Substrate Reduction Therapy Prior Authorization with Quantity Limit Program Summary

This prior authorization program applies to Commercial, 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 DRUGS
Cerdelga® (eliglustat)
Zavesca® (miglustat) [a]
[a]- generic available and included in program

QUANTITY LIMIT TARGET DRUG- RECOMMENDED LIMIT

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

[a]- generic available and included in program

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

Initial Criteria
1. The patient is 18 years of age or older
   AND
2. The prescriber is a specialist in the area of practice related to the patient's diagnosis (for example: 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 Gaucher disease type 1 as defined by no neuropathic symptoms
   AND
4. 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
5. The prescriber has drawn baseline levels of hemoglobin, platelets, liver volume, and spleen volume
   AND
6. Prior to any enzyme replacement therapy, the patient had ONE of the following:
   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. 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

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

AND

8. The patient does not have an FDA labeled contraindication to the requested agent

AND

9. 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

1. The patient has been previously approved for therapy with 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 (for example: 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

This pharmacy policy is not an authorization, certification, explanation of benefits or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All pharmacy policies are based on (i) information in FDA approved package inserts (and black box warning, alerts, or other information disseminated by the FDA as applicable); (ii) research of current medical and pharmacy literature; and/or (iii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

The purpose of Blue Cross and Blue Shield of Alabama's pharmacy policies are to provide a guide to coverage. Pharmacy policies are not intended to dictate to physicians how to practice medicine. Physicians should exercise their medical judgment in providing the care they feel is most appropriate for their patients.

Neither this policy, nor the successful adjudication of a pharmacy claim, is guarantee of payment.

FDA APPROVED INDICATIONS AND DOSAGE

Cerdelga

FDA Indication[1]: Cerdelga is indicated for the 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.

Limitations of Use[1]:

- Patients who are 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)

Dosing[1]:

Select patients with Gaucher disease type 1 based on their CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype.

The recommended dosage of Cerdelga is 84 mg twice daily in CYP2D6 EMs and IMs. The recommended dosage in CYP2D6 PMs is 84 mg once daily; appropriate adverse event monitoring is recommended. The predicted exposures with 84 mg once daily in patients who are CYP2D6 PMs are expected to be similar to exposures observed with 84 mg twice daily in CYP2D6 IMs.

Some inhibitors of CYP2D6 and CYP3A are contraindicated with Cerdelga depending on the patient's metabolizer status. Co-administration of Cerdelga with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potentially significant adverse reactions.

Reduce the dosage of Cerdelga to 84 mg once daily for:

- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors
- CYP2D6 EMs taking strong or moderate CYP3A inhibitors

Zavesca

FDA Indication[5]: Zavesca is a glucosylceramide synthase inhibitor indicated as 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).

Dosing[5]: 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. It may be necessary to reduce the dose to one 100 mg capsule once or twice a day in some patients due to adverse reactions, such as tremor or diarrhea.

CLINICAL RATIONALE

Gaucher Disease

Gaucher disease is an inherited lipid storage disorder resulting from the deficiency of glucocerebrosidase. Severity varies significantly with some patients presenting in childhood with multiple complications and others remaining asymptomatic until late adulthood. There are 3 subtypes based on the absence or presence of neurologic involvement and disease progression. Type 1 is a nonneuropathic form often presenting in childhood (presents with hepatosplenomegaly [hepatomegaly is defined as a liver mass > 1.25 times the normal 2.5% of total body weight; splenomegaly is defined as a splenic mass > the normal 2% of total body weight in kg][2], pancytopenia, and skeletal disease). Type 2 is an acute, rapidly progressive neuropathic form causing death during infancy or the first years of life. Type 3 is a chronic, less progressive neuropathic form. Factors thought to contribute to the neurologic involvement of

Type 2 and 3 include accumulation of glucosylsphingosine (a cytotoxic agent) in the brain. Gaucher cells are macrophages engorged with lipid. The macrophages present with a crumple-tissue-paper appearance with a displaced nuclei. Accumulation of glycolipid in the bone marrow, liver, spleen, lungs and other organs results in pancytopenia, hepatosplenomegaly, and diffuse infiltrative pulmonary disease. There are approximately 6,000 individuals diagnosed with Gaucher disease in the United States.[4] Diagnosis can be confirmed via measurement of glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.[3] A finding of <15% of mean normal is diagnostic of disease.[3,7] These patients often have anemia, thrombocytopenia, and leucopenia but diagnosis is differentiated from chronic myeloid leukemia and lymphomas with expression in peripheral blood bone marrow biopsy and aspirate showing infiltration of Gaucher cells.[3] Anemia is defined as a mean hemoglobin (Hb) concentration of: Hb <12.0 g/dL in males > 12 years of age and <11.0 g/dL for females > 12 years of age; however, other standards have been quoted by varying organizations.[2,8] Thrombocytopenia sufficient to justify ERT therapy is defined as a repeated platelet count < 100,000/µL.

Enzyme replacement therapy (ERT) [imiglucerase, velaglucerase, or taliglucerase] is the standard of care for type 1 patients who exhibit clinical signs and symptoms including anemia, thrombocytopenia, skeletal disease, or visceromegaly. Both velaglucerase and taliglucerase have demonstrated equivalent maintenance of hemoglobin and platelet counts to imiglucerase in patients previously treated with imiglucerase.[7,8] Intravenous ERT has been shown to decrease hepatomegaly by an average of 25% with average increases in hemoglobin on 1.5 g/dL. Skeletal disease and platelet counts are slower to respond to therapy and can take a year or more. Response to therapy varies by patient but isn't correlated to genotype, severity, splenectomy or age. Intravenous ERT dosing is typically given every other week at high doses but can be given every week at a medium dose or multiple times a week at low doses. Positive results have been seen with all dosing regimens and controversy exists on the most suitable initial and maintenance dosing regimens.[2] Substrate reduction therapy (SRT) is considered second-line therapy after ERT; however, clinical trials found eliglustat noninferior to imiglucerase in the composite endpoint of decreased hematologic measurements (hemoglobin and platelet count) and increased organ volume (spleen and liver). These findings suggested eliglustat can be used as first-line or maintenance therapy in adult patients with GD1.[1,6]

REFERENCES

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