BlueCross BlueShield of Arizona
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PHARMACY COVERAGE GUIDELINES
SECTION: DRUGS

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Gaucher Disease: Oral Substance Reduction Therapy
CERDELGA™ (eliglustat) oral capsule
ZAVESCA® (miglustat) oral capsule
MIGLUSTAT oral capsule

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.

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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)

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864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

Cerdelga (eliglustat)

Criteria:

- **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
    - P450 2D6 metabolism types include:
        - CYP2D6 extensive metabolizer (EM)
        - CYP2D6 intermediate metabolizer (IM)
        - CYP2D6 poor metabolizer (PM)

4. Enzyme replacement therapy (**ERT**) is **not** a therapeutic **option** (because of allergy, hypersensitivity, or poor venous access)
    - Enzyme replacement therapy includes:
        - Cerezyme (imiglucerase)
        - Elelyso (taliglucerase alfa)
        - Vpriv (velaglucerase alfa)

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. There are **NO** contraindications:
    - Contraindications include:
        - Use in patients taking CYP2D6 or CYP3A inhibitors, depending the patient's CYP2D6 metabolizer status, the type of inhibitor, or degree of hepatic impairment

Initial approval duration: 6 months

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- **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:

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
   - Response is defined as **THREE** of the following:
     - Improvement in hemoglobin level is **one** of the following:
       - Hg level ≥ 11 g/dL for children (≤ 12 years of age)
       - Hg level ≥ 11 g/dL for females (> 12 years of age)
       - Hg level ≥ 12 g/dL for males (> 12 years of age)
     - Platelet count is at least low normal
     - Reduction in liver size
     - Reduction in spleen size
     - Reduction in bone pain, no fractures

3. Individual has been adherent with the medication

4. Individual has not developed any contraindications or other significant level 4 adverse drug effects that may exclude continued use
   - Contraindications as listed in the criteria for initial therapy section

5. There are no significant interacting drugs

Renewal duration: 12 months

Zavesca (miglustat)
Miglustat

Criteria:

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

4. **Additional criteria for brand Zavesca**: Individual has failure, contraindication or intolerance to **generic miglustat**

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
    - Response is defined as **THREE** of the following:
        - Improvement in hemoglobin level is **one** of the following:
            - Hg level ≥ 11 g/dL for children (≤ 12 years of age)
            - Hg level ≥ 11 g/dL for females (> 12 years of age)
            - Hg level ≥ 12 g/dL for males (> 12 years of age)
        - Platelet count is at least low normal
        - Reduction in liver size
        - Reduction in spleen size
        - Reduction in bone pain, no fractures

3. Individual has been adherent with the medication

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

5. There are no significant interacting drugs

Renewal duration: 12 months

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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

- Gaucher disease is an inherited lysosomal storage disorder 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 lysosomal storage disorders (LSD)
    - LSD is caused by dysfunction of lysosomal function as a result of enzymes needed for the metabolism of lipids, glycoproteins or mucoploysacchraides
    - 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
        - 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
    - 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

- 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)
    - ERT uses an analog of the naturally occurring enzyme, glucocerebrosidase, that is infused
    - Current options for ERT includes:
      - Cerezyme (imiglucerase)
      - Elelyso (taliglucerase alfa)
      - 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 from carrot cells
      - Velaglucerase from human fibroblast-like cells
    - For those 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
  - Oral substrate reduction therapy (SRT)
    - SRT is used in those individuals who are unable to use ERT
    - SRT inhibits the formation of glucosylcermaide 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:

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- Cerdelga (eliglustat) partially inhibits the enzyme glucosylceramide synthase
- Miglustat (brand Zavesca and generic) functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase

Definitions:

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 Grape fruit juice Verapamil Diltiazem	Indinavir Nelfinavir Ritonavir Clarithromycin Itraconazole Ketoconazole Nefazodone Saquinavir Suboxone

Resources:

Cerdelga (eliglustat) product information accessed 03-10-20 at DailyMed

Zavesca (miglustat) product information accessed 03-10-20 at DailyMed

Miglustat product information accessed 03-10-20 at DailyMed

Cerdelga. Package Insert. Reference ID 3613065. Revised by manufacturer 8/2014. Accessed 10-28-2014, 10-13-2015, 09-28-2016

Zavesca. Package Insert. Revised by manufacturer 02/2014. Accessed 11-12-2014, 10-13-2015

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Rosenbloom BE and Weinreb NJ: Gaucher Disease: A comprehensive review. Crit Rev Oncogenesis 2013; 18 (3): 163-175

Harmanci O and Bayraktar Y: Gaucher disease: New developments in treatment and etiology. World J Gastroenterol 2008; July 7; 14(25): 3968-3973

Zavesca. Package Insert. Revised by manufacturer 02/2016. Accessed 09-28-2016

UpToDate: Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis. Current through Sep 2017

UpToDate: Gaucher disease: Initial assessment, monitoring, and clinical course. Current through Sep 2017

UpToDate: Gaucher disease: Treatment. Current through Sep 2017