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Subject: Oral Therapy for Gaucher and Pompe Disease

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Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions

Related Guidelines | Other | References | Updates

DESCRIPTION:

Gaucher disease is characterized by a deficiency of ß-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 glucocerebroside 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/mm^3, 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). Algucosidase is approved for treatment of both infantile-onset Pompe disease and late-onset Pompe disease. Avalglucosidase and cipaglucosidase alfa-atga (in combination with miglustat) areapproved 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 Yargesa, or brand Zavesca) **meets the definition of medical necessity** for the following indications:

1. Indication for use is Type 1 Gaucher disease and member meets **ALL** of the following criteria:
    a. Member is diagnosed with Type 1 Gaucher disease confirmed by either of the following:
        i. Genotype testing indicating a mutation of two alleles of the glucocerebrosidase genome – laboratory documentation must be provided
        ii. Glucocerebrosidase activity deficiency in the white blood cells/skin fibroblasts – laboratory documentation must be provided
    b. 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])
    c. Member meets **ALL** criteria for requested product:
        i. Eliglustat: Member has undergone an FDA-approved test and been proven to be **ONE** of the following:
            - Extensive CYP2D6 metabolizer – laboratory documentation must be provided
            - Intermediate CYP2D6 metabolizer – laboratory documentation must be provided
            - Poor CYP2D6 metabolizer – laboratory documentation must be provided
        ii. Miglustat (generic), Yargesa (generic):
            - 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
        iii. Zavesca (brand):
            - 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
            - 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:
                a. Completed Medwatch reporting form (FDA 3500) - https://www.fda.gov/safety/medical-product-safety-information/forms-reporting-fda
                b. Completed Naranjo Adverse Drug reaction probability scale - https://assets.guidewell.com/m/2736e82ff52fe22d/original/mcg-naranjo-algorithm.pdf
    d. Member is currently receiving enzyme replacement therapy **OR** has one or more of the following conditions:
        i. Hemoglobin at least 1.0 g/dL below lower limit of normal for age and gender
        ii. Thrombocytopenia (platelet count less than 120,000)
        iii. Clinically significant hepatomegaly
        iv. Clinically significant splenomegaly

v. Evidence of bone disease other than Erlenmeyer flask deformity or mild osteopenia.

e. Member is 18 years of age or older

f. Dose does not exceed:

i. Eliglustat:

- Extensive CYP2D6 metabolizer: 84 mg twice daily
- Intermediate CYP2D6 metabolizer: 84 mg twice daily
- Poor CYP2D6 metazolizer: 84 mg once daily

ii. Miglustat (generic), Yargesa (generic): 300 mg/day

iii. Zavesca: 300 mg/day

2. Indication for use is Niemann-Pick disease type C (NPC) and all of the following criteria are met:

a. Member is 2 years of age or older with a diagnosis of Niemann-Pick disease type C (NPC)

b. One of the following: - Laboratory documentation of the genetic testing results must be submitted

i. Genetic test demonstrating biallelic known or likely pathogenic variants in the NPC1 or NPC2 gene

ii. Both of the following:

- Genetic test demonstrating two pathogenic alleles with 1 or 2 potential variants of unknown significance in the NPC1 or NPC2 gene
- Filipin test is highly positive with 'classical' staining or moderately positive with 'variant' staining

c. Miglustat is prescribed as monotherapy or in combination with arimoclomol (Miplyffa)

d. Miglustat is **NOT** being administered in combination with levacetylleucin (Aqneursa)

e. For Zavesca (brand) only:

i. Member has tried and had intolerable adverse effects to generic miglustat or generic Yargesa– 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

f. Miglustat is prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.

g. Dose does **NOT** exceed 200 mg three times a day

Approval duration: 1 year (Type 1 Gaucher disease); 6 months (NPC)

Continuation of eliglustat (Cerdelga) or miglustat (generic Yargesa, or brand Zavesca) **meets the definition of medical necessity** for the following indications:

1. Indication for use is Type 1 Gaucher disease and all of the following criteria are met:

a. 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

b. Member demonstrates a clinical improvement in symptoms following initiation of eliglustat or miglustat – documention from the medical record must be provided

c. 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])

d. Dose does not exceed:

i. Eliglustat:

1. Extensive CYP2D6 metabolizer: 84 mg twice daily
2. Intermediate CYP2D6 metabolizer: 84 mg twice daily
3. Poor CYP2D6 metazolizer: 84 mg once daily

ii. Miglustat (generic), Yargesa (generic): 300 mg/day

iii. Zavesca: 300 mg/day

2. Indication for use is Niemann-Pick disease type C (NPC) and all of the following criteria are met:

a. Authorization/reauthorization for the requested agent has been previously approved by Florida Blue or another health plan in the past 2 years (if another health plan, documentation of a health plan-paid claim during the 90 days before the authorization request must be submitted), OR the member has previously met ALL indication-specific initiation criteria.

b. Member has a clinical meaningful response (e.g., improvement, stabilization, and/or slowed decline in ambulation, speech, swallow, and fine motor skills) with no significant adverse drug reactions (e.g., severe hypersensitivity reactions) necessitating discontinuation of therapy.

c. Miglustat is prescribed as monotherapy or in combination with arimoclomol (Miplyffa)

d. Miglustat is **NOT** being administered in combination with levacetylleucin (Aqneursa)

e. Miglustat is prescribed by a specialist who treats patients with NPC such as a neurologist, neuromuscular specialist, or geneticist.

f. Dose does **NOT** exceed 200 mg three times a day

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), Yargesa (generic), Zavesca: 100 mg orally three times daily

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

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

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.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J8499	Prescription drug, oral, non-chemotherapeutic, NOS

ICD-10 Diagnosis Codes That Support Medical Necessity:

E75.22	Gaucher disease
E75.242	Niemann-Pick disease type C

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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request

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:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 08/12/26.

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.
01/01/25	Revision to guideline; consisting of updating position statement, dosage/administration
07/15/25	Review and revision to guideline; consisting of updating references and position statement.
01/15/26	Revision to guideline; consisting of updating position statement, dosage/administration, precautions, billing/coding, and references; removed Opfolda from guideline
07/15/26	Review and revision to guideline; consisting of updating references and position statement.
09/15/26	Revision to guideline; consisting of updating position statement, coding.