Medical Policy

BlueCross BlueShield of Kansas
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Title: Substrate Reduction Therapy

- **Prime Therapeutics will review Prior Authorization requests**

Prior Authorization Form:
http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6507KS-SRET.pdf

Link to Drug List (Formulary):
https://www.bcbsks.com/drugs/

Professional
Original Effective Date: August 1, 2015
Revision Date(s): August 1, 2015; January 1, 2017; July 1, 2017; June 15, 2018
Current Effective Date: June 15, 2018

Institutional
Original Effective Date: August 1, 2015
Revision Date(s): August 1, 2015; January 1, 2017; July 1, 2017; June 15, 2018
Current Effective Date: June 15, 2018

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 Agents

- **Cerdelga®** (eliglustat)
- **Zavesca®** (miglustat)

FDA Approved Indications and Dosage[1]

Agent	Indication	Dosing and Administration
Cerdelga™ (eliglustat) 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 Limitations of Use: • 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)	CYP2D6 extensive metabolizer (EM) or intermediate metabolizer (IM): 84 mg orally twice daily CYP2D6 poor metabolizer (PM): 84 mg orally once daily
Zavesca® (miglustat) 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

POLICY

Prior Authorization and Quantity Limit 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)
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

Brand (generic)	Quantity Per Day Limit
Cerdelga (eliglustat)	
84 mg capsule	2 capsules
Zavesca (miglustat)	
100 mg capsule	3 capsules

RATIONALE

Gaucher Disease

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]

REVISIONS	
08-01-2015	Policy added to the bcbsks.com web site on 06-23-2015 for an effective date of 08-01-2015.
01-01-2017	Policy published 12-20-2016. Policy effective 01-01-2017.
	In Policy section: ▪ In Initial Criteria Item 8 and Renewal Criteria Item 4 added "to the requested agent" to read "The patient does not have an FDA labeled contraindication to the requested agent" This update had no impact on the policy position.
07-01-2017	Revised Title to "Substrate Reduction Therapy" from "Cerdelga® (eliglustat)"
	Description updated ▪ Added Zavesca (miglustate) as a Target Drug and updated FDA Approved Indications and Dosing information
	In Policy section: Initial Criteria ▪ Removed "Cerdelga will be approved when following are met:" In Item 4 a added "a baseline" and "or other nucleated cells" to read "The patient has a baseline glucocerebrosidase activity of <15% of mean normal in fibroblasts, leukocytes, or other nucleated cells" ▪ In Item 4 b removed "mutations on 2" and added "two (2)" and "(GBA gene)" to read "Genetic analysis with two (2) disease-causing alleles on the glucocerebrosidase genome (GBA gene)" ▪ In Item 6 a removed "of <12.0 g/dL in males > 12 years of age and <11.0 g/dL for females > 12 years of age" and added "level below the testing laboratory's lower limit of

REVISIONS	
	the normal range based on age and gender" to read "Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of the normal range based on age and gender" ▪ In Item 6 c removed "Liver mass > 1.25 times the normal 2.5% of total body 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)" <u>Renewal Criteria</u> ▪ 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
06-15-2018	Description section updated
	In Policy section: <u>Initial Evaluation</u> ▪ In Item 3 remove "as defined by no neuropathic symptoms" to read "The patient has a diagnosis of Gaucher Disease type 1" ▪ Added "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))" ▪ In Item 7 removed "Prior to any enzyme replacement therapy" and added "has as least" and "clinical presentations at baseline:" to read "The patient has at least ONE of the following clinical presentations at baseline:" ▪ In Item 7 b added "Thrombocytopenia" to read "Thrombocytopenia (platelet count of < 100,000/µL on at least 2 measurements)" <u>Renewal Evaluation</u> ▪ Added "Cerdelga (eliglustat) or Zavesca (miglustat) will be approved when the following are met:" ▪ Quantity limit chart updated
	Rationale section updated
	References updated

REFERENCES

1. Cerdelga prescribing information. Genzyme. August 2014.
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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