

09-J0000-76

Original Effective Date: 09/15/08

Reviewed: 06/14/23

Revised: 04/01/24

Subject: Oral Therapy for Gaucher and Pompe Disease

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

[Gaucher disease](#) is characterized by a deficiency of β -glucocerebrosidase activity, resulting in accumulation of glucocerebrosidase in tissue macrophages which become engorged and are typically found in the liver, spleen and bone marrow and occasionally in lung, kidney and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia, with secondary pathological fractures. Some forms of Gaucher disease cause significant disability and can be fatal.

Symptoms of Gaucher disease include fatigue, prolonged bleeding, easy bruising, bone pain, and pathological fractures. Signs of Gaucher disease include an enlarged spleen and liver, severe anemia, abnormal pigmentation, bone lesions, and occasionally lung dysfunction. In more severe cases, toxic levels of glycolipids accumulate in the nervous system, causing neuronal loss. Most cases have no neurological involvement and are not diagnosed until adulthood (Type I). The clinical severity of type 1 is variable; some individuals never become symptomatic, and are only diagnosed after death (from other causes) upon autopsy. Other individuals with type 1 disease develop crippling skeletal symptoms during childhood.

The preferred treatment of type 1 Gaucher disease is enzyme replacement therapy (e.g., imiglucerase [Cerezyme[®]], velaglucerase [Vpriv[™]], or taliglucerase [Elelyso[™]]), which increases the degradation of glucocerebrosidase in macrophages with resultant reduction in the manifestations of Gaucher disease. However, oral treatment is available with Eliglustat (Cerdelga[®]) and Miglustat (Zavesca[®]).

Eliglustat is an oral glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1). Unlike enzyme replacement therapies, which break down fatty deposits that build up in cells of patients with Gaucher disease, eliglustat slows the accumulation of

the fatty deposits by inhibiting the metabolic process that forms them. Although ease of oral administration provides substantial benefit over intravenous enzyme replacement therapy, eliglustat use is somewhat limited by cytochrome P450 (CYP450) 2D6 genotype. Eliglustat is primarily metabolized via CYP2D6 and, to a lesser extent, CYP3A. Patient selection should take into account CYP2D6 metabolizer status, as established by a FDA-cleared test. Patients who are CYP2D6 ultra-rapid metabolizers may not achieve therapeutic concentrations of eliglustat. Poor metabolizers require dosage reduction. In addition, depending on the patient's CYP2D6 metabolizer status, concomitant administration of some CYP2D6 and CYP3A inhibitors may be contraindicated or require dosage adjustment to reduce the risk of potentially significant ECG changes.

Miglustat is approved for the management of mild to moderate nonneuronopathic (type1) Gaucher disease in individuals for whom enzyme replacement therapy is unsuitable (e.g., because of allergy, hypersensitivity, poor venous access). Unlike enzyme replacement therapy, miglustat inhibits the formation of the substrate (glucocerebroside) for the deficient enzyme (substrate reduction therapy). Because all individuals with type 1 Gaucher disease have some level of residual glucocerebrosidase activity, reduction in the amount of substrate allows the residual activity of the deficient enzyme to be more effective, decreasing glucocerebroside accumulation in macrophages. Of note, the safety and efficacy of miglustat have not been established in individuals with severe type 1 Gaucher disease (i.e., hemoglobin less than 9 g/dL, platelet count less than 50,000/mm³, or active bone disease).

Pompe Disease

Pompe disease, or glycogen storage disease type II (GSD II), is an autosomal-recessive lysosomal storage disorder that causes a deficiency of the enzyme acid alpha-glucosidase (GAA). When GAA is not present in adequate amounts, lysosomal glycogen accumulates in tissues throughout the body, most often in the skeletal, cardiac, and smooth muscles. The severity of the disease varies based on the age of onset, organ involvement, rate of progression, and severity/degree of muscle involvement. Pompe disease is diagnosed by GAA enzyme activity in the blood and/or other tissue, and genetic sequencing. The presence of two pathogenic variants in the GAA gene is sufficient to diagnose Pompe disease; however, some patients may only have one pathogenic variant.

Pompe disease is treated with enzyme replacement therapy (ERT) – currently there are three FDA approved products available: alglucosidase alfa (Lumizyme), avalglucosidase alfa-ngpt (Nexviazyme), and cipaglucosidase alfa-atga (Pombiliti) in combination with miglustat (Opfolda). Alglucosidase is approved for treatment of both infantile-onset Pompe disease and late-onset Pompe disease. Avalglucosidase and cipaglucosidase alfa-atga (in combination with miglustat) are approved for treatment of late-onset Pompe disease only.

The safety and efficacy of cipaglucosidase alfa-atga were evaluated in adult patients (n=123) with late-onset Pompe disease in the PROPEL study. Patients were randomized 2:1 to receive either cipaglucosidase alfa 20 mg/kg IV every 2 weeks plus miglustat 195 mg for patients weighing 40 to less than 50 kg or 260 mg for patients weighing 50 kg or greater (n=85), or alglucosidase alfa 20 mg/kg IV every 2 weeks plus placebo (n=38); miglustat and placebo were administered 1 hour prior to the IV infusions.

After 52 weeks, the mean change in 6-minute walk distance (6MWD) in patients receiving cipaglucosidase alfa plus miglustat was numerically but not significantly greater than that of patients receiving alglucosidase alfa plus placebo (20.8 m vs 7.2 m; between-group difference, 13.6 m [95% CI, -2.8 to 29.9]). The change from baseline in percent predicted sitting FVC was significantly lower at week 52 in the cipaglucosidase alfa plus miglustat group compared with alglucosidase alfa (mean change, -0.9% vs -4%; between-group difference, 3% [95% CI, 0.7 to 5.3]); sitting FVC (% predicted) stabilized in enzyme-replacement therapy (ERT)-experienced patients treated with cipaglucosidase alfa compared with worsening in ERT-experienced patients treated with alglucosidase alfa. In ERT-naïve patients, alglucosidase plus placebo was associated with a numerical but not significant advantage over cipaglucosidase alfa plus miglustat in the mean change in 6MWD and sitting FVC. In the overall population, ERT-experienced, and ERT-naïve patients, creatine kinase and urinary glucose tetrasaccharide (Hex4) levels were significantly reduced at week 52 in the cipaglucosidase alfa plus miglustat group compared with alglucosidase alfa plus placebo.

Serious treatment-emergent adverse events occurred in 9% of patients receiving cipaglucosidase alfa plus miglustat compared with 3% receiving alglucosidase alfa plus placebo; only 1 event in the cipaglucosidase alfa group was attributed to study treatment. The most frequently reported adverse events included falls (29% vs 39%), headache (24% vs 24%), nasopharyngitis (22% vs 8%), myalgia (16% vs 13%), arthralgia (15% vs 13%), and urinary tract infection (14% vs 5%). Infusion-associated reactions occurred in 25% and 26% of patients, and 3 patients in the cipaglucosidase alfa group and 1 patient in the alglucosidase alfa group withdrew from the study due to adverse events.

POSITION STATEMENT:

Initiation of eliglustat (Cerdelga) or miglustat (generic or brand Zavesca) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with Type 1 Gaucher disease confirmed by either of the following:
 - a. Genotype testing indicating a mutation of two alleles of the glucocerebrosidase genome – laboratory documentation must be provided
 - b. Glucocerebrosidase activity deficiency in the white blood cells/skin fibroblasts – laboratory documentation must be provided
2. Drug will be used as monotherapy (i.e., not in combination with eliglustat [Cerdelga], miglustat [Zavesca], imiglucerase [Cerezyme], alglucerase [Ceredase], velaglucerase [Vpriv], or taliglucerase [Elelyso])
3. Member meets **ALL** criteria for requested product:
 - a. Eliglustat: Member has undergone an FDA-approved test and been proven to be **ONE** of the following:
 - i. Extensive CYP2D6 metabolizer – laboratory documentation must be provided
 - ii. Intermediate CYP2D6 metabolizer – laboratory documentation must be provided
 - iii. Poor CYP2D6 metabolizer – laboratory documentation must be provided

- b. Miglustat (generic):
 - i. Intravenous enzyme replacement therapy is not a therapeutic option due to allergy, hypersensitivity, or poor venous access – documentation from the medical record must be provided
 - c. Zavesca (brand):
 - i. Intravenous enzyme replacement therapy is not a therapeutic option due to allergy, hypersensitivity, or poor venous access – documentation from the medical record must be provided
 - ii. Member has tried and had intolerable adverse effects to generic miglustat – specific intolerance to generic miglustat and rationale for use of brand Zavesca must be provided in addition to BOTH of the following:
 - Completed Medwatch reporting form (FDA 3500) - <https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda>
 - Completed Naranjo Adverse Drug reaction probability scale - <https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf>
4. Member is currently receiving enzyme replacement therapy **OR** has one or more of the following conditions:
 - a. Hemoglobin at least 1.0 g/dL below lower limit of normal for age and gender
 - b. Thrombocytopenia (platelet count less than 120,000)
 - c. Clinically significant hepatomegaly
 - d. Clinically significant splenomegaly
 - e. Evidence of bone disease other than Erlenmeyer flask deformity or mild osteopenia.
 5. Member is 18 years of age or older
 6. Dose does not exceed:
 - a. Eliglustat:
 - i. Extensive CYP2D6 metabolizer: 84 mg twice daily
 - ii. Intermediate CYP2D6 metabolizer: 84 mg twice daily
 - iii. Poor CYP2D6 metazolizer: 84 mg once daily
 - b. Miglustat (generic): 300 mg/day
 - c. Zavesca: 300 mg/day

Approval duration: 1 year

Continuation of eliglustat (Cerdelga) or miglustat (generic or brand Zavesca) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another health plan in the past two years for treatment of Type 1 Gaucher disease, OR the member has previously met all indication-specific criteria
2. Member demonstrates a clinical improvement in symptoms following initiation of eliglustat or miglustat – documentation from the medical record must be provided
3. Drug will be used as monotherapy (i.e., not in combination with eliglustat [Cerdelga], miglustat [Zavesca], imiglucerase [Cerezyme], alglucerase [Ceredase], velaglucerase [Vpriv], or taliglucerase [Elelyso])
4. Dose does not exceed:
 - a. Eliglustat:
 - i. Extensive CYP2D6 metabolizer: 84 mg twice daily
 - ii. Intermediate CYP2D6 metabolizer: 84 mg twice daily
 - iii. Poor CYP2D6 metabolizer: 84 mg once daily
 - b. Miglustat (generic): 300 mg/day
 - c. Zavesca: 300 mg/day

Approval duration: 1 year

Initiation of miglustat (Opfolda) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Member is diagnosed with late-onset Pompe Disease
2. Use will be in combination with cipaglucosidase alfa-atga (Pombiliti) – documentation from the medical record must be provided
3. Member meets **ONE** of the following:
 - a. Member has been approved for treatment with cipaglucosidase alfa-atga (Pombiliti) by Florida Blue as demonstrated by an active authorization – documentation of approved authorization must be provided
 - b. Member meets **ALL** of the following:
 - i. Member's diagnosis is confirmed by one of the following:
 - Acid alpha-glucosidase (GAA) enzyme activity level less than or equal to 40% of normal – laboratory documentation must be provided
 - Two mutations in the GAA gene – laboratory documentation must be provided
 - ii. Member disease is symptomatic (e.g., cardiac hypertrophy, respiratory distress, skeletal muscle weakness, etc.) – documentation from the medical record must be provided
 - iii. Member is currently treated with enzyme replacement therapy **AND** is not improving – documentation from the medical record must be provided
 - iv. Member weighs at least 40 kg
4. Dose does not exceed 260 mg every two weeks

Approval duration: 1 year

Continuation of miglustat (Opfolda) **meets the definition of medical necessity** when **ALL** of the following criteria are met:

1. Authorization/reauthorization has been previously approved by Florida Blue or another healthplan for the treatment of Pompe Disease (if another health plan, documentation of a health plan-paid claim for Opfolda during the 90 days immediately before the request must be submitted), **OR** the member has previously met all indication-specific criteria
2. Member meets **ONE** of the following:
 - a. Member has been approved for treatment with cipaglucosidase alfa-atga (Pombiliti) by Florida Blue as demonstrated by an active authorization – documentation of approved authorization must be provided
 - b. Member is receiving a beneficial response (such as, but not limited to, improved motor function, endurance, % predicted FVC) to treatment with Opfolda – documentation from the medical record must be provided
3. Member weighs at least 40 kg
4. Dose does not exceed: 260 mg every two weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-Approved:

- Eliglustat: 84 mg orally twice daily
- Miglustat (generic), Zavesca: 100 mg orally three times daily
- Opfolda:
 - 260 mg for patients weighing ≥ 50 kg
 - 195 mg for patients weighing ≥ 40 kg to < 50 kg

Dosage Adjustments

- Eliglustat:
 - CYP2D6 extensive metabolizers (EMs): 84 mg/dose PO twice daily
 - CYP2D6 intermediate metabolizers (IMs): 84 mg/dose PO twice daily
 - CYP2D6 poor metabolizers (PMs): 84 mg/dose PO once daily
- Miglustat (generic), Zavesca:
 - Renal Impairment:
 - Mild impairment (CrCl 50-70 ml/min): Reduce dose to 100 mg twice daily
 - Moderate impairment (CrCl 30-50 ml/min): Reduce dose to 100 mg daily

- Severe impairment (CrCl less than 30 ml/min): Avoid use
- Adverse Reactions (e.g., diarrhea or tremor): Reduce dose to 100 mg once or twice daily

Drug Availability:

- Eliglustat is available as an 84 mg capsule
- Miglustat (generic) and Zavesca are available as a 100 mg hard gelatin capsule
- Opfolda is available as a 65 mg capsule

PRECAUTIONS:

CONTRAINDICATIONS

- Eliglustat:
 - CYP2D6 EMs and IMs taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor
 - CYP2D6 IMs and PMs taking a strong CYP3A inhibitor
- Miglustat: None
- Opfolda: Pregnancy

WARNINGS

- Eliglustat:
 - ECG Changes and Potential for Cardiac Arrhythmias
- Miglustat:
 - **Peripheral Neuropathy:** Members should undergo baseline and repeat neurological evaluations at approximately 6-month intervals. Development of symptoms such as numbness and tingling require careful re-assessment of risk/benefit of miglustat therapy and treatment discontinuation may be considered.
 - **Gastrointestinal:** Diarrhea and weight loss were common in clinical studies. Members with persistent gastrointestinal events should be evaluated to determine if significant underlying gastrointestinal disease is present.
 - **Tremor:** In clinical studies, tremor was observed, usually occurring within the first month of therapy and in many cases resolved between 1 to 3 months during treatment. Dose reduction may ameliorate tremor usually within days, but discontinuation may sometimes be required.
- Opfolda
 - **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

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

G0138	Intravenous infusion of cipaglucosidase alfa-atga, including provider/supplier acquisition and clinical supervision of oral administration of miglustat in preparation of receipt of cipaglucosidase alfa-atga [related to Opfolda only]
J1202	Miglustat, oral, 65 mg [for Opfolda only]
J8499	Prescription drug, oral, non-chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity:

E75.22	Gaucher disease
E74.02	Pompe disease [for Opfolda only]

REIMBURSEMENT INFORMATION:

Refer to section entitled [POSITION STATEMENT](#).

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

DEFINITIONS:

Gaucher disease: Is a familial disorder of lipid metabolism resulting in an accumulation of abnormal glucocerebrosides in reticuloendothelial cells, and manifested clinically by hepatosplenomegaly, skin pigmentation, skeletal lesions, and pingueculae.

Type C Niemann-Pick Disease: Niemann-pick disease refers to a group of inherited diseases in which lipids collect in the cells of the spleen, liver, and brain. There are four most commonly recognized forms of the disease: Types A, B, C, and D. Type C occurs when the body cannot properly break down cholesterol and other lipids. It usually affects school-aged children.

RELATED GUIDELINES:

[Intravenous Enzyme Replacement Therapy for Gaucher Disease, 09-J0000-41](#)

OTHER:

None applicable.

REFERENCES:

1. Actelion Pharmaceuticals. Zavesca (miglustat). 2019 [cited 6/2/23]. In: DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=817892d1-ee12-4632-85fc-57ccdf16d7b8/>.
2. Amicus Therapeutics. Miglustat (Opfolda) capsule. 2023 [cited 2/1/24]. In DailyMed [Internet]. Bethesda (MD): National Library of Medicine. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7c38298-37db-5a80-e053-2995a90aee40>.
3. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2020 [cited 6/2/23]. Available from: <http://www.clinicalpharmacology.com/>.
4. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine; 2000 Feb 29 - [cited 6/2/23]. Available from: <http://clinicaltrials.gov/>.
5. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 6/2/23].
6. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2020 [cited 6/2/23]. Available from: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/>.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 02/14/24.

GUIDELINE UPDATE INFORMATION:

09/15/08	New Medical Coverage Guideline.
10/15/09	Review and revision; consisting of adding definition and updating references.
12/15/10	Review and revision; consisting of updating coding and references.
12/15/11	Review and revision to guideline; consisting of updating precautions and references.
12/15/12	Review and revision to guideline; consisting of revising description, position statement, dosage administration, and precaution sections; added contraindications section.
07/15/13	Review and revision to guideline; consisting of revising position statement to include approval duration and updating program exceptions and references.
07/15/14	Review and revision to guideline; consisting of reformatting position statement, updated dosage/administration section, references, and coding.
11/15/14	Revision to guideline; consisting of description, position statement, dosage/administration, precautions/warnings, references.
01/15/15	Revision to guideline; consisting of updating position statement.
07/15/15	Review and revision to guidelines; consisting of updating description, position statement, coding, references.
11/01/15	Revision: ICD-9 Codes deleted.
01/15/16	Revision to guideline; consisting of updating position statement.
07/15/16	Review and revision to guideline; consisting of updating position statement.
07/15/17	Review and revision to guideline; consisting of updating position statement and description.

07/15/18	Review and revision to guideline; consisting of updating references and position statement.
07/15/19	Review and revision to guideline; consisting of updating references.
07/15/20	Review and revision to guideline; consisting of updating position statement and references.
07/15/23	Review and revision to guideline; consisting of updating references.
04/01/24	Review and revision to guideline; consisting of updating position statement, dosage/administration, and references.