Medical Policy

Title: Substrate Reduction Therapy

- Prime Therapeutics will review Prior Authorization requests

Prior Authorization Form:  

Link to Drug List (Formulary):  

<table>
<thead>
<tr>
<th>Professional</th>
<th>Institutional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original Effective Date: August 1, 2015</td>
<td>Original Effective Date: August 1, 2015</td>
</tr>
<tr>
<td>Revision Date(s): August 1, 2015; January 1, 2017; July 1, 2017</td>
<td>Revision Date(s): August 1, 2015; January 1, 2017; July 1, 2017</td>
</tr>
<tr>
<td>Current Effective Date: July 1, 2017</td>
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</tbody>
</table>

State and Federal mandates and health plan member contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. To verify a member’s benefits, contact Blue Cross and Blue Shield of Kansas Customer Service.

The BCBSKS Medical Policies contained herein are for informational purposes and apply only to members who have health insurance through BCBSKS or who are covered by a self-insured group plan administered by BCBSKS. Medical Policy for FEP members is subject to FEP medical policy which may differ from BCBSKS Medical Policy.

The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents of Blue Cross and Blue Shield of Kansas and are solely responsible for diagnosis, treatment and medical advice.

If your patient is covered under a different Blue Cross and Blue Shield plan, please refer to the Medical Policies of that plan.
DESCRIPTION
The intent of the Substrate Reduction Therapy Prior Authorization (PA) 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 Drug
- Cerdelga® (eliglustat)
- Zavesca® (miglustat)

FDA Approved Indications and Dosing

Cerdelga
FDA Indication¹: 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 Use¹:
• 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)

Dosing¹: 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: 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: 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.

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

Initial Criteria

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

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  OR
   b. hemoglobin level  OR
   c. liver volume  OR
   d. platelet count (sufficient to decrease the risk of bleeding)  OR
   e. growth  OR
   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

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>Quantity Per Day Limit</th>
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<tbody>
<tr>
<td>Cerdelga (eliglustat)</td>
<td>2 capsules</td>
</tr>
<tr>
<td>Zavesca (miglustat)</td>
<td>3 capsules</td>
</tr>
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**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.⁵ A finding of <15% of mean normal is diagnostic of disease.⁵,⁷ These patients often have anemia, thrombocytopenia, and leukopenia 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.⁵ 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. 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. 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. 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.

REVISIONS

<table>
<thead>
<tr>
<th>Date</th>
<th>Changes</th>
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<tbody>
<tr>
<td>08-01-2015</td>
<td>Policy added to the bcbsks.com web site on 06-23-2015 for an effective date of 08-01-2015.</td>
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<tr>
<td></td>
<td>In Policy section:</td>
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<tr>
<td></td>
<td>- In Initial Criteria Item 8 and Renewal Criteria Item 4 added &quot;to the requested agent&quot; to read &quot;The patient does not have an FDA labeled contraindication to the requested agent&quot; This update had no impact on the policy position.</td>
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<tr>
<td>07-01-2017</td>
<td>Revised Title to &quot;Substrate Reduction Therapy&quot; from &quot;Cerdelga® (eliglustat)&quot;</td>
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<td>Description updated</td>
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<td></td>
<td>- Added Zavesca (miglustate) as a Target Drug and updated FDA Approved Indications and Dosing information</td>
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<tr>
<td></td>
<td>In Policy section:</td>
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<tr>
<td></td>
<td>Initial Criteria</td>
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<tr>
<td></td>
<td>- Removed &quot;Cerdelga will be approved when following are met:&quot;</td>
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<tr>
<td></td>
<td>In Item 4 a added &quot;a baseline&quot; and &quot;or other nucleated cells&quot; to read &quot;The patient has a baseline glucocerebrosidase activity of &lt;15% of mean normal in fibroblasts, leukocytes, or other nucleated cells&quot;</td>
</tr>
<tr>
<td></td>
<td>- In Item 4 b removed &quot;mutations on 2&quot; and added &quot;two (2)&quot; and &quot;(GBA gene)&quot; to read &quot;Genetic analysis with two (2) disease-causing alleles on the glucocerebrosidase genome (GBA gene)&quot;</td>
</tr>
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<td></td>
<td>- In Item 6 a removed &quot;of &lt;12.0 g/dL in males &gt; 12 years of age and &lt;11.0 g/dL for females &gt; 12 years of age&quot; and added &quot;level below the testing laboratory’s lower limit of the normal range based on age and gender&quot; to read &quot;Anemia defined as mean hemoglobin (Hb) level below the testing laboratory’s lower limit of the normal range based on age and gender&quot;</td>
</tr>
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<td></td>
<td>- In Item 6 c removed &quot;Liver mass &gt; 1.25 times the normal 2.5% of total body</td>
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weight" and added "Hepatomegaly" to read "Hepatomegaly"
- In Item 6 d removed "Splenic mass > the normal 2% of total body weight in kg" and added "Splenomegaly" to read "Splenomegaly"
- In Item 6 e added "(i.e., growth velocity is below the standard mean for age)" to read "Growth failure (i.e., growth velocity is below the standard mean for age)"
- In Item 6 f added "disease with other causes ruled out" to read "Evidence of bone disease with other causes ruled out"
- In Item 7 a added "If Cerdelga is requested, then" to read "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."
- Added Item 7 b "If Zavesca is requested, then enzyme replacement therapy is NOT a therapeutic option (e.g. contraindication, intolerance, previous ERT failure)"

Renewal Criteria
- In Item 1 added "with the requested agent" to read "The patient has been previously approved for therapy with the requested agent through Prime Therapeutics Prior Authorization Review process"
- In Item 3 added "from baseline" to read "The patient has shown improvement in or stabilization from baseline of ONE of the following:"
- Updated Quantity Limit chart to add Zavesca (miglustat).

Rationale section updated
References updated

REFERENCES