Medical Policy

BlueCross BlueShield of Kansas
An independent licensee of the Blue Cross Blue Shield Association

Title: Cerdelga® (eliglustat)

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

  Prior Authorization Form:
  http://www.bcbsks.com/CustomerService/Forms/pdf/PriorAuth-6352KS-CERD.pdf

  Link to Drug List (Formulary):
  http://www.bcbsks.com/CustomerService/PrescriptionDrugs/drug_list.shtml

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

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

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 Cerdelga (eliglustat) 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)

FDA Approved Indications and Dosing

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

POLICY

Prior Authorization and Quantity Limit Criteria for Approval

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

Initial Criteria

Cerdelga will be approved when following 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 glucocerebrosidase activity of <15% of mean normal in fibroblasts or leukocytes
      OR
   b. Genetic analysis with disease causing mutations on 2 alleles of glucocerebrosidase genome
   AND
5. The patient is a CYP2D6 extensive metabolizer (EMs), intermediate metabolizer (IMs), or poor metabolizer (PMs) established by an FDA-cleared test.
   AND
6. The prescriber has drawn baseline levels of hemoglobin, platelets, liver volume and spleen volume
   AND
7. Prior to any enzyme replacement therapy, ONE of the following:
   a. Anemia defined as mean hemoglobin (Hb) of <12.0 g/dL in males > 12 years of age and <11.0 g/dL for females > 12 years of age
      OR
   b. Platelet count of < 100,000/µL on at least 2 measurements
      OR
   c. Liver mass > 1.25 times the normal 2.5% of total body weight
      OR
   d. Splenic mass > the normal 2% of total body weight in kg
      OR
   e. Growth failure
      OR
   f. Evidence of bone disease
   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 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 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

Brand (generic)	Quantity Per Day Limit
Cerdelga (eliglustat) 84 mg	2 capsules

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 or fibroblasts.[3] A finding of <15% of mean normal is diagnostic of disease. 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.[2] 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]

Cerdelga is the first oral option for enzyme replacement therapy. The efficacy of Cerdelga was evaluated in three clinical trials, two of which are included in the prescribing information. Trial 1 was a randomized, double-blind, placebo-controlled, multicenter clinical study involving treatment naïve Gaucher disease type 1 patients. All had pre-existing splenomegaly and hematological abnormalities. The trial stratified the patients based on baseline spleen volume (≤ 20 or > 20 multiples of normal [MN]) and randomized in a 1:1 fashion to receive Cerdelga or placebo. The primary endpoint was the percentage change in spleen volume (in MN) from baseline to 9 months compared to placebo. The secondary endpoints included absolute change in hemoglobin level, percentage change in liver volume (in MN), and percentage change in platelet count from baseline to 9 months compared to placebo. There were statistically significant improvements in all primary and secondary endpoints in the Cerdelga group compared to placebo.[1]

Trial 2 evaluated patients switching from intravenous enzyme replacement therapy to Cerdelga. It was a randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluating the efficacy and safety of Cerdelga compared to imiglucerase. There were 159 Gaucher disease type 1 patients included who all were previously treated with enzyme replacement therapy. All patients had to meet the following pre-specified baseline therapeutic goals: no bone crisis and free of symptomatic bone disease within the last year; mean hemoglobin level of ≥ 11 g/dL in females and ≥ 12 g/dL in males; mean platelet count ≥ 100,000/mm3; spleen volume < 10 times normal and liver volume < 1.5 times normal. Patients were randomized 2:1 to receive Cerdelga or imiglucerase for the 12 month primary analysis period. The primary composite endpoint required stability in all four components (hemoglobin level, platelet count, liver volume, and spleen volume) from baseline to 12 months. Stability was defined by the following pre-specified thresholds of change: hemoglobin level <1.5 g/dL decrease, platelet count < 25% decrease, liver volume <20% increase and spleen volume <25% increase. Cerdelga was found to be non-inferior to imiglucerase in maintaining patient stability. After the 12 months treatment period, 84.8% and 93.6% in the Cerdelga and imiglucerase groups respectively met the primary composite endpoint.[1]

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.

REFERENCES

1. Cerdelga prescribing information. Genzyme August 2014.
2. Pastores GM, Weinreb NJ, Aerts H et al. Therapeutic goals in treatment of Gaucher Disease. *Semin Hematol* 2004;41(suppl 5):4-14.
3. 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
4. NORD (National Organization for Rare Disoders). Gaucher Disease. http://www.rarediseases.org/rare-disease-information/rare-diseases/byID/12/viewFullReport. Accessed 9/12/14.