**Substrate Reduction Therapy**

**Prior Authorization with Quantity Limit Program Summary**

This program applies to FlexRx Open, FlexRx Closed, GenRx Open, GenRx Closed, Health Insurance Marketplace, FocusRx and KeyRx formularies.

This is a FlexRx Standard and GenRx Standard prior authorization.

The BCBS MN Step Therapy Supplement also applies to this program for all Commercial/HIM lines of business.

### FDA APPROVED INDICATIONS AND DOSAGE\(^1,2\)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Dosage</th>
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</table>
| Cerdelga\(^\circledR\)  | Long-term 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 for determining CYP2D6 genotype | CYP2D6 extensive metabolizer (EM) or intermediate metabolizer (IM): 84 mg orally twice daily  
CYP2D6 poor metabolizer (PM): 84 mg orally once daily |
| capsule                | Limitations of Use:                                                         |                                                                        |
|                        | • CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect  
• A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) |                                                                        |
| Zavesca\(^\circledR\)   | Monotherapy for 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) | 100 mg administered orally three times a day at regular intervals |
| (miglustat)\(^a\)       |                                                                             |                                                                        |
| capsule                |                                                                             |                                                                        |

\(^a\) - generic available

### CLINICAL RATIONALE

Gaucher disease (GD), the most common of the lysosomal storage disorders (LSDs), is a rare autosomal recessive metabolic disorder affecting only 1 in 40,000 in the general United States population.\(^4,7\) Mutations in the *GBA* (glucocerebrosidase) gene cause reduced activity of the lysosomal enzyme glucocerebrosidase (also known as acid beta-glucosidase), resulting in the accumulation of harmful quantities of the glycolipid glucocerebroside (also known as...
glucosylceramide, or GLC) and other related sphingolipids. This multisystemic accumulation of GLC in various tissues, especially in lysosomes of macrophages, consequently compromises the bone marrow, spleen, and liver, and less often the lungs, skin, kidneys, and heart.\textsuperscript{3,4,7,8}

GD is classified into 3 clinical types, distinguished by their clinical features, management, and prognosis. However, as with most genetic diseases, there is a continuum of clinical findings and overlap within and between types, resulting in identification of additional subtypes.\textsuperscript{4,5,7} GD Type 1 (GD1) is distinguished from GD Types 2 (GD2) and 3 (GD3) by the lack of characteristic involvement of the central nervous system (CNS).\textsuperscript{3,4,5,7,8} As such, it is also known as non-neuronopathic GD.\textsuperscript{3,4,7} In the United States, Europe, and Israel, 90% of GD patients have GD1, with a high carrier frequency in the Ashkenazi-Jewish population.\textsuperscript{3,4,5,7,8} Age of onset for GD1 is variable, with some patients presenting between 12 and 24 months of age and others having no clinical signs until late adulthood.\textsuperscript{3,4,7} Manifestation in the first or second decades of life typically results in more aggressive and severe symptoms than those manifesting at a later stage of life.\textsuperscript{7} Presentation of symptoms among patients with GD1 is variable. Splenomegaly is the most common symptom; hepatomegaly is also common but the liver increases relatively less than the spleen. Other common presenting symptoms are anemia, thrombocytopenia, bone disease, and delayed growth.\textsuperscript{3,4,5,7,8}

GD2 is an acute neuronopathic form of GD characterized by early onset, typically in the first year after birth. Neurologic complications are extensive and severe, with limited psychomotor development. Death occurs within the first 2 years of life, usually due to respiratory failure.\textsuperscript{3,5,7} GD3 is the subacute or chronic neuronopathic form, has later onset than GD2, and has slower disease progression with patients typically surviving to second or third decades of life. The distinction between GD2 and GD3 is difficult.\textsuperscript{3,4}

A diagnosis of GD should be considered in patients with unexplained anemia and easy bruising, particularly if they have enlargement of the spleen and liver.\textsuperscript{3} Definitive diagnosis of GD can be confirmed by the finding of reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.\textsuperscript{3,4,5,7} This enzyme assay test is typically known as BGL (beta-glucosidase leukocyte), and a finding of 15% or less of mean normal glucocerebrosidase enzyme activity is indicative of GD.\textsuperscript{4,5} If BGL results are not conclusive and/or further confirmatory testing is desired, genetic testing is an option. Identification of two pathogenic alleles in the \textit{GBA} gene can also determine diagnosis of GD.\textsuperscript{3-5} The presence of neurologic complications has critical implications for prognosis and treatment and should be determined as soon as possible after diagnosis. Neuronopathic symptoms indicative of GD2 and GD3 include bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonus, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, and ataxia. If not already performed as part of the diagnostic process, baseline measurement of hemoglobin level, platelet count, liver volume, and spleen volume should be documented.\textsuperscript{4,5,7}

When possible, management of a patient with GD should occur with a multidisciplinary team at a Comprehensive Gaucher Treatment Center\textsuperscript{5} (list of facilities nationwide available at www.gaucherdisease.org). Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. An additional goal in children is optimization of growth.\textsuperscript{3,6,8} Currently, two different therapeutic approaches for the treatment of GD1 are used: enzyme replacement therapy (ERT) [Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), Elelyso (taliglucerase alfa)] and substrate reduction therapy (SRT) [Cerdelga (eliglustat), Zavesca (miglustat)].\textsuperscript{3,5,6,8} ERT, intravenously administered, targets macrophages and increases the breakdown of accumulated glycolipids.\textsuperscript{5} SRT, orally administered, reduces the amount of synthesized GLC to a level that can be effectively cleared by the mutated enzyme’s residual activity.\textsuperscript{5,6,8}
The decision to offer ERT or SRT in patients with GD1 is based upon disease severity and/or significant disease progression.\textsuperscript{6-8} To begin treatment with ERT or SRT, clinically significant manifestations must be present. Thrombocytopenia of sufficient magnitude to justify initiation of treatment is defined by platelet counts less than 100,000 µL, as well as symptomatic presentation of splenomegaly, anemia, bone disease, and/or delayed growth.\textsuperscript{3,4,5,7,8}

**Efficacy**

Until the FDA approval of the SRT Cerdelga in 2014, ERT was the mainstay of therapy in patients with GD1. A 12-month phase 3, open-label, noninferiority study (ENCORE) in 106 adults (18 years of age and older) with GD1, stable after ≥ 3 years of ERT with Cerezyme or VPRIV, found Cerdelga noninferior to Cerezyme in maintaining stability of four component domains (i.e., hemoglobin level, platelet count, liver volume, spleen volume). A 9-month randomized, double-blind, placebo-controlled study (ENGAGE) in 40 treatment-naïve GD1 patients 16 years of age and older, demonstrated that treatment with Cerdelga led to greater improvements in spleen and liver volume, platelet count, and hemoglobin level compared to placebo. These findings provided Cerdelga its designation as first-line or maintenance therapy in adult patients with GD1.\textsuperscript{1,5,6,8} The SRT Zavesca, approved in 2003, is indicated only for GD1 patients for whom ERT is not an option (e.g., due to allergy, hypersensitivity, or poor venous access). Studies of Zavesca have demonstrated significant reductions from baseline in liver and spleen volume, and a non-significant increase from baseline in hemoglobin level and platelet count.\textsuperscript{2,5,6}

**Safety\textsuperscript{1,2}**

Cerdelga (eliglustat) is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals:

- **Extensive metabolizers (EMs):**
  - Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
  - Moderate or severe hepatic impairment
  - Mild hepatic impairment taking a strong or moderate CYP2D6 inhibitor

- **Intermediate metabolizers (IMs):**
  - Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor
  - Taking a strong CYP3A inhibitor
  - Any degree of hepatic impairment

- **Poor metabolizers (PMs):**
  - Taking a strong CYP3A inhibitor
  - Any degree of hepatic impairment

Zavesca (miglustat) has no contraindications.

**REFERENCES**


Substrate Reduction Therapy Prior Authorization with Quantity Limit

TARGET AGENTS

Cerdelga® (eliglustat)
Zavesca® (miglustat)*

* generic available, included as a target

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerdelga (eliglustat)</td>
<td>82700040600120</td>
<td>M, N, O, or Y</td>
<td>2 capsules</td>
</tr>
<tr>
<td>Zavesca (miglustat)</td>
<td>82700070000120</td>
<td>M, N, O, or Y</td>
<td>3 capsules</td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

Initial Evaluation

Target Agent will be approved when ALL of the following are met:

1. The patient is 18 years of age or over
   AND
2. The patient has a diagnosis of Gaucher disease type 1 (GD1)
   AND
3. The patient does NOT have any neuropathic symptoms indicative of Gaucher disease type 2 or type 3 [e.g., bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonus, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, ataxia]
   AND
4. ONE of the following:
   a. The patient has baseline glucocerebrosidase enzyme activity of ≤15% of mean normal in fibroblasts, leukocytes, or other nucleated cells
      OR
   b. Genetic analysis confirmed two (2) pathogenic alleles in the glucocerebrosidase (GBA) gene
      AND
5. The prescriber has assessed baseline status of hemoglobin level, platelet count, liver volume, and spleen volume
   AND
6. The patient has at least ONE of the following clinical presentations at baseline:
   a. Anemia defined as mean hemoglobin (Hb) level below the testing laboratory’s lower limit of the normal range based on age and gender
      OR
   b. Thrombocytopenia (platelet count < 100,000/µL on at least 2 measurements)
      OR
   c. Hepatomegaly
      OR
   d. Splenomegaly
      OR
   e. Growth failure (i.e., growth velocity is below the standard mean for age)
      OR
   f. Evidence of bone disease with other causes ruled out
   AND
7. If the requested agent is Cerdelga (eliglustat), the patient is a CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM), as detected by an FDA-cleared test for determining CYP2D6 genotype
AND
8. If the requested agent is Zavesca or miglustat, BOTH of the following:
   a. Enzyme replacement therapy (ERT) is NOT a therapeutic option (e.g., due to allergy, hypersensitivity, poor venous access, previous ERT failure)
      AND
   b. ONE of the following:
      i. The request is for a generic equivalent
      OR
      ii. The patient’s medication history includes use of the generic equivalent in the past 999 days
      OR
      iii. BOTH of the following:
           1. The prescriber has stated that the patient has tried the generic equivalent
              AND
           2. The generic equivalent was discontinued due to lack of effectiveness or an adverse event
      OR
      iv. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent
      OR
      v. The patient is currently being treated with the requested agent as indicated by ALL of the following:
         a. A statement by the prescriber that the patient is currently taking the requested agent
            AND
         b. A statement by the prescriber that the patient is currently receiving a positive therapeutic outcome on requested agent
            AND
         c. The prescriber states that a change in therapy is expected to be ineffective or cause harm
      OR
      vi. The prescriber has provided documentation that the generic equivalent cannot be used due to a documented medical condition or comorbid condition that is likely to cause an adverse reaction, decrease ability of the patient to achieve or maintain reasonable functional ability in performing daily activities or cause physical or mental harm
      AND
9. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis
   AND
10. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Zavesca) for the requested indication
   AND
11. The patient does NOT have any FDA labeled contraindications to the requested agent
   AND
12. ONE of the following:
    a. The requested quantity (dose) does NOT exceed the program quantity limit
    OR
    b. ALL of the following:
       i. The requested quantity (dose) is greater than the program quantity limit
The requested quantity (dose) does NOT exceed the maximum FDA labeled dose

The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

OR

ALL of the following:

i. The requested quantity (dose) is greater than the program quantity limit

ii. The requested quantity (dose) is greater than the maximum FDA labeled dose

iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

Length of Approval: 12 months

Renewal Evaluation

Target Agent will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process

2. The patient has had benefit and/or stabilization with the requested agent as indicated by improvement of at least ONE of the following:
   a. Spleen volume
   b. Hemoglobin level
   c. Liver volume
   d. Platelet count (sufficient to decrease the risk of bleeding)
   e. Growth
   f. Bone pain or crisis

3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of patient’s diagnosis

4. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Zavesca) for the requested indication

5. The patient does NOT have any FDA labeled contraindications to the requested agent

6. ONE of the following:
   a. The requested quantity (dose) does NOT exceed the program quantity limit

   OR

   b. ALL of the following:
      i. The requested quantity (dose) is greater than the program quantity limit

      AND

      ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose

      AND

      iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit
OR

c. ALL of the following:
i. The requested quantity (dose) is greater than the program quantity limit

AND

ii. The requested quantity (dose) is greater than the maximum FDA labeled dose

AND

iii. The prescriber has provided information in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months