Gaucher Disease: Oral Substance Reduction Therapy
CERDELGA™ (eliglustat) oral capsule and ZAVESCA® (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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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). Zavesca (miglustat) 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 that results from the inability to produce the enzyme beta-glucocerebrosidase (also known as acid beta-glucosidase). This enzyme catalyzes the conversion of the
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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 mucopolysaccharides. There are approximately 50 rare inherited metabolic disorders arising from defects in lysosomal function.

There are 3 subtypes of Gaucher disease, of which type 1 (non-neuropathic) is the most common form of the disease; symptoms may begin early in life or in adulthood. 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. The range and severity of symptoms can vary dramatically between individuals. 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. Other 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) or oral substrate reduction therapy (SRT). ERT uses an analog of the naturally occurring enzyme that is infused. SRT inhibits the formation of glucosylceramide accomplished by inhibiting the enzyme glucosylceramide synthase. SRT is used in those individuals who are unable to use ERT. Other supportive therapy may be needed such as blood products, bisphosphonate therapy and/or analgesia.

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. Current management options for ERT include use of Cerezyme (imiglucerase) or Elelyso (taliglucerase alfa) or Vpriv (velaglucerase alfa). All three 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; and Velaglucerase from human fibroblast-like cells.
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Oral SRT inhibit the enzyme glucosylceramide synthase, resulting 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. Cerdelga (eliglustat) partially inhibits the enzyme glucosylceramide synthase. It is a specific inhibitor. Zavesca (miglustat) functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase.

Definitions:

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

<table>
<thead>
<tr>
<th>CYP2D6</th>
<th>Weak inhibitors:</th>
<th>Moderate inhibitors:</th>
<th>Strong inhibitors:</th>
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<tbody>
<tr>
<td></td>
<td>Duloxetine</td>
<td>Sertraline</td>
<td>Bupropion</td>
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<td>Cinacalcet</td>
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<td>Terbinafine</td>
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<td>Quinidine</td>
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<thead>
<tr>
<th>CYP3A4</th>
<th>Cimetidine</th>
<th>Aprepitant</th>
<th>Indinavir</th>
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<tr>
<td></td>
<td>Ranitidine</td>
<td>Erythromycin</td>
<td>Nelfinavir</td>
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<td></td>
<td></td>
<td>Fluconazole</td>
<td>Ritonavir</td>
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<td>Grape fruit juice</td>
<td>Clarithromycin</td>
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<td>Verapamil</td>
<td>Itraconazole</td>
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<td>Diltiazem</td>
<td>Ketoconazole</td>
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<td>Nefazodone</td>
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<td>Saquinavir</td>
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<td>Suboxone</td>
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Drug related events:

Ineffective / failure
Use of a drug employing optimal doses (FDA-recommended doses) for optimal duration; where the condition being treated has not improved or worsened

A request for branded agent due to generic drug failure or ineffectiveness will be assessed for potential approval with documentation of use of optimal dose / duration of the generic product and meeting other criteria within the coverage guideline. When the drug in question is a combination product, there must be documentation of failure / ineffectiveness of concurrent use (each ingredient used at the same time) of individual generic components. When the drug in question is a low dose formulation, there must be documentation of failure / ineffectiveness of low dose generic formulation.

Adverse Drug Event: Allergic reaction / Hypersensitivity / Intolerance
Use of a drug produced a significant reaction where continued use of the drug places the individual at risk for either lack of improvement or worsening of the condition being treated or at risk for harm and the concern is documented in medical record. A significant adverse drug event is when an individual’s outcome is death, life-threatening, hospitalization (initial or prolonged), disability resulting in a significant, persistent, or
permanent change, impairment, damage or disruption in the individuals’ body function/structure, physical activities or quality of life, or requires intervention to prevent permanent impairment or damage.

Allergic reaction / hypersensitivity – may or may not involve the active ingredient. When the active ingredient is involved, use of same or a chemically similar agent places the individual at risk for harm when the same or chemically similar agent is used. The subsequent reaction may be the same as the original reaction or a more exaggerated response may be seen, potentially placing the individual at even greater risk for harm. If the reaction occurred from the active/main generic ingredient; request for branded agent with same active ingredient will not be considered unless it is proven (documented) that active ingredient did not cause reaction and the request meets other criteria within the coverage guideline

Intolerance – these events represent circumstance(s) where use of a drug produced a significant reaction and continued use may result in non-adherence to proposed therapy and this concern is documented in medical record

Contraindication
Use of a drug that is not recommended by the manufacturer or FDA labelling

Use of any drug in the face of a contraindication is outside of the FDA and manufacturer’s labelled recommendation and is considered investigational or experimental

Non-adherence
Individual does not follow prescribe regimen that places the individual at risk for lack of improvement or worsening of the condition being treated and this concern is documented in medical record

Precertification:

Precertification (Prior Authorization) is required for members with a Blue Cross Blue Shield of Arizona (BCBSAZ) pharmacy benefit for medication(s) or product(s) indicated in this guideline.

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.
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Criteria:

See “Resources” section for FDA-approved dosage.

- Precertification for Cerdelga and Zavesca requires completion of the specific request form in its entirety. 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 will be returned.

Criteria for Cerdelga:

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Cerdelga is considered medically necessary with medical record documentation of ALL of the following:
  1. Individual is 16 years of age or older
  2. Confirmed diagnosis of Gaucher disease type 1 in an individual who is either CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM)
  3. ALL of the following baseline tests have been completed before initiation of treatment:
     - CYP2D6 genotype metabolism type is known and identified by an FDA-cleared test
  4. Absence of ALL of the following contraindications:
     - Drug interaction due to cytochrome P450 metabolism:
       - CYP2D6 genotype metabolism EM or IM taking another drug that is a strong or moderated CYP2D6 inhibitor with a drug that is a strong or moderate CYP3A4 inhibitor
       - CYP2D6 genotype metabolism IM or PM taking a drug that is a strong CYP3A4 inhibitor
  5. Absence of ALL of the following exclusions:
     - Individuals whose CYP2D6 genotype cannot be determined
     - CYP2D6 Ultra-rapid metabolizers (URM) genotype
     - Individual with pre-existing heart disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia)
     - Individuals with long QT syndrome
     - Simultaneous use with Class IA antiarrhythmic agents
     - Simultaneous use with Class III antiarrhythmic agents
     - Moderate to severe renal impairment or end stage renal disease
     - Hepatic impairment, any stage
     - Woman of child bearing potential is who is pregnant or likely to become pregnant, unless using effective contraception
     - Individual is breast feeding an infant or child
     - Significant drug interactions
       - CYP2D6 genotype metabolism IM or PM taking a drug that is a moderate CYP3A4 inhibitor
       - CYP2D6 genotype metabolism PM taking a drug that is a weak CYP3A4 inhibitor
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- Simultaneous use with strong CYP3A4 inducers (rifampin, carbamazepine, phenobarbital, phenytoin, St John’s Wort)
- Simultaneous use with grapefruit or grapefruit juice

Cerdelga for all other indications not previously listed is considered experimental or investigational based upon:

1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Combination SRT and ERT
- Gaucher disease type 2 and type 3

Criteria for Zavesca:

- FDA-approved product labeling (indication, age, dosage, testing, contraindications, exclusions, etc.) of Zavesca is considered medically necessary with medical record documentation of ALL of the following:

1. Individual is 18 years of age or older

2. Confirmed diagnosis of mild to moderate Gaucher disease type 1

3. Unable to use enzyme replacement therapy (ERT) due to ONE of the following:
   - Condition worsened or did not improve with ERT
   - Experienced a significant adverse drug event such as hypersensitivity, allergy from ERT
   - Unable to establish or re-establish venous access

4. ALL of the following baseline tests have been completed before initiation of treatment:
   - Neurologic examination
   - Creatinine clearance is greater than or equal to 30 mL/min/1.73 meter squared

5. Absence of ALL of the following exclusions:
   - Severe renal impairment (creatinine clearance < 30 mL/min/1.73 meter square)
   - Woman of child bearing potential is who is pregnant or likely to become pregnant, unless using effective contraception
   - Individual is breast feeding an infant or child

Zavesca for all other indications not previously listed is considered experimental or investigational based upon:
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1. Lack of final approval from the Food and Drug Administration, and
2. Insufficient scientific evidence to permit conclusions concerning the effect on health outcomes, and
3. Insufficient evidence to support improvement of the net health outcome, and
4. Insufficient evidence to support improvement of the net health outcome as much as, or more than, established alternatives, and
5. Insufficient evidence to support improvement outside the investigational setting.

This includes but is not limited to the following:
- Combination SRT and ERT
- Gaucher disease type 2 and type 3

Resources:


FDA-approved indication and dosage:

<table>
<thead>
<tr>
<th>Indication</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>Cerdelga is a glucosylceramide synthase inhibitor indicated for the longterm treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.</td>
<td>- Select patients using an FDA-cleared test for determining CYP2D6 genotype</td>
</tr>
<tr>
<td>Limitations of Use:</td>
<td>- CYP2D6 EMs or IMs: 84 mg orally twice daily</td>
</tr>
<tr>
<td>• CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect</td>
<td>• CYP2D6 PMs: 84 mg orally once daily</td>
</tr>
<tr>
<td>• A specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers</td>
<td>• Swallow capsules whole, do not crush, dissolve or open capsules</td>
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<tr>
<td></td>
<td>• Avoid eating grapefruit or drinking grapefruit juice</td>
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</tbody>
</table>
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| Zavesca 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). | The recommended dose for the treatment of adult patients with type 1 Gaucher disease is one 100 mg capsule administered orally three times a day at regular intervals. |