PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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Gaucher Disease: Oral Substance Reduction Therapy
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Miglustat
ZAVESCA® (miglustat)

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes**

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will be returned.

Criteria:

CERDELGA (eliglustat)

- **Criteria for initial therapy:** Cerdelga (eliglustat) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Geneticist, Pediatrician, Gastroenterologist, or Hepatologist
  2. Individual is 16 years of age or older
  3. A confirmed diagnosis of Gaucher disease type 1 in an individual whose cytochrome P450 2D6 metabolism type is known and identified by an FDA-cleared test (See Definitions section for P450 2D6 metabolism type)
  4. Individual is either an extensive metabolizer (EM) or intermediate metabolizer (IM) or poor metabolizer (PM) of cytochrome P450 2D6 (See Definitions section)
  5. Enzyme replacement therapy (**ERT**) is **not** a therapeutic **option** because of allergy, hypersensitivity, or poor venous access (See Definitions section for enzyme replacement therapy)
  5. Individual does not have pre-existing cardiac conditions such as congestive heart failure, recurrent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmias, or long QT syndrome
  6. Individual is not concurrently using Class IA (such as quinidine, procainamide) and Class III (such as amiodarone, sotalol) antiarrhythmic agents
  7. Dose is appropriate for renal impairment, hepatic impairment, CYP 2D6 metabolizer status and other drugs used by the patient (See Definitions section)
  8. There are **NO** FDA-label contraindications, such as:
     a. Use in patients taking CYP2D6, CYP3A inhibitors, depending on the patient's CYP2D6 metabolizer status, the type of inhibitor, or degree of hepatic impairment

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cerdelga (eliglustat) is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Geneticist, Pediatrician, Gastroenterologist, or Hepatologist

2. Individual's condition responded while on therapy
    a. Response is defined as **THREE** of the following:
        i. Improvement in hemoglobin level is **one** of the following:
            1. Hg level ≥ 11 g/dL for children (≤ 12 years of age)
            2. Hg level ≥ 11 g/dL for females (> 12 years of age)
            3. Hg level ≥ 12 g/dL for males (> 12 years of age)
        ii. Platelet count is at least in the low normal range
        iii. Reduction in liver size
        iv. Reduction in spleen size
        v. Reduction in bone pain, no fractures

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant adverse drug effects that may exclude continued use
    a. Contraindications as listed in the criteria for initial therapy section
    b. Significant adverse effect such as:
        i. Cardiac arrhythmia
        ii. Prolongation of the PR, QTc, and/or QRS cardiac interval

5. Individual does not have pre-existing cardiac conditions such as congestive heart failure, recurrent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmias, or long QT syndrome

6. Dose is appropriate for renal impairment, hepatic impairment, CYP 2D6 metabolizer status and other drugs used by the patient (See Definitions section)

7. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

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- **Criteria for initial therapy:** Brand Zavesca (miglustat) and generic miglustat is considered ***medically necessary*** with medical record documentation of **ALL** of the following:

  1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with a Geneticist, Pediatrician, Gastroenterologist, or Hepatologist
  2. Individual is 18 years of age or older
  3. A confirmed diagnosis of mild to moderate Gaucher disease type 1 for whom enzyme replacement therapy (**ERT**) is **not** a therapeutic **option** because of allergy, hypersensitivity, or poor venous access (See Definitions section for enzyme replacement therapy)
  4. There is a baseline neurological evaluation to detect peripheral neuropathy
  5. **Additional criteria for brand Zavesca**: Individual has failure, contraindication per FDA label or intolerance to **generic miglustat**
  6. Individual does not have severe renal impairment (creatinine clearance less than 30 mL/min/1.73m^2)

  Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Brand Zavesca (miglustat) and generic miglustat is considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

  1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with a Geneticist, Pediatrician, Gastroenterologist, or Hepatologist
  2. Individual's condition responded while on therapy
     a. Response is defined as **THREE** of the following:
        i. Improvement in hemoglobin level is **one** of the following:
           1. Hg level ≥ 11 g/dL for children (≤ 12 years of age)
           2. Hg level ≥ 11 g/dL for females (> 12 years of age)
           3. Hg level ≥ 12 g/dL for males (> 12 years of age)
        ii. Platelet count is at least low normal
        iii. Reduction in liver size
        iv. Reduction in spleen size
        v. Reduction in bone pain, no fractures
  3. Individual has been adherent with the medication

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4. Individual has not developed any significant adverse drug effects that may exclude continued use
    a. Significant adverse effect such as:
        i. Peripheral neuropathy to assess risk/benefit for possible discontinuation
        ii. Tremor that does not resolve within days of dose reduction

5. Individual does not have severe renal impairment (creatinine clearance less than 30 mL/min/1.73m^2)

6. There are no significant interacting drugs

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Cerdelga (eliglustat) is a glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are cytochrome P450 (CYP) 2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga (eliglustat) to achieve a therapeutic effect. A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).

Miglustat (brand Zavesca and generic) is a glucosylceramide synthase inhibitor indicated as monotherapy for the 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).
Gaucher disease is an inherited lysosomal storage disorder (LSD) that results from the inability to produce the enzyme beta-glucocerebrosidase (also known as acid beta-glucosidase). This enzyme catalyzes the conversion of the glycosphingolipid glucocerebroside (also known as glucosylceramide, a glycolipid) into glucose and ceramide. Deficiency of the enzyme results in the accumulation of glucosylceramide in lysosomes of macrophages giving rise to foam cells (Gaucher cells) in the spleen, liver, kidneys, lungs, brain, bone marrow, and other organs.

Gaucher disease is the most common of the LSDs. LSD is caused by dysfunction of lysosomal function as a result of enzymes needed for the metabolism of lipids, glycoproteins or mucoploysaccharides. There are approximately 50 rare inherited metabolic disorders arising from defects in lysosomal function. There are 3 subtypes of Gaucher disease: type 1 (non-neuropathic) is the most common form of the disease; type 2 refers to

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the acute, infantile neuropathic form typically beginning within 6 months of birth; and type 3 refers to the chronic sub-acute, neuropathic form that can begin at any time in childhood or adulthood.

All types of Gaucher disease are associated with a variety of symptoms, including pain, fatigue, anemia, thrombocytopenia, jaundice, bone damage, and enlargement of the liver and spleen. Manifestations may include liver dysfunction, skeletal disorders and bone lesions that may be painful, neurologic complications (except type 1), swelling of lymph nodes and occasionally adjacent joints, distended abdomen, a brownish tint to the skin, and yellow fatty deposits on the sclera. The individual may also be more susceptible to infection

Therapeutic options include enzyme replacement therapy (ERT) and oral substrate reduction therapy (SRT). ERT uses an analog of the naturally occurring enzyme, glucocerebrosidase, that is infused. Current options for ERT includes: Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), and Vpriv (velaglucerase alfa). All three ERT are based on the human gene sequence for the native enzyme but are differentiated from each other according to cell type used in production. Imiglucerase is derived from Chinese hamster ovary cells, taliglucerase is from carrot cells, and velaglucerase is from human fibroblast-like cells. For those patients with type 1 and most type 3, ERT with intravenous recombinant glucocerebrosidase can decrease liver and spleen size, reduce skeletal abnormalities, and may reverse other manifestations.

SRT is used in those individuals who are unable to use ERT. SRT inhibits the formation of glucosylceramide by inhibiting the enzyme glucosylceramide synthase. Inhibition of the enzyme, results in reduced rate of production of glucosylceramide biosynthesis so that the amount of glycosphingolipid substrate is lowered to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective. Other supportive therapy may be needed such as blood products, bisphosphonate therapy and/or analgesia. Current options for SRT includes: Cerdelga (eliglustat) that partially inhibits the enzyme glucosylceramide synthase and Miglustat (brand Zavesca and generic) which functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase.

Definitions:

Gaucher disease subtypes:

- Type 1 (non-neuropathic) is the most common form of the disease
  - Symptoms may begin early in life or in adulthood
  - The range and severity of symptoms can vary dramatically between individuals
  - The brain is not affected so there are no neurologic symptoms, but lung and kidney impairment may occur
  - Depending on disease onset and severity, type 1 patients may live well into adulthood
  - This type occurs mainly in Jewish population of Ashkenazi origin
- Type 2 refers to the acute, infantile neuropathic form typically beginning within 6 months of birth
  - Symptoms include an enlarged liver and spleen, extensive and progressive brain damage, eye movement disorders, spasticity, seizures, limb rigidity, and a poor ability to suck and swallow
  - Affected individuals usually die by age of two or three

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- Type 3 refers to the chronic sub-acute, neuropathic form that can begin at any time in childhood or adulthood
  - It is characterized by slowly progressive, but milder neurologic symptoms compared to the acute type 2 subtype
  - Other major symptoms include an enlarged spleen and/or liver, seizures, poor coordination, skeletal irregularities, eye movement disorders, blood disorders including anemia, and respiratory problems

Enzyme replacement therapy (ERT) includes:
- Cerezyme (imiglucerase)
- Elelyso (taliglucerase alfa)
- Vpriv (velaglucerase alfa)

Substrate reduction therapy (SRT) includes:
- Cerdelga (eliglustat)
- Miglustat (brand Zavesca and generic)

Cytochrome P450 2D6 metabolism types include:
- CYP2D6 ultra-rapid metabolizer (UM)
- CYP2D6 extensive metabolizer (EM)
- CYP2D6 intermediate metabolizer (IM)
- CYP2D6 poor metabolizer (PM)

Dosing of Cerdelga (eliglustat) in:
Renal Impairment - Use is based on the patient's CYP2D6 metabolizer status
- Extensive metabolizer (EM)
  - Avoid in patients with end-stage renal disease (ESRD) (estimated creatinine clearance (eCLcr) less than 15 mL/min not on dialysis or requiring dialysis).
  - No dosage adjustment is recommended in patients with mild, moderate, or severe renal impairment (eCLcr at least 15 mL/min).
- Intermediate metabolizer (IM) and poor metabolizer (PM)
  - Avoid in patients with any degree of renal impairment.

Hepatic Impairment - Use is based on CYP2D6 metabolizer status and concomitant use of CYP2D6 or CYP3A inhibitors.
- Extensive metabolizer (EM)
  - It is contraindicated in patients with:
    - Severe (Child-Pugh Class C) hepatic impairment
    - Moderate (Child-Pugh Class B) hepatic impairment
    - Mild (Child-Pugh Class A) hepatic impairment taking a strong or moderate CYP2D6 inhibitor
  - Reduce dosage frequency of Cerdelga 84 mg to once daily in patients with mild hepatic impairment taking:
    - A weak CYP2D6 inhibitor
    - A strong, moderate, or weak CYP3A inhibitor

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- No dosage adjustment is recommended in patients with mild hepatic impairment, unless otherwise specified above.

- Intermediate metabolizer (IM) and poor metabolizer (PM)
  - Contraindicated in patients with any degree of hepatic impairment

Inhibitors of Cytochrome P450 (CYP) isoforms: (not an all-inclusive list):

	Weak inhibitors:	Moderate inhibitors:	Strong inhibitors:
CYP2D6		Duloxetine Sertraline Terbinafine	Bupropion Cinacalcet Fluoxetine Paroxetine Quinidine
CYP3A4	Cimetidine Ranitidine	Aprepitant Erythromycin Fluconazole Grapefruit juice Verapamil Diltiazem	Indinavir Nelfinavir Ritonavir Clarithromycin Itraconazole Ketoconazole Nefazodone Saquinavir Suboxone

Resources:

Cerdelga (eliglustat) product information, revised by Genzyme Corporation 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 24, 2022.

Zavesca (miglustat) product information, revised by Actelion Pharmaceuticals US, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 24, 2022.

Miglustat product information, revised by CoTherix, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed April 24, 2022.

Hughes D. Gaucher disease: Treatment. In: UpToDate, Hahn S, TePas E (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed April 24, 2022.