Substrate Reduction Therapy Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

The BCBS MN Step Therapy Supplement also applies to this program for Medicaid.

POLICY REVIEW CYCLE

Effective Date	Date of Origin
07-01-2024	05-01-2017

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cerdelga® (eliglustat) Capsule	Long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test for determining CYP2D6 genotype Limitations of Use: • CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect • A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers)		1
Opfolda™ (miglustat) Capsule	Treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing greater than or equal to 40 kg and who are not improving on their current enzyme replacement therapy (ERT); Opfolda (an enzyme stabilizer) is indicated in combination with Pombiliti (a hydrolytic lysosomal glycogen-specific enzyme)		11
Zavesca® (miglustat)* Capsule	Monotherapy for treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access)	* Generic available	2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

Gaucher Disease	Gaucher disease (GD), the most common of the lysosomal storage disorders (LSDs), is a rare autosomal recessive metabolic disorder affecting only 1 in 40,000 in the general United States population.(4,7) Mutations in the *GBA* (glucocerebrosidase) gene cause reduced activity of the lysosomal enzyme glucocerebrosidase (also known as acid beta-glucosidase), resulting in the accumulation of harmful quantities of the glycolipid glucocerebroside (also known as glucosylceramide, or GLC) and other related sphingolipids. This multisystemic accumulation of GLC in various tissues, especially in lysosomes of macrophages, compromises the bone marrow, spleen, and liver, and less often the lungs, skin, kidneys, and heart.(3,4,7,8,9,10)

	GD is classified into 3 clinical types, distinguished by their clinical features, management, and prognosis. However, as with most genetic diseases, there is a continuum of clinical findings and overlap within and between types, resulting in identification of additional subtypes.(4,5,7,9) GD Type 1 (GD1) is distinguished from GD Types 2 (GD2) and 3 (GD3) by the lack of characteristic involvement of the central nervous system (CNS).(3,4,5,7,8) As such, it is also known as non-neuronopathic GD.(3,4,7) In the United States, Europe, and Israel, 90% of GD patients have GD1, with a high carrier frequency in the Ashkenazi-Jewish population.(3,4,5,7,8) Age of onset for GD1 is variable, with some patients presenting between 12 and 24 months of age and others having no clinical signs until late adulthood.(3,4,7) Manifestation in the first or second decades of life typically results in more aggressive and severe symptoms than those manifesting at a later stage of life.(7) Presentation of symptoms among patients with GD1 is variable. Splenomegaly is the most common symptom; hepatomegaly is also common, but the liver increases relatively less than the spleen. Other common presenting symptoms are anemia, thrombocytopenia, bone disease, and delayed growth.(3,4,5,7,8,10) GD2 is an acute neuronopathic form of GD characterized by early onset, typically in the first year after birth. Neurologic complications are extensive and severe, with limited psychomotor development. Death occurs within the first 2 years of life, usually due to respiratory failure.(3,5,7) GD3 is the subacute or chronic neuronopathic form, has later onset than GD2, and has slower disease progression with patients typically surviving to second or third decades of life. The distinction between GD2 and GD3 is difficult.(3,4) A diagnosis of GD should be considered in patients with unexplained anemia and easy bruising, particularly if they have enlargement of the spleen and liver.(3) Definitive diagnosis of GD can be confirmed by the finding of reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.(3,4,5,7,9,10) This enzyme assay test is typically known as BGL (beta-glucosidase leukocyte), and a finding of 15% or less of mean normal glucocerebrosidase enzyme activity is indicative of GD.(4,5) If BGL results are not conclusive and/or further confirmatory testing is desired, genetic testing is an option. Identification of two pathogenic alleles in the *GBA* gene can also determine diagnosis of GD.(3,4,5,9) The presence of neurologic complications has critical implications for prognosis and treatment and should be determined as soon as possible after diagnosis. Neuronopathic symptoms indicative of GD2 and GD3 include bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonus, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, and ataxia. If not already performed as part of the diagnostic process, baseline measurement of hemoglobin level, platelet count, liver volume, and spleen volume should be documented.(4,5,7,10) When possible, management of a patient with GD should occur with a multidisciplinary team at a Comprehensive Gaucher Treatment Center(5) (list of facilities nationwide available at www.gaucherdisease.org. Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. An additional goal in children is optimization of growth.(3,6,8) Currently, two different therapeutic approaches for the treatment of GD1 are used: enzyme replacement therapy (ERT) [Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), Elelyso (taliglucerase alfa)] and substrate reduction therapy (SRT) [Cerdelga (eliglustat), Zavesca (miglustat)].(3,5,6,8,9) ERT, intravenously administered, targets macrophages and increases the breakdown of accumulated glycolipids.(8) SRT, orally administered, reduces the amount of synthesized GLC to a level that can be effectively cleared by the mutated enzyme's residual activity.(5,6,8) The decision to offer ERT or SRT in patients with GD1 is based upon disease severity and/or significant disease progression.(6,7,8,10) To begin treatment with ERT or SRT, clinically significant manifestations must be present. Thrombocytopenia of sufficient magnitude to justify initiation of treatment is defined by platelet counts less than 100,000 microliter, as well as symptomatic presentation of splenomegaly, anemia, bone disease, and/or delayed growth.(3,4,5,7,8,9)

Pompe Disease	Pompe disease, also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by mutations in the *GAA* gene for enzyme acid alpha-glucosidase (GAA).(12,13) Deficiency of lysosomal enzyme GAA leads to accumulation of glycogen in lysosomes and cytoplasm, resulting in tissue destruction.(13) Infantile-onset Pompe disease (IOPD) is characterized by cardiomyopathy, severe generalized hypotonia, respiratory distress typically requiring ventilator support, and failure to thrive. Most patients with this form die within the first year or two of life without treatment. The juvenile-adult form (late onset Pompe disease [LOPD]) is characterized by skeletal myopathy, delayed gross-motor development, and respiratory insufficiency and/or failure.(12,13) Diagnosis can be confirmed by demonstration of reduced acid alpha-glucosidase glycogen enzyme activity in dried blood spots or leukocytes (skin fibroblasts or skeletal muscle tissue are also options). *GAA* gene mutational analysis is the preferred test to confirm the diagnosis (with two pathogenic alleles), since it is routinely available, less invasive, and may help predict cross-reactive immunologic material (CRIM) status.(12,13,14) Prenatal diagnosis is possible by DNA analysis of cultured amniocytes or chorionic villus samples, if the mutation in the family is known.(13,14) Guidelines note that a trial of ERT may be considered in patients who receive invasive ventilation support, if there are predefined outcomes which can be evaluated and which, if achieved, would improve the functional status of the patient. After one year, decisions regarding the continuation of ERT in patients receiving invasive ventilation support should be made on a case-by-case basis.(15,16) Opfolda (miglustat) in combination with Pombiliti (an ERT; cipaglucosidase alfa) was approved by the FDA in September 2023 as a new treatment for adults with LOPD. Pombiliti provides an exogenous source of GAA, which exerts enzymatic activity in cleaving accumulating glycogen. Opfolda binds with, stabilizes, and reduces inactivation of Pombiliti in the blood after infusion.(11)
Efficacy - Gaucher Disease	Until the FDA approval of the SRT Cerdelga in 2014, ERT was the mainstay of therapy in patients with GD1. A 12-month phase 3, open-label, noninferiority study (ENCORE) in 106 adults (18 years of age and older) with GD1, stable after greater than or equal to 3 years of ERT with Cerezyme or VPRIV, found Cerdelga noninferior to Cerezyme in maintaining stability of four component domains (i.e., hemoglobin level, platelet count, liver volume, spleen volume). A 9-month randomized, double-blind, placebo-controlled study (ENGAGE) in 40 treatment-naïve GD1 patients 16 years of age and older, demonstrated that treatment with Cerdelga led to greater improvements in spleen and liver volume, platelet count, and hemoglobin level compared to placebo. These findings provided Cerdelga its designation as first-line or maintenance therapy in adult patients with GD1.(1,5,6,8) The SRT Zavesca, approved in 2003, is indicated only for GD1 patients for whom ERT is not an option (e.g., due to allergy, hypersensitivity, or poor venous access). Studies of Zavesca have demonstrated significant reductions from baseline in liver and spleen volume, and a non-significant increase from baseline in hemoglobin level and platelet count.(2,5,6)
Efficacy - Pompe Disease	PROPEL was a randomized, double-blind, active-controlled, international, multi-center clinical trial (NCT#03729362) in patients greater than or equal to 18 years old diagnosed with late-onset Pompe disease (LOPD). Patients were randomized 2:1 to receive Pombiliti in combination with Opfolda, or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT-experienced) and 28 (23%) were ERT-naïve. More than two thirds (n=64, 67%) of ERT-experienced patients had been on ERT treatment for more than 5 years prior to entering the trial (mean of 7.4 years). Demographics, baseline sitting forced vital capacity (FVC) (% predicted), and 6-minute walk distance (6MWD) were generally

	similar between the 2 treatment groups. Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6MWD. The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in sitting FVC from baseline at Week 52 (p=0.006).(11) Patients treated with combination Pombiliti and Opfolda walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28). The ERT-experienced patients treated with Opfolda in combination with Pombiliti showed a numerically favorable change in 6MWD from baseline at Week 52 (p=0.047).(11) Opfolda in combination with Pombiliti is not approved for use in ERT-naïve patients with LOPD. The ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data.(11) A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and Opfolda in combination with Pombiliti for the treatment of adult patients with LOPD.(11)

Safety	Cerdelga (eliglustat) is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals:(1)
	
	• Extensive metabolizers (EMs):
	  ○ Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
	  ○ Moderate or severe hepatic impairment
	  ○ Mild hepatic impairment taking a strong or moderate CYP2D6 inhibitor
	• Intermediate metabolizers (IMs):
	  ○ Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
	  ○ Taking a strong CYP3A inhibitor
	  ○ Any degree of hepatic impairment
	• Poor metabolizers (PMs):
	  ○ Taking a strong CYP3A inhibitor
	  ○ Any degree of hepatic impairment
	
	Opfolda in combination with Pombiliti is contraindicated in pregnancy.(11)
	
	Zavesca (miglustat) has no contraindications.(2)

REFERENCES

Number	Reference
1	Cerdelga prescribing information. Genzyme Corporation. December 2022.
2	Zavesca prescribing information. Actelion Pharmaceuticals US, Inc. August 2022.
3	National Organization for Rare Disorders (NORD) – Physicians Guides. Gaucher Disease. Last updated March 2020. Available at: https://rarediseases.org/physician-guide/gaucher-disease/.
4	Hughes D, Sidransky E, et al. Gaucher Disease: Pathogenesis, Clinical Manifestations, and Diagnosis. UpToDate. Last updated June 2022. Literature review current through December 2023.
5	Pastores GM, Hughes DA. Gaucher Disease. July 2000 [Updated December 2023]. In: Adam MP, Ardinger HH, Pago RA, et al. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1269/.
6	Hughes D, Sidransky E, et al. Gaucher Disease: Treatment. UpToDate. Last updated August 2022. Literature review current through December 2023.

Number	Reference
7	Martins AM, Valadares ER, Porta G, et al. Recommendations on Diagnosis, Treatment, and Monitoring for Gaucher Disease. J Pediatr. 2009;155(4):S10-S18.
8	Biegstraaten M, Cox TM, Belmatoug N, et al. Management Goals for Type 1 Gaucher Disease: An Expert Consensus Document from the European Working Group on Gaucher Disease. Blood Cells Mol Dis. 2018;68:203-208.
9	Wang RY, Bodamer OA, Watson MS, et al. American College of Medical Genetics (ACMG) Work Group on Lysosomal Storage Diseases: Diagnostic Confirmation and Management of Presymptomatic Individuals. Genet Med. 2011 May;13(5):457-484.
10	Weinreb NJ, Aggio MC, Andersson HC, et al. Gaucher Disease Type 1: Revised Recommendations on Evaluations and Monitoring for Adult Patients. Semin Hematol. 2004;41(suppl 5):15-22.
11	Opfolda prescribing information. Amicus Therapeutics US, LLC. September 2023.
12	Kronn DF, Day-Salvatore D, Hwu WL, et al. The Pompe Disease Newborn Screening Working Group on Management of Confirmed Newborn-Screened Patients with Pompe Disease Across the Disease Spectrum. J Pediatrics. 2017 Jul;140(1):S24-S45.
13	Hahn S, et al. Lysosomal Acid Alpha-Glucosidase Deficiency (Pompe Disease, Glycogen Storage Disease II, Acid Maltase Deficiency). UpToDate. Last updated November 2021. Literature review current through December 2023.
14	Reuser AJJ, et al. Pompe Disease. National Organization for Rare Disorders (NORD). Last updated January 2024. Available at: https://rarediseases.org/rare-diseases/pompe-disease/.
15	Cupler EJ, Berger KI, Leshner RT, et al. American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Position Statement: Consensus Treatment Recommendations for Late-Onset Pompe Disease. Muscle Nerve. 2012 Mar;45(3):319-333.
16	Tarnopolsky M, Katzberg H, Petrof BJ, et al. Pompe Disease Diagnosis and Management: Evidence-Based Guidelines from a Canadian Expert Panel. Can J Neurol Sci. 2016;43:472-485.

POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Cerdelga	eliglustat tartrate cap	84 MG	M ; N ; O ; Y	N		
Opfolda	miglustat (gaa deficiency) cap	65 MG	M ; N ; O ; Y	N		
Yargesa ; Zavesca	miglustat cap	100 MG	M ; N ; O ; Y	O ; Y		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Cerdelga	Eliglustat Tartrate Cap 84 MG (Base Equivalent)	84 MG	60	Capsules	30	DAYS			
Opfolda	miglustat (gaa deficiency) cap	65 MG	8	Capsules	28	DAYS			
Yargesa ; Zavesca	Miglustat Cap 100 MG	100 MG	90	Capsules	30	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Cerdelga	eliglustat tartrate cap	84 MG	Medicaid
Opfolda	miglustat (gaa deficiency) cap	65 MG	Medicaid
Yargesa ; Zavesca	miglustat cap	100 MG	Medicaid

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Cerdelga	Eliglustat Tartrate Cap 84 MG (Base Equivalent)	84 MG	Medicaid
Opfolda	miglustat (gaa deficiency) cap	65 MG	Medicaid
Yargesa ; Zavesca	Miglustat Cap 100 MG	100 MG	Medicaid

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Cerdelga, Zavesca	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND BOTH of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. ONE of the following: A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **AND** 2. The prescriber has assessed current status of the following: spleen volume, hemoglobin level, liver volume, platelet count, growth, bone pain or crisis **OR** B. ALL of the following: 1. The patient has a diagnosis of Gaucher disease type 1 (GD1) **AND** 2. ONE of the following: A. The patient has baseline (prior to therapy for the requested indication) glucocerebrosidase enzyme activity of less than or equal to 15% of mean normal in fibroblasts, leukocytes, or other nucleated cells **OR** B. Genetic analysis confirmed two (2) pathogenic alleles in the glucocerebrosidase (*GBA*) gene **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The patient does NOT have any neuronopathic symptoms indicative of Gaucher disease type 2 or type 3 [e.g., bulbar signs (e.g., stridor,

Module	Clinical Criteria for Approval

strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonos, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, ataxia] **AND**

5. The prescriber has assessed baseline (prior to therapy for the requested indication) status of hemoglobin level, platelet count, liver volume, and spleen volume **AND**
6. The patient has at least ONE of the following clinical presentations at baseline (prior to therapy for the requested indication):
    A. Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of the normal range based on age and gender **OR**
    B. Thrombocytopenia (platelet count less than 100,000/microliter on at least 2 measurements) **OR**
    C. Hepatomegaly **OR**
    D. Splenomegaly **OR**
    E. Growth failure (i.e., growth velocity is below the standard mean for age) **OR**
    F. Evidence of bone disease with other causes ruled out **AND**
7. If the requested agent is Zavesca or miglustat, enzyme replacement therapy (ERT) is NOT a therapeutic option (e.g., due to allergy, hypersensitivity, poor venous access, previous ERT failure) **AND**

2. If the requested agent is Cerdelga or eliglustat, the patient is a CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM), as detected by an FDA-cleared test for determining CYP2D6 genotype **AND**
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
    A. The patient's medication history includes use of the generic equivalent **OR**
    B. BOTH of the following:
        1. The prescriber has stated that the patient has tried the generic equivalent **AND**
        2. The generic equivalent was discontinued due to lack of effectiveness or an adverse event **OR**
    C. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
    D. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
    E. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent **OR**

Brand	Generic Equivalent
Zavesca	miglustat

    F. The patient is currently being treated with the requested agent as indicated by ALL of the following:
        1. A statement by the prescriber that the patient is currently taking the requested agent **AND**
        2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND**
        3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR**
    G. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
5. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Opfolda, Zavesca) for the requested indication **AND**

Module	Clinical Criteria for Approval

6. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
   A. Spleen volume **OR**
   B. Hemoglobin level **OR**
   C. Liver volume **OR**
   D. Platelet count (sufficient to decrease the risk of bleeding) **OR**
   E. Growth **OR**
   F. Bone pain or crisis **AND**
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
   A. The patient's medication history includes use of the generic equivalent **OR**
   B. BOTH of the following:
      1. The prescriber has stated that the patient has tried the generic equivalent **AND**
      2. The generic equivalent was discontinued due to lack of effectiveness or an adverse event **OR**
   C. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
   D. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
   E. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent **OR**

Brand	Generic Equivalent
Zavesca	**miglustat**

   F. The patient is currently being treated with the requested agent as indicated by ALL of the following:
      1. A statement by the prescriber that the patient is currently taking the requested agent **AND**
      2. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent **AND**
      3. The prescriber states that a change in therapy is expected to be ineffective or cause harm **OR**
   G. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of patient's diagnosis **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>5. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Opfolda, Zavesca) for the requested indication AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.</td></tr>
<tr><td>Opfolda</td><td>Initial Evaluation

Opfolda will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Opfolda</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient has a diagnosis of late-onset Pompe disease (acid maltase deficiency [AMD]; glycogen storage disease type II [GSDII]) confirmed by at least ONE of the following:
A. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the GAA gene OR
B. The patient has deficient acid alpha-glucosidase glycogen enzyme activity in dried blood spots, leukocytes, skin fibroblasts, and/or skeletal muscle tissue AND
2. The patient is not improving on their current enzyme replacement therapy (ERT) AND
3. The requested agent will be taken in combination with Pombiliti AND
4. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient’s age for the requested indication AND
2. The prescriber has assessed current status of the following: gross motor function (e.g., walking distance), pulmonary function (e.g., forced vital capacity [FVC]) AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

Renewal Evaluation

Opfolda will be approved when ALL of the following are met:</td></tr>
</table>

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Gross motor function (e.g., walking distance) **OR** B. Pulmonary function (e.g., forced vital capacity [FVC]) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months