Pharmacy Policy Bulletin: J-0406 Glucosylceramide Synthase Inhibitorsfor Gaucher Disease and Niemann-Pick Disease – Commercial and Healthcare Reform	
Number: J-0406	**Category:** Prior Authorization
Line(s) of Business: ☒ Commercial ☒ Healthcare Reform ☐ Medicare	**Benefit(s):** **Commercial:** **Prior Authorization (1.)**: **1.** Miscellaneous Specialty Drugs Oral = Yes w/ Prior Authorization **Quantity Limits (1., 2., 3., or 4.)**: **1.** Rx Mgmt Quantity Limits = Safety/Specialty **2.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt **3.** Rx Mgmt Quantity Limits = Safety/Specialty + Dose Opt + Watchful **4.** Quantity Limits = QPC = Yes **Healthcare Reform:** Not Applicable
Region(s): ☒ All ☐ Delaware ☐ New York ☐ Pennsylvania ☐ West Virginia	**Additional Restriction(s):** None
Version: J-0406-017	**Original Date:** 09/03/2014
Effective Date: 12/20/2024	**Review Date:** 12/04/2024

Drugs Product(s):	• Cerdelga (eliglustat) • Yargesa (miglustat) • Zavesca (miglustat)

FDA-Approved Indication(s):	• Cerdelga (eliglustat)
	  ○ 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.
	• Yargesa (miglustat)
	  ○ Monotherapy for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.
	  ○ In combination with Miplyffa (arimoclomol) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older. (non-FDA approved, medically necessary).
	• Zavesca (miglustat)

	○ Monotherapy for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option. ○ In combination with Miplyffa (arimoclomol) for the treatment of neurological manifestations of Niemann-Pick disease type C (NPC) in adult and pediatric patients 2 years of age and older. (non-FDA approved, medically necessary)

Background:	• Cerdelga is a specific inhibitor of glucosylceramide synthase (IC_{50} = 10 ng/mL) and acts as a substrate reduction therapy (SRT) for Gaucher disease type 1 by reducing glucosylceramide (GL-1) production. Reduced production of GL-1 results in less accumulation of it in the target organs. • Yargesa and Zavesca (miglustat) are competitive and reversible inhibitors of glucosylceramide synthase, the first enzyme in a series of reactions that synthesizes most glycosphingolipids. By inhibiting the enzyme, it reduces the rate and amount of glycosphingolipid biosynthesis. A smaller amount of glycosphingolipids allows the residual activity of the deficient glucosylceramidase enzyme (of which glycosphingolipid is the substrate) to be more effective. This is an example of substrate reduction therapy (SRT). • Gaucher disease is caused by a deficiency of the lysosomal enzyme glucosylceramidase (also called acid β-glucosidase or glucocerebrosidase). Glucosylceramidase catalyzes the conversion of the sphingolipid GL-1 (also called glucocerebroside) into glucose and ceramide. The enzymatic deficiency causes an accumulation of GL-1 primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells". • Gaucher disease is an autosomal recessive inherited disorder that can affect different tissues and organs in the body, with a varying range of signs and symptoms among individuals. There are several types of the disease based on distinctive features and characteristics. • Gaucher disease type 1 (non-neuropathic form) is the most common form and does not affect the central nervous system (brain and spinal cord). Signs and symptoms may include hepatosplenomegaly, anemia, thrombocytopenia, lung disease, and bone abnormalities like pain. • Gaucher disease type 2 and Gaucher disease type 3 (neuropathic forms) involve the central nervous system and may result in seizures, brain damage, and abnormal eye movements in addition to the symptoms observed in type 1 disease. Type 2 disease and type 3 disease are differentiated based on severity and progression of disease – type 2 disease begins to cause life-threatening medical problems in infancy while type 3 disease takes longer to worsen. • Treatment and dosing with Cerdelga is dependent on the Cytochrome P450 2D6 (CYP2D6) metabolizer status of the patient. Patients are referred to a lab by their physicians for CYP2D6 genotyping, which serves to identify ultra-rapid, extensive, intermediate, or poor metabolizers. The recommended dosage for extensive metabolizers (EMs) and intermediate metabolizers (IMs) is 84 mg twice daily, while the recommended dosage for poor metabolizers (PMs) is 84 mg once daily. • Niemann-Pick disease type C (NPC) is an ultra-rare progressive genetic disorder characterized by impaired cellular processing and transport of low-density lipoprotein (LDL) cholesterol and other macromolecules, including glycosphingolipids. This leads to the abnormal accumulation of these substances within various tissues of the body, including brain tissue. The accumulation of these substances damages the affected areas.

- NPC has a heterogeneous clinical presentation and includes systemic, neurologic, and psychiatric involvement. About one per million people in the United States (US) are diagnosed and/or miglustat-treated for NPC.
- Neurological symptoms of NPC include developmental delays or regression, speech delay, clumsiness and frequent falls, progressive ataxia (loss of coordination), dystonia, dysarthria, dysphagia, and seizures.
- ICD-10 Code Information:
    - ICD-10: E75.22 “Gaucher disease” may apply to Gaucher disease type 1; however, the prescriber must confirm that the member has a specific diagnosis of Gaucher disease type 1.
    - ICD-10: E75.242: Niemann-Pick disease type C (NPC).
- Prescribing considerations:
    - Cerdelga, Yargesa, or Zavesca should not be used in patients with Gaucher disease type 2 or type 3.
    - The member should not take Cerdelga, Yargesa, or Zavesca in combination with substrate reduction therapy (SRT), an enzyme replacement therapy (ERT) (i.e., Cerezyme [imiglucerase], Elelyso [taliglucerase alfa], VPRIV [velaglucerase alfa]), or with each other.
    - **Cerdelga**:
        - Gaucher disease type 1 treatment and dosing with Cerdelga is dependent on the CYP2D6 metabolizer status of the patient. Patients are referred to a lab by their physicians for Cytochrome P450 2D6 (CYP2D6) genotyping, which serves to identify ultra-rapid, extensive, intermediate, or poor metabolizers.
        - CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect.
        - A specific dose cannot be recommended for CYP2D6 indeterminate metabolizers.
        - CYP2D6 intermediate metabolizers (IMs) or poor metabolizers (PMs) should not be on concomitant therapy with a strong CYP3A inhibitor (refer to Table 1 for examples of strong CYP3A inhibitors). Use of Cerdelga in IMs and PMs is also contraindicated if they have any degree of hepatic impairment.
        - CYP2D6 extensive metabolizers (EMs) or IMs should not be on concomitant therapy with a strong or moderate CYP2D6 inhibitor and a strong or moderate CYP3A inhibitor. Use of Cerdelga is contraindicated in EMs with mild hepatic impairment when taking a strong or moderate CYP2D6 inhibitor. Refer to Table 1 for examples of strong & moderate CYP2D6 inhibitors and strong & moderate CYP3A inhibitors.
        - For additional information on the relationship between a particular genotype and CYP2D6 metabolizer status, please visit: https://www.pharmgkb.org/guidelineAnnotation/PA166127636.

Table 1. Examples of clinical inhibitors for P450-mediated metabolisms

Strong CYP3A Inhibitors	Victrelis (boceprevir), Tybost (cobicistat), Vitekta (elvitegravir) and Norvir (ritonavir), Crixivan (indinavir) and Norvir (rironavir), Sporanox (itraconazole), Onmel (itraconazole), ketoconazole, Kaletra (lopinavir and ritonavir), Viekira & Viekira XR (paritaprevir, ritonavir, ombitasvir, and dasabuvir), Technivie (paritaprevir,

	ritonavir, and ombitasvir), Noxafil (posaconazole), Norvir (ritonavir), Invirase (saquinavir) and Norvir (ritonavir), Aptivus (tipranavir) and Norvir (ritonavir), Vfend (voriconazole), Biaxin (clarithromycin), Zydelig (idelalisib), nefazodone, Viracept (nelfinavir)
Moderate CYP3A Inhibitors	Cinvanti (aprepitant), Emend (aprepitant), Cipro (ciprofloxacin), Xalkori (crizotinib), Sandimmune (cyclosporine), Gengraf (cyclosporine), Neoral (cyclosporine), Multaq (dronedarone), E.E.S (erythromycin), EryPed (erythromycin), Ery-Tab (erythromycin), PCE (erythromycin), Erythrocin (erythromycin), Diflucan (fluconazole), Luvox (fluvoxamine), Gleevec (imatinib), Verelan (verapamil), Calan (verapamil), Isoptin (verapamil), Vaprisol (conivaptan), Cardizem (diltiazem), Cartia (diltiazem), Diltzac (diltiazem), Taztia (diltiazem), Matzim (diltiazem),
Strong CYP2D6 Inhibitors	Aplenzin (bupropion), Wellbutrin (bupropion), Zyban (bupropion), Budeprion (bupropion), Prozac (fluoxetine), Sarafem (fluoxetine), Paxil (paroxetine), Pexeva (paroxetine), Brisdelle (paroxetine), Lamisil (terbinafine), quinidine
Moderate CYP2D6 Inhibitors	Sensipar (cinacalcet), Cymbalta (duloxetine), Irenka (duloxetine), Myrbetriq (mirabegron), Yonsa (abiraterone), Zytiga (abiraterone)

- **Yargesa or Zavesca (miglustat)**:
  - Yargesa or Zavesca is not recommended for use in patients with severe renal impairment (CrCL < 30 mL/min/1.73 m^2). A dose adjustment is recommended in patients with mild or moderate renal impairment.
  - Dose may be reduced in some patients due to tremors or diarrhea.
  - Monitoring of platelet count is recommended as Yargesa or Zavesca may cause a reduction in platelet count.

Approval Criteria

I. Initial Authorization

A. Cerdelga

When a benefit, coverage of Cerdelga may be approved when all of the following criteria are met **(1. through 5.)**:

1. The member is 18 years of age or older.

2. The member has a diagnosis of type 1 Gaucher disease (no ICD-10 code) confirmed by one (1) of the following **(a. or b.)**:
- **a.** Deficiency in glucocerebrosidase activity in peripheral leukocytes.
- **b.** Genetic testing confirms mutant alleles.

3. The member exhibits one (1) of the following symptoms **(a. through e.)**:
- **a.** Hepatomegaly (defined as liver size ≥ 1.25 times normal which is 2.5% of the total body weight)
- **b.** Splenomegaly (defined as splenic mass which is larger than normal size which is 0.2% of the total body weight)
- **c.** Bone disease (i.e., osteonecrosis, osteopenia, secondary pathologic fractures, bone infarct)
- **d.** Bone marrow complications defined as one (1) of the following **(i. or ii.)**:
  - **i.** Anemia with hemoglobin of one (1) of the following **(1) or 2))**:
    - **1)** ≤ 11.5 g/dL for females
    - **2)** ≤ 12.5 g/dL for males

ii. Thrombocytopenia with platelet count ≤ 120,000/mm^3

e. Symptomatic disease, including abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia

4. The member has documentation of an FDA-cleared test which confirms the member has one (1) of the following CYP2D6 genotypes **(a., b., or c.)**:

a. Extensive metabolizer (EM)

b. Intermediate metabolizer (IM)

c. Poor metabolizer (PM)

5. An appropriate quantity is being utilized based on CYP2D6 metabolizer status (see **III. Quantity Limitations**).

B. Yargesa or Zavesca (miglustat)

1. Gaucher's disease

When a benefit, coverage of Yargesa or Zavesca (miglustat) for the treatment of Gaucher disease may be approved when all of the following criteria are met **(a. through e.)**:

a. The member is 18 years of age or older.

b. The member has a diagnosis of mild to moderate type 1 Gaucher disease confirmed by one of the following criteria **(i. or ii.)**:

i. Deficiency in glucocerebrosidase activity in peripheral leukocytes.

ii. Genetic testing confirms mutant alleles.

c. The member has one (1) of the following symptoms **(i. through v.)**:

i. Hepatomegaly (defined as liver size ≥ 1.25 times normal, which is 2.5% of the total body weight.

ii. Splenomegaly defined as splenic mass which is larger than normal size which is 0.2% of the total body weight.

iii. Bone disease (i.e., osteonecrosis, osteopenia, secondary pathologic fractures, bone infarct).

iv. Bone marrow complications defined as one (1) of the following **(A. or B.)**:

A. Anemia with hemoglobin **(1. or 2.):**

1. ≤ 11.5 g/dL for females

2. ≤ 12.5 g/dL for males

B. Thrombocytopenia with platelet count ≤ 120,000/mm^3**.**

v. Symptomatic disease (e.g., abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia.

d. The member has experienced therapeutic failure, contraindication, or intolerance to one (1) ERT product (e.g., Cerezyme [imiglucerase], Elelyso [taliglucerase], or VPRIV [velaglucerase alfa]).

e. If the request is for brand Zavesca, the member has experienced therapeutic failure or intolerance to generic miglustat.

2. Niemann-Pick Disease, type C (NPC)

When a benefit, coverage of Yargesa or Zavesca (miglustat) for the treatment of neurological complications of NPC may be approved when all of the following criteria are met **(a. through d.)**:

a. The prescriber attests that the member has a molecularly confirmed diagnosis of NPC. (ICD-10: E75.242)

b. The member is experiencing neurological symptoms from NPC.

c. Miglustat will be given in combination with Miplyffa.

d. If the request is for brand Zavesca, the member has experienced therapeutic failure or intolerance to generic miglustat.

3. Reauthorization

A. Cerdelga, Yargesa, or Zavesca (miglustat) for the treatment of Gaucher disease: When a benefit, reauthorization of Cerdelga, Yargesa, or Zavesca (miglustat) for the treatment of Gaucher disease may be approved when the following criterion is met **(1.)**:

1. The member has experienced positive clinical response to therapy defined as one (1)

of the following (**a. through d.**):

- **a.** Reduction in liver volume
- **b.** Reduction in spleen volume
- **c.** Increase in hemoglobin levels
- **d.** Increase in platelet counts

B. Yargesa or Zavesca (miglustat) for the treatment of Neimann-Pick disease type C: When a benefit, reauthorization of Yargesa or Zavesca (miglustat) for the treatment of NPC may be approved when all of the following criteria are met **(1. and 2.):**

1. The prescriber attests that the member has experienced positive clinical response to therapy.
2. The member continues to take Miplyffa (arimoclomol) in combination with Yargesa or Zavesca (miglustat).

C. If the request is for Cerdelga, an appropriate quantity is being utilized based on CYP2D6 metabolizer status (see **III. Quantity Limitations**).

D. If the request is for Yargesa or Zavesca (miglustat), an appropriate quantity is being utilized based on the age and BSA of the member (see **III, Quantity Limitations**).

E. If the request is for brand Zavesca, the member has experienced therapeutic failure or intolerance to the generic miglustat.

2. Quantity Limitations

A. Cerdelga

When prior authorization is approved and benefit applies, Cerdelga may be authorized in quantities as follows:

CYP2D6 Metabolizer Status [a]	Dosage
Extensive metabolizers (EMs) or Intermediate metabolizers (IMs)	84 mg twice daily
Poor metabolizers (PMs)	84 mg once daily

[a] The member must NOT be a CYP2D6 ultra-rapid metabolizer (URM)

Patient Level Authorization (PLA) will be needed for authorized quantities of Cerdelga capsules that **exceed** 84 mg per day. Application of a PLA for additional quantities will be approved when the following criterion is met **(1.)**:

1. The member has documentation of CYP2D6 metabolizer status of either extensive metabolizer (EM) or intermediate metabolizer (IM)

B. Yargesa or Zavesca (miglustat)

When prior authorization is approved for a diagnosis of NPC and benefit applies, Yargesa or Zavesca (miglustat) may be authorized in quantities as follows:

Population	Dosage
Adults and adolescents ≥ 12 years of age	600 mg daily in three divided doses (6x100 mg capsules per day)
Children 4-11 years of age, body surface area (BSA) > 1.25 m^2	600 mg daily in three divided doses (6x100 mg capsules per day)
Children 4-11 years of age, BSA 0.89 to 1.25 m^2	400 mg daily in two divided doses (4x100 mg capsules per day)

3. An exception to some or all of the criteria above may be granted for select members and/or circumstances based on state and/or federal regulations.

Limitations of Coverage

I. Coverage of drug(s) addressed in this policy for disease states outside of the FDA-approved indications should be denied based on the lack of clinical data to support effectiveness and safety in other conditions unless otherwise noted in the approval criteria.

II. For Commercial or HCR members with a closed formulary, a non-formulary product will only be approved if the member meets the criteria for a formulary exception in addition to the criteria outlined within this policy

Authorization Duration

- Commercial and HCR plans: If approved, up to a 12 month authorization may be granted

Automatic Approval Criteria

None

References:

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11. NORD. Niemann Pick Disease Type C. Available at: https://www.rarediseases.org/rare-diseases/niemann-pick-disease-type-c/. Accessed October 11, 2024.
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