# Substrate Reduction Therapy Prior Authorization with Quantity Limit Program Summary

This prior authorization program applies to Commercial, GenPlus, NetResults A series, SourceRx and Health Insurance Marketplace formularies.

**OBJECTIVE**
The intent of the Substrate Reduction Therapy Prior Authorization (PA) with quantity limit program is to ensure that patients prescribed therapy meet the selection requirements defined in product labeling and/or clinical guidelines and/or clinical studies. The PA defines appropriate use as the Food and Drug Administration (FDA) labeled indication or as supported by guidelines and/or clinical evidence.

**TARGET AGENTS**
**Cerdelga®** (eliglustat)
**Zavesca®** (miglustat)

| Brand (generic) | GPI | Multisource Code | Quantity per Day Limit |
|---|---|---|---|
| Cerdelga (eliglustat) | | | |
| 84 mg capsule | 82700040600120 | M, N, O, Y | 2 capsules |
| Zavesca (miglustat) | | | |
| 100 mg capsule | 82700070000120 | M, N, O, Y | 3 capsules |

**PRIOR AUTHORIZATION CRITERIA FOR APPROVAL**
**Initial Evaluation**
**Cerdelga** (eliglustat) or **Zavesca** (miglustat) will be approved when the following are met:

1. The patient is 18 years of age or over
   **AND**
2. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of practice related to the patient's diagnosis
   **AND**
3. The patient has a diagnosis of Gaucher Disease type 1
   **AND**
4. The patient does NOT have any neuropathic symptoms (e.g. convulsive crisis, ataxia, supranuclear horizontal ocular palsy, dementia, alteration in ocular movement, bulbar (swallowing difficulties, stridor, convergent strabismus))
   **AND**
5. ONE of the following:
   a. The patient has a baseline glucocerebrosidase activity of <15% of mean normal in fibroblasts, leukocytes, or other nucleated cells
      **OR**
   b. Genetic analysis with two (2) disease-causing alleles on the glucocerebrosidase genome (*GBA* gene)

   **AND**
6. The prescriber has drawn baseline levels of hemoglobin, platelets, liver volume, and spleen volume
   **AND**
7. 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 of < 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**

8. ONE of the following:
    a. If the requested agent is Cerdelga, the patient is a CYP2D6 extensive metabolizer (EMs), intermediate metabolizer (IMs), or poor metabolizer (PMs) established by an FDA-cleared test
    **OR**
    b. If the requested agent is Zavesca, enzyme replacement therapy is NOT a therapeutic option (e.g. contraindication, intolerance, previous ERT failure)

**AND**

9. The patient does NOT have an FDA labeled contraindication to the requested agent

**AND**

10. ONE of the following:
    a. The quantity requested is less than or equal to the program quantity limit
    **OR**
    b. The quantity (dose) requested is within FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength
    **OR**
    c. The quantity (dose) requested is greater than the maximum dose recommended in FDA labeling and prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval**: 12 months

**Renewal Criteria**

**Cerdelga** (eliglustat) or **Zavesca** (miglustat) will be approved when the following are met:

1. The patient has been previously approved for the requested agent through Prime Therapeutics Prior Authorization Review process

**AND**

2. The prescriber is a specialist in the area of practice related to the patient's diagnosis (e.g., endocrinologist, geneticist) or has consulted with a specialist in the area of practice related to the patient's diagnosis

**AND**

3. The patient has shown improvement in or stabilization from baseline of 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

**AND**

4. The patient does NOT have an FDA labeled contraindication to the requested agent

**AND**

5. ONE of the following:
    a. The quantity requested is less than or equal to the program quantity limit
       **OR**
    b. The quantity (dose) requested is within FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength
       **OR**
    c. The quantity (dose) requested is greater than the maximum dose recommended in FDA labeling and prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval**: 12 months

## FDA APPROVED INDICATIONS AND DOSAGE[1]

| Agent | Indication | Dosing and Administration |
|---|---|---|
| **Cerdelga™** (eliglustat)<br><br>Capsule | Long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test<br><br>Limitations of Use:<br>• Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.<br>• A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) | CYP2D6 extensive metabolizer (EM) or intermediate metabolizer (IM): 84 mg orally twice daily<br><br>CYP2D6 poor metabolizer (PM): 84 mg orally once daily |
| **Zavesca®** (miglustat)<br><br>capsule | 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 |

## CLINICAL RATIONALE

Gaucher disease (GD) is a rare, inherited metabolic disorder in which deficiency of the enzyme glucocerebrosidase results in the accumulation of harmful quantities of certain fats (lipids), specifically the glycolipid glucocerebroside, throughout the body especially within the bone marrow, spleen, and liver. Common manifestations of Gaucher disease include anemia, hepatomegaly, splenomegaly, thrombocytopenia, and skeletal abnormalities (bone pain, bone crisis, growth retardation, osteopenia).[3,4]

There are 3 classifications of GD. Type 1 is distinguished from type 2 and 3 by the lack of characteristics involvement of the central nervous system (CNS). Presentation of symptoms is variable among patients with Type 1. Splenomegaly is the most common symptom in patients with Type 1. Bone disease, hepatomegaly, delay in puberty, bleeding, anemia, thrombocytopenia, and fatigue are other common presenting symptoms of Type 1. Age of onset for Type 1 is also variable, some patients present symptoms between 12 and 24 months of age, whereas others have no clinical signs until late adulthood. Type 2 is the acute, neuropathic form of GD. It is characterized by early onset, typically in the first year after birth. Visceral involvement (splenomegaly, hepatomegaly) is extensive and severe in Type 2 GD. The first sign of CNS disease typically is oculomotor dysfunction, which may include strabismus, saccade (fast eye movement) initiation abnormalities, and bulbar palsy or paresis. Neurologic progression is marked by severe hypertonia, rigidity, arching (opisthotonus), swallowing impairment, and seizures. Type 3 GD is the subacute or chronic neuronopathic form, has later onset than Type 2, and has slower disease progression. The distinction between Type 2 and Type 3 is difficult. Associated

neurological symptoms are mental deterioration, inability to coordinate voluntary movements (ataxia), and myoclonic seizures.[3,4]

Diagnosis of GD can be confirmed with reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.[3-5] A finding of less than 15% of normal glucocerebrosidase activity is indicative of GD. Genetic testing and identification of two disease-causing alleles on *GBA* variant could also determine diagnosis of GD.[5] Patients with GD often present with anemia, thrombocytopenia, and splenomegaly.[5] Skeletal manifestations are associated with the greatest morbidity, and once present are the least responsive to enzyme-replacement therapy.[6]

Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. Additional goal in children is optimization of growth. Enzyme replacement therapy (ERT) (imiglucerase, velaglucerase, or taliglucerase) or substrate reduction therapy (SRT) are preferred treatments for patients with clinically significant manifestations of non-neuronopathic GD (Type 1). ERT is indicated in the following non-neuronopathic disease: symptomatic children (including those with malnutrition, growth retardation, impaired psychomotor development, and/or fatigue) since early presentation is associated with more severe disease and adult patients with symptomatic disease (e.g., platelet count <60,000/microL, liver > 2.5 times normal size, spleen >15 times normal size, radiologic evidence of skeletal disease).[6]

SRT reduces glycolipid accumulation by decreasing the synthesis of glucocerebroside and is an alternative to ERT for some adults. Eliglustat is approved for a broader range of use than miglustat. Eliglustat is not indicated in patients who are CYP2D6 ultra-rapid metabolizers, since they may not achieve adequate concentrations of eliglustat to achieve therapeutic effect. Miglustat is approved in the U.S. for use in adults with GD who are medically unable to receive ERT.[6]

**REFERENCES**


1. Cerdelga prescribing information. Genzyme August 2014.
2. Zavesca prescribing information. Actelion Pharmaceuticals US, Inc. November 2017.
3. National Organization for Rare Disorders (NORD). Gaucher Disease. Available at: https://rarediseases.org/rare-diseases/gaucher-disease/. Accessed February 5, 2018.
4. Hughes, Derralynn, MD., et al. Gaucher Disease: Pathogenesis, Clinical Manifestations, and Diagnosis. UpToDate. Last Updated November 2017.
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6. Hughes, Derralynn, MD., et al. Gaucher Disease: Treatment. UpToDate. Last Updated November 2017.
7. Martins AM, Valadares ER, Porta G et al. Recommendations on Diagnosis, Treatment, and Monitoring for Gaucher Disease. *The Journal of Pediatrics* 2009;155(4):Suppl 2:S10-S18. http://www.jpeds.com/article/S0022-3476(09)00674-X/fulltext