



## 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, Medicaid, 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.

Program specific denial language for prerequisite step therapy component does not apply. Instead, supplemental program denial language will apply.

### FDA APPROVED INDICATIONS AND DOSAGE<sup>1</sup>

Agent	Indication	Dosing and Administration
<b>Cerdelga<sup>®</sup></b> (eliglustat)  capsule	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  Limitations of Use: <ul style="list-style-type: none"> <li>• Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.</li> <li>• A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers)</li> </ul>	CYP2D6 extensive metabolizer (EM) or intermediate metabolizer (IM): 84 mg orally twice daily  CYP2D6 poor metabolizer (PM): 84 mg orally once daily
<b>Zavesca<sup>®</sup></b> (miglustat) <sup>a</sup>  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

<sup>a</sup> – generic available

### 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).<sup>3,4</sup>

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.<sup>3,4</sup>

Diagnosis of GD can be confirmed with reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.<sup>3-5</sup> 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.<sup>5</sup> Patients with GD often present with anemia, thrombocytopenia, and splenomegaly.<sup>5</sup> Skeletal manifestations are associated with the greatest morbidity, and once present are the least responsive to enzyme-replacement therapy.<sup>6</sup>

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)<sup>6</sup>

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.<sup>6</sup>

## REFERENCES

1. Cerdelga prescribing information. Genzyme Corporation. August 2018.
2. Zavesca prescribing information. Actelion Pharmaceuticals US, Inc. November 2018.
3. National Organization for Rare Disorders (NORD). Gaucher Disease. Available at: <https://rarediseases.org/rare-diseases/gaucher-disease/>. Accessed December 2018.
4. Hughes, Derralynn, MD., et al. Gaucher Disease: Pathogenesis, Clinical Manifestations, and Diagnosis. UpToDate. Last Updated November 2017.
5. Pastores, G. and Derralynn A Hughes. GeneReviews. Gaucher Disease. National Center for Biotechnology Information, U.S. National Library of Medicine. February 26, 2015. Accessed at <https://www.ncbi.nlm.nih.gov/books/NBK1269/>.
6. Hughes, Derralynn, MD., et al. Gaucher Disease: Treatment. UpToDate. Literature review through November 2018. Last Updated April 2018.

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](http://www.jpeds.com/article/S0022-3476(09)00674-X/fulltext)

## Substrate Reduction Therapy Prior Authorization with Quantity Limit

### TARGET AGENTS

**Cerdelga**® (eliglustat)

**Zavesca**® (miglustat)<sup>a</sup>

<sup>a</sup>- generic available and included in program

Brand (generic)	GPI	Multisource Code	Quantity Limit per Day
<b>Cerdelga (eliglustat)</b>			
84 mg capsule	82700040600120	M, N, O, Y	2 capsules
<b>Zavesca (miglustat)<sup>a</sup></b>			
100 mg capsule	82700070000120	M, N, O, Y	3 capsules

<sup>a</sup>- generic available and included in program

### 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 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**
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/ $\mu$ L 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 (eliglustat), 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 (miglustat), 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 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 submitted documentation 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 Prime Therapeutics Prior Authorization Review process  
**AND**
- 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or has consulted with a specialist in the area of 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 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 submitted documentation in support of therapy with a higher dose for the requested indication

**Length of Approval:** 12 months



## Step Therapy Supplement

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

Please note, this does not include or apply to quantity limit questions.

### **STEP THERAPY SUPPLEMENT OBJECTIVE**

The intent of the Step Therapy Supplement is to provide additional questions, to ensure compliance to MN Statute 62Q.184. These questions will apply if the step therapy component within a Prior Authorization or Step Therapy program is not able to be approved.

### **CONDITIONS FOR APPROVAL**

The requested agent will be approved when ONE of the following are met:

1. 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**
2. The patient's medication history include the required prerequisite/preferred agent(s) as indicated by:
  - a. Evidence of a paid claim(s) within the past 999 days  
**OR**
  - b. The prescriber has stated that the patient has tried the required prerequisite/preferred agent(s) in the past 999 days AND the required prerequisite/preferred agent(s) was discontinued due to lack of effectiveness or an adverse event
- OR**
3. The prescriber has provided documentation that the required prerequisite/preferred agent(s) 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

**Length of Approval:** As per program specific criteria