miglustat (Zavesca®); miglustat (Opfolda™) eliglustat (Cerdelga®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO135

Description
Miglustat (Zavesca, Opfolda) and eliglustat (Cerdelga) are orally administered glucosylceramide synthase inhibitors.

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

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
miglustat (generic Zavesca)	Mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option	100 mg capsules	90 capsules/30 days
miglustat (Zavesca)		100 mg capsules	
miglustat (Opfolda)	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)	65 mg capsules	8 capsules/28 days
eliglustat (Cerdelga)	Type 1 Gaucher disease; CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs)	84 mg capsules	56 capsules/28 days
	Type 1 Gaucher disease; CYP2D6 poor metabolizers (PMs)		28 capsules/28 days

Initial Evaluation

I. **Miglustat (Zavesca) or eliglustat (Cerdelga)** may be considered medically necessary when the following criteria are met:
   A. Member is 18 years of age or older; **AND**

B. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Gaucher disease (e.g., endocrinologist, geneticist, hematologist, etc.); **AND**
C. Will not be used in combination with other medications used to treat type 1 Gaucher disease [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv), other agents listed in this policy, etc.]; **AND**
D. A diagnosis of **type 1 Gaucher disease** when the following are met:
    1. Diagnosis is confirmed by **one** of the following:
        i. Deficiency of glucocerebrosidase (acid β-glucosidase) enzyme activity in peripheral blood leukocytes or cultured fibroblasts; **OR**
        ii. Genetic testing confirming mutation in glucocerebrosidase (*GBA*) gene; **AND**
    2. The request is for generic miglustat or brand miglustat (Zavesca); **AND**
        i. Treatment with **ONE** enzyme replacement therapy (ERT) [e.g., imiglucerase (Cerezyme), taliglucerase (Elelyso), velaglucerase (Vpriv)] has been ineffective, contraindicated, or not tolerated; **AND**
        ii. If the request is for brand miglustat (Zavesca), the member has an intolerance or contraindication to generic miglustat; **OR**
    3. The request is for eliglustat (Cerdelga); **AND**
        i. The member has undergone CYP2D6 genotyping by an FDA-cleared test and is classified as one of the following: [Note: eliglustat (Cerdelga) is not indicated for ultra-rapid metabolizers]
            a. Poor Metabolizer (PM); **OR**
            b. Intermediate Metabolizer (IM); **OR**
            c. Extensive Metabolizer

II. **Miglustat (Opfolda)** may be considered medically necessary when the following criteria are met:
A. Member is 18 years of age or older; **AND**
B. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Pompe disease (e.g., neurologist, geneticist, pulmonologist, etc.); **AND**
C. Medication will not be used in combination with any other enzyme replacement therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)]; **AND**
D. A diagnosis of **late-onset Pompe disease [Acid Alpha-Glucosidase (GAA) deficiency]** when the following are met:
    1. Diagnosis is confirmed by one of the following:
        i. Enzyme assay showing a deficiency of acid alpha-glucosidase (GAA) activity in the blood, skin, or muscle; **OR**
        ii. Detection of biallelic pathogenic variants in the GAA gene by molecular genetic testing; **AND**
    2. Attestation member has an actual body weight of at least 40 kilograms; **AND**
    3. Documentation of baseline values for percent predicted forced vital capacity (FVC) and/or 6-minute walk test (6MWT); **AND**

4. Treatment with enzyme replacement therapy [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme) has been ineffective or not tolerated; **AND**
5. Medication will be used in combination with cipaglucosidase alfa-atga (Pombiliti)

III. Miglustat (Zavesca), miglustat (Opfolda), and/or eliglustat (Cerdelga) are considered investigational when used for all other conditions, including but not limited to:
   A. Type 3 Gaucher disease
   B. Gangliosidases (GM1 and GM2)
   C. Cystic Fibrosis
   D. Infantile Pompe Disease
   E. HIV Infection
   F. Niemann-Pick Disease
   G. Tay-Sachs Disease
   H. Sandhoff Disease

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
   A. For a diagnosis of type 1 Gaucher disease:
      1. Miglustat (Zavesca) or eliglustat (Cerdelga) will not be used in combination with other medications used for the treatment of type 1 Gaucher disease (i.e. will be used as monotherapy); **AND**
      2. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in mean liver volume and/or spleen volumes, changes in hemoglobin levels and platelet count, etc.] and/or symptoms [e.g., fatigue, bleeding episodes, bruising, bone pain, etc.]; **OR**
   B. For a diagnosis of late-onset Pompe disease [Acid Alpha-Glucosidase (GAA) deficiency**; AND**
      1. Medication will not be used in combination with any other enzyme replacement therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)]; **AND**
      2. Medication will be used in combination with cipaglucosidase alfa-atga (Pombiliti); **AND**
      3. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in 6MWT, FVC, etc.]

Supporting Evidence

Gaucher Disease

I. Miglustat (Zavesca) obtained FDA approval for treatment of type 1 Gaucher disease in 2003 based on the result of two open-label, uncontrolled studies and one randomized, open-label, active-controlled study. In the uncontrolled open-label trials, patients experienced a significant mean reduction in liver and spleen volume from baseline and non-significant change in platelet counts and hemoglobin concentration. These results were maintained or further decreased during the extension period of both trials. In the randomized, active-controlled study, patients were randomized to receive miglustat (Zavesca) alone, imiglucerase (Cerezyme) alone, or miglustat (Zavesca) in combination with imiglucerase (Cerezyme). There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant reduction in platelet counts between the miglustat (Zavesca) and imiglucerase (Cerezyme) monotherapy groups. During the open-label extension period, all patients were transitioned to miglustat (Zavesca) monotherapy and no significant changes liver volume, spleen volume, or hemoglobin concentration were observed.

II. Eliglustat (Cerdelga) obtained FDA approval for treatment of type 1 Gaucher disease under priority review in 2014 based on the results of one randomized, double-blind, placebo-controlled study in treatment naïve patients and one randomized, open-label, active-controlled, non-inferiority study in patients transitioning from enzyme replacement therapy.

III. A randomized, double-blind, placebo-controlled trial investigated eliglustat (Cerdelga) against placebo in type 1 Gaucher disease treatment naive patients. The results showed a statistically significant improvement in percentage change in spleen volume and liver volume, absolute change in hemoglobin level, and percentage change in platelet count from baseline to nine months compared to placebo. During the open label extension phase, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the two-year trial duration and through four years in a separate uncontrolled trial.

IV. A randomized, open-label, active-controlled, non-inferiority study evaluated eliglustat (Cerdelga) versus imiglucerase in patients who were previously treated with enzyme replacement therapy. The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume and spleen volume) based on changes between baseline and 12 months according to pre-specified thresholds of change. Eliglustat (Cerdelga) met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. During the open-label extension phase, patients continued to show stability, as previously defined in the initial 12 months of the trial, at two years of treatment.

V. Patients enrolled in the studies for miglustat (Zavesca) and eliglustat (Cerdelga) were 18 and older. The safety and/or efficacy of use in pediatric and adolescent patients has not been evaluated.

VI. Miglustat (Zavesca) and eliglustat (Cerdelga) have largely been studied as monotherapy, with the exception of one treatment arm in a single study involving miglustat (Zavesca). Long-term safety and efficacy of either agent used in combination with enzyme replacement therapy, or other agents used to treat type 1 Gaucher disease has not been evaluated.

VII. Gaucher disease is a rare autosomal recessive lysosomal storage disorder (LCD) that is caused by mutations in the glucocerebrosidase enzyme (*GBA*) and/or deficiency of the enzyme glucocerebrosidase. Diagnosis of Gaucher disease type 1 should be confirmed by a physician specializing in the treatment of Gaucher disease via blood tests to confirm deficiency of the glucocerebrosidase enzyme (acid β-glucosidase) in peripheral leukocytes or cultured fibroblasts or genetic testing to confirm mutation in *GBA* prior. Treatment is not necessary for all patients with Gaucher disease type 1, as some patients are asymptomatic. However, treatment is generally lifelong for symptomatic patients once treatment is initiated.

VIII. According to recent guidelines, treatment with enzyme replacement therapy (ERT) remains first-line treatment for type 1 Gaucher disease and is delivered intravenously. Miglustat (Zavesca) is a second line oral treatment indicated when ERT is no longer accepted by the patient or cannot be tolerated. Eliglustat (Cerdelga) may be used as a first-line treatment alternative to ERT.

IX. Miglustat (Zavesca) is commonly discontinued due to adverse effects including diarrhea (observed in over 85% of patients during clinical trials), weight loss (~65%), tremor and peripheral neuropathy. Eliglustat (Cerdelga) is generally better tolerated with the most common adverse events comprising of arthralgia (45%), back pain (12%), fatigue (14%) and headache (13 to 40%).

X. Miglustat (Zavesca) is contraindicated in women who are or may become pregnant. Providers should discuss the risks of teratogenicity when administered to women of reproductive potential.

XI. Eliglustat (Cerdelga) was found to be heavily affected by a patient's CYP2D6 metabolizer status and therefore requires CYP2D6 genotyping before prescribing. Recommended dosing differs between poor metabolizers and intermediate/extensive metabolizers. Eliglustat (Cerdelga) is not recommended for ultra-rapid metabolizers due to difficulty obtaining reliable blood levels of the drug. Concurrent use of strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, etc.) is not recommended and these agents should be discontinued prior to initiating therapy with eliglustat (Cerdelga).

Late-onset Pompe Disease

I. Pompe disease (acid alpha-glucosidase deficiency) is characterized by the accumulation of glycogen within the lysosomes of all tissues. The defect in the lysosomal GAA enzyme affects lysosomal-mediated degradation of glycogenesis. Therapies for Pompe disease aim to mimic the GAA enzyme [i.e., enzyme replacement therapy (ERT)].

II. Pompe disease manifests in one of two forms: infantile-onset disease, also known as classic disease which presents within the first few months of life, or late-onset disease which can present at any age. The course of late-onset disease is variable and progresses differently for

each individual patient ranging from asymptomatic to severe progressive myopathy. In late-onset Pompe disease, the primary clinical finding is skeletal myopathy, with a more protracted course leading to respiratory failure. Adults may also progress with progressive, proximal weakness in a limb-girdle distribution which impacts the ability to walk. This weakness can affect the diaphragm leading to respiratory insufficiency early in the course of disease. In untreated patients with late-onset disease, the estimated five-year survival rate from the time of diagnosis was 95 percent and dropped to 40 percent at 30 years post-diagnosis.

III. GAA deficiency can be confirmed via enzyme assay from the blood, skin, or muscle. Additionally, pathogenic variants of the GAA gene can be identified via molecular genetic testing. The late-onset form of GAA deficiency should be suspected in children and adults with progressive proximal weakness in a limb-girdle distribution. Additionally, the forced vital capacity (FVC) on pulmonary function testing typically is reduced substantially in adults. GAA enzyme activity can be measured in white blood cells or dried blood spots. Though gene sequencing is the preferred test to confirm the diagnosis since it is routinely available, is less invasive, may provide genotype-phenotype information, and may help predict cross-reactive immunologic material (CRIM) status (amount of residual endogenous GAA production) in some cases. The finding of two pathogenic variants in trans in the GAA gene is considered confirmatory.

IV. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was FDA approved in 2023 for the treatment of adults living with late-onset Pompe disease (LOPD) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy (ERT). The combination has not been approved for use as a front-line ERT. Miglustat (Opfolda) is to be administered approximately one hour before the intravenous (IV) administration of cipaglucosidase alfa-atga (Pombiliti). As cipaglucosidase alfa-atga (Pombiliti) is an IV infusion it is coverable under the medical benefit.

V. The combination acts together by joint mechanisms. Cipaglucosidase alfa-atga (Pombiliti) is a recombinant human GAA enzyme (rhGAA) designed for increased uptake into muscle cells. Once in the cell, cipaglucosidase alfa-atga (Pombiliti) can be properly processed into its most active and mature form to break down glycogen. Miglustat (Opfolda) is an enzyme stabilizer designed to stabilize the enzyme in the blood. Miglustat (Opfolda) itself is not an ERT, its use as an enzyme stabilizer has not been studied in combination with other ERT therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)].

VI. Cipaglucosidase alfa-atga (Pombiliti) and miglustat (Opfolda) are not FDA approved for the treatment of those under the age of 18 or for those less than 40 kilograms. Given the complexities of the treatment of Pompe disease treatment under the care of a specialist is required (e.g., neurologist, geneticist, pulmonologist, etc.).

VII. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was approved based on the result of a phase III, randomized, double-blind, parallel-group trial. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was studied against alglucosidase-alfa plus placebo. Both regimens were administered in blinded dosage forms every

two weeks. Both ERT-experienced and ERT-naïve patients were included. All patients were required to have a sitting forced vital capacity (FVC) of at least 30% of the predicted value for healthy adults and to have performed two valid 6-min walk tests (both 6-min walk test screening values had to be ≥75 m and ≤90% of the predicted value for healthy adults).

VIII. In the overall population, at week 52, mean change from baseline in 6MWD was 20.8 m (SE 4.6) in the cipaglucosidase alfa (Pombiliti) plus miglustat (Opfolda) group versus 7.2 m (6.6) in the alglucosidase alfa plus placebo group using last observation carried forward (between-group difference 13.6 m [95% CI –2·8 to 29.9]); however, the difference did not reach statistical significance (trial was powered for superiority). The relationship of this improvement in 6MTD is only an indirect measure as compared to other marketed products as the result was not statistically significant. The change from baseline at week 52 for FVC was measured as -0.9% in the treatment group as compared to -4.0% in the comparator group. While there are numerical differences between the treatment groups, statistical analyses of secondary endpoints were not performed as the primary endpoint did not achieve statistical significance. As such, numerical comparisons may be made, but the applicability of these results should be used with caution.

IX. Twelve serious adverse events occurred in eight patients in the cipaglucosidase alfa plus miglustat group; only one event (anaphylaxis) was deemed related to study drug. One serious adverse event (stroke) occurred in the alglucosidase alfa plus placebo group, which was deemed unrelated to study drug. Common adverse effects included fall (29% vs 39%), headache (24% vs 24%), nasopharyngitis (22% vs 8%), myalgia (16% vs 13%), and arthralgia (15% vs 13%) in the cipaglucosidase alfa (Pombiliti) + miglustat (Opfolda) and alglucosidase alfa + placebo groups respectively.

Investigational or Not Medically Necessary Uses

I. Miglustat (Zavesca) and/or eliglustat (Cerdelga) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
   A. Type 3 Gaucher disease
   B. Gangliosidases (GM1 and GM2)
   C. Cystic Fibrosis
   D. Infantile Onset Pompe Disease
   E. HIV Infection
   F. Niemann-Pick Disease
   G. Tay-Sachs Disease
   H. Sandhoff Disease

References

1. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int. J. Mol. Sci.* 2017, 18, 441; doi: 10.3390/ijms18020441

2. Gary SE, Ryan E, et al. Recent advances in the diagnosis and management of Gaucher disease. *Expert Rev Endocrinol Metab*. 2018 March; 13(2):107-118. Doi:10.1080/17446651.2018.1445524.
3. Wang RY, Bodamer OA, et al. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. ACMG Standards and Guidelines. *Genetics in Medicine*. 2011 May; 13(5).
4. Miglustat [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. November 2017.
5. Eliglustat [Prescribing Information]. Genzyme Ireland, Ltd.: Waterford, Ireland. August 2018.
6. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial Schoser B, Roberts M, Byrne BJ, et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial [published correction appears in Lancet Neurol. 2023 Oct;22(10):e11]. *Lancet Neurol*. 2021;20(12):1027-1037.
7. Schoser B, Kishnani PS, Bratkovic D, et al. 104-week efficacy and safety of cipaglucosidase alfa plus miglustat in adults with late-onset Pompe disease: a phase III open-label extension study (ATB200-07). J Neurol. 2024;271(5):2810-2823.
8. Opfolda [Prescribing Information]. Amicus Therapeutics US, LLC. Philadelphia, PA. September 2023.
9. Pombiliti [Prescribing Information]. Amicus Therapeutics US, LLC. Philadelphia, PA. September 2023.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to include Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) for the treatment of late-onset Pompe disease. Updated E/I criteria from Pompe disease to include the infantile-onset subtype of Pompe disease specifically. Updated formatting of the supporting evidence.	06/2024
Transitioned criteria to new policy format and combined previous miglustat and eliglustat criteria into one policy and added the following requirements: age 18 and older, prescribed by or in consultation with specialist, used as monotherapy and diagnosis confirmed by genetic and/or blood testing	11/2020
Miglustat (Zavesca) criteria created	05/2018
Eliglustat (Cerdelga) criteria created	11/2014