PATIENTS

See full prescribing information for complete boxed warning

Hypersensitivity Reactions Including Anaphylaxis

Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available. If a severe hypersensitivity reaction occurs, POMBILITI should be discontinued immediately and appropriate medical treatment should be initiated. (5.1)

Infusion-Associated Reactions (IARs)

If severe IARs occur, immediately discontinue POMBILITI and initiate appropriate medical treatment. (5.2)

Risk of Acute Cardiorespiratory Failure in Susceptible Patients

Patients susceptible to fluid volume overload, or those with acute underlying respiratory illness or compromised cardiac or respiratory function, may be at risk of serious exacerbation of their cardiac or respiratory status during POMBILITI infusion. (5.3)

----------INDICATIONS AND USAGE----------

POMBILITI is a hydrolytic lysosomal glycogen-specific enzyme indicated, in combination with Opfolda, an enzyme stabilizer, for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy (ERT). (1)

----------DOSAGE AND ADMINISTRATION----------

- Verify pregnancy status in females of reproductive potential prior to initiating treatment. (2.1)
- Administer POMBILITI in combination with Opfolda. (2.2)
- Consider administering antihistamines, antipyretics, and/or corticosteroids prior to POMBILITI administration. (2.2)
- Recommended POMBILITI dosage is 20 mg/kg (of actual body weight) administered every other week as an intravenous infusion over approximately 4 hours. (2.2)
- Start POMBILITI in combination with Opfolda 2 weeks after the last ERT dose. (2.2)
- Initiate the POMBILITI infusion approximately 1 hour after oral administration of Opfolda. If the POMBILITI infusion cannot be started within 3 hours of oral administration of Opfolda, reschedule POMBILITI in combination with Opfolda at least 24 hours after Opfolda was last taken. If POMBILITI in combination with Opfolda are both missed, re-start treatment as soon as possible. (2.2)
- See the full prescribing information for dosage modifications due to hypersensitivity reactions or IARs. (2.3)
- Must be reconstituted and diluted prior to use. (2.4)
- See the full prescribing information for administration instructions. (2.5)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 105 mg of cipaglucosidase alfa-atga as a lyophilized powder in a single-dose vial for reconstitution. (3)

----------CONTRAINDICATIONS----------

Pregnancy (4, 5.4, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- See boxed warning. (5.1, 5.2, 5.3)
- *Embryo-Fetal Toxicity:* May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for at least 60 days after the last dose. (4, 5.4, 8.1, 8.3)
- *Risks Associated with Opfolda:* Refer to the Opfolda Prescribing Information for a description of additional risks for Opfolda. (5.5)

----------ADVERSE REACTIONS----------

Most common adverse reactions ≥ 5% are headache, diarrhea, fatigue, nausea, abdominal pain, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amicus Therapeutics at 1-877-4AMICUS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2023

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

OPFOLDA (miglustat) capsules, for oral use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

OPFOLDA is an enzyme stabilizer indicated, in combination with Pombiliti, a hydrolytic lysosomal glycogen-specific enzyme, for the treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy (ERT). (1)

----------DOSAGE AND ADMINISTRATION----------

- Verify pregnancy status in females of reproductive potential prior to initiating treatment. (2.1)
- Administer OPFOLDA in combination with Pombiliti. (2.2)
- Recommended OPFOLDA dosage (based on actual body weight), administered orally every other week, is: (2.2)
  - 260 mg for patients weighing ≥50 kg.
  - 195 mg for patients weighing ≥40 kg to <50 kg.
- Start OPFOLDA in combination with Pombiliti 2 weeks after the last ERT dose. (2.2)
- Take OPFOLDA with an unsweetened beverage approximately 1 hour before the start of Pombiliti infusion; do not consume other beverages or food for at least 2 hours prior to and 2 hours after taking OPFOLDA. (2.2)
- Missed dose: If the OPFOLDA dosage is missed, Pombiliti should not be administered and treatment should be rescheduled at least 24 hours after OPFOLDA was last taken. If OPFOLDA in combination with Pombiliti are both missed, re-start treatment as soon as possible. (2.2)
- See full prescribing information for recommended OPFOLDA dosage in patients with renal impairment. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 65 mg (3)

----------CONTRAINDICATIONS----------

Pregnancy. (4, 5.1, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- *Embryo-Fetal Toxicity:* May cause embryo-fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for at least 60 days after the last dose. (4, 5.1, 8.1, 8.3)
- *Risks Associated with Pombiliti:* Refer to the Pombiliti Prescribing Information for a description of additional risks for Pombiliti. (5.2)

----------ADVERSE REACTIONS----------

Most common adverse reactions ≥5% are headache, diarrhea, fatigue, nausea, abdominal pain, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amicus Therapeutics at 1-877-4AMICUS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Breastfeeding not recommended. (8.2)

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

Revised: 9/2023

Appendix 5: Key Inclusion Criteria

Population	Adults with LOPD
Intervention	Cipaglucosidase alfa in combination with miglustat
Comparator	Alglucosidase alfa in combination with placebo
Outcomes	Symptoms, function, quality of life
Timing	52 weeks
Setting	Outpatient

Agents for Pompe Disease

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 physician administered claims)
- Avalglucosidase alfa (pharmacy and physician administered claims)

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 patient is switching enzyme replacement therapy (ERT) agents due to lack of benefit with prior therapy?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #4
4. 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 #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for continuation of therapy previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. 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 #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Is this request from a metabolic specialist, biochemical geneticist, or has provider documented experience in the treatment of Pompe disease?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the request for treatment of late-onset Pompe disease (LOPD)?	**Yes:** Go to #12	**No:** Go to #9

Approval Criteria		
9. 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 #10	**No:** Pass to RPh. Deny; medical appropriateness
10. Is the patient CRIM-negative?	**Yes:** Go to #11	**No:** Approve for 3 months If approved, a referral will be made to case management by the OHA.
11. 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
12. Is the request for cipaglucosidase alfa?	**Yes:** Go to #13	**No:** Go to #14
13. Does the request include plans to premedicate with miglustat as outlined in Table 1?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness
14. Is the patient 5 years of age or older?	**Yes:** Go to #15	**No:** Go to #16
15. 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

Approval Criteria		
16. 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
3. Is this the <u>first</u> 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?	**Yes:** Approve for 3 months	**No:** Go to #7

Renewal Criteria		
7. Has the patient received the requested therapy for at least 6 months?	**Yes:** Approve for 12 months	**No:** Approve for 3 months

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