**Definition:** Enzyme replacement therapy (e.g., imiglucerase, taliglucerase alfa, velaglucerase alfa) substitutes an analogue of the deficient human lysosomal enzyme β-glucocerebrosidase (β-D-glucosyl-N-acylsphingosine glucohydrolase) to catalyze the hydrolysis of glucocerebroside (glucosylceramide, acid beta-glucocerebrosidase, GBA), thereby reducing the accumulation of glucocerebroside and other glycolipids within macrophage lysosomes. Imiglucerase (Cerezyme®), taliglucerase (Elelyso™) and velaglucerase alfa (Vpriv®) are produced by recombinant DNA technology. Enzyme replacement therapy does not correct the underlying genetic abnormality but has been reported to be effective for long-term treatment of Gaucher disease. Miglustat (Zavesca®) is an oral treatment approved for adult patients with mild to moderate type I Gaucher disease if enzyme replacement therapy is not a therapeutic option (for example, allergy, hypersensitivity or poor venous access). Miglustat works differently than enzyme replacement by inhibiting the enzyme that makes glucosphingolipid. Miglustat’s role in decreasing the rate of glycosphingolipid biosynthesis allows a reduction of the substance to a level which can be cleared by the remaining activity of the naturally occurring defective enzyme. Eliglustat (Cerdelga™) is an oral glucosylceramide synthase inhibitor indicated for the 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.

Gaucher disease is an autosomal recessive lipid storage disorder characterized by a deficiency of glucocerebrosidase. Decreased glucocerebrosidase activity leads to accumulation of glucocerebroside within cell lysosomes in the liver, spleen, bone marrow and bone. Gaucher disease is classified into three clinical types:

**Type I Gaucher disease**, known as non-neuronopathic because there is no central nervous system involvement, is the most common form and occurs at any age, predominantly in individuals of Ashkenazi Jewish descent. The disease involves visceral organs (e.g., liver, spleen), bone marrow and bone.

**Types II and III Gaucher disease**, known as neuronopathic, are very rare forms with neurological involvement in addition to other organs affected by type I Gaucher disease. Type II Gaucher disease typically begins during the first year of life and is characterized as a rapidly progressive form, whereas type III is typically a slowly progressive form that appears in early childhood.

**Recommended Authorization Criteria**
Coverage of Cerdelga, Cerezyme, Elelyso, Vpriv, Zavesca are recommended in those who meet the following criteria:

**FDA-Approved Indications**

1) **Type I Gaucher Disease.**

   A. **Adults (≥18 years of age):** Approve for 1 year in patients who meet all of the following criteria:
- Diagnosis of type I Gaucher disease established by **at least one** of the following:
  1. White blood cell or skin fibroblast glucocerebrosidase activity ≤30% of normal; OR
  2. Mutation of two glucocerebrosidase genome alleles; AND

- **At least one** of the following:
  1. Hemoglobin ≥1.0g/dL below lower limit of normal for age and sex (≤11.5g/dL for females or ≤12.5g/dL for males); OR
  2. Platelet count ≤120,000/mm³; OR
  3. Clinically significant hepatomegaly (liver ≥1.25 times normal size established by magnetic resonance imaging or computed tomography); OR
  4. Clinically significant splenomegaly (spleen ≥5 times normal size established by magnetic resonance imaging or computed tomography); OR
  5. Skeletal involvement (e.g., Erlenmeyer flask deformity, osteopenia, pathological fracture, radiological evidence of joint deterioration, avascular necrosis).

**Note:** Cerdelga and Zavesca are for treatment Type I Gaucher Disease in adults only. The safety and effectiveness of Cerdelga and Zavesca in pediatric patients has not been established. Cerdelga is for the treatment of adult patients with mild to moderate type I Gaucher disease if enzyme replacement therapy is not a therapeutic option (for example, allergy, hypersensitivity or poor venous access). Zavesca is for the 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.

B. **Children (≤18 years of age):** Approve for 1 year in patients who meet **all** of the following criteria:

- Diagnosis of type I Gaucher disease established by **at least one** of the following:
  1. White blood cell or skin fibroblast glucocerebrosidase activity ≤30% of normal; OR
  2. Mutation of two glucocerebrosidase genome alleles; AND

- **At least one** of the following:
  1. Abdominal or bone pain; OR
  2. Fatigue; OR
  3. Exertional limitations; OR
  4. Growth rate below normal for age and sex not associated with other conditions; OR
  5. Unintentional weight loss and muscle wasting; OR
  6. Platelet count <60,000/mm³ and/or documented abnormal bleeding episode(s); OR
  7. Hemoglobin ≤2.0g/dL below the lower limit of normal for age and sex; OR
  8. Skeletal involvement (e.g., Erlenmeyer flask deformity, osteopenia, pathological fracture, radiological evidence of joint deterioration, avascular necrosis).

2) **Type III Gaucher Disease (Cerezyme, Elelyso, and Vpriv only).**

A. **Adults (≥18 years of age):** Approve for 1 year in patients who meet **all** of the following criteria:
- Mutation of two glucocerebrosidase genome alleles for neuropathic Gaucher disease; AND
- Neurology, ophthalmology and audiology clinical findings are consistent with type III Gaucher disease; AND
- Brain imaging, electroencephalography and diagnostic brain stem evoked responses are consistent with type III Gaucher disease; AND
- At least one of the following:
  1. Hemoglobin ≥1.0 g/dL below lower limit of normal for age and sex (≤11.5 g/dL for females or ≤12.5 g/dL for males); OR
  2. Platelet count ≤120,000/mm$^3$; OR
  3. Clinically significant hepatomegaly (liver ≥1.25 times normal size according to magnetic resonance imaging or computed tomography); OR
  4. Clinically significant splenomegaly (spleen ≥5 times normal size according to magnetic resonance imaging or computed tomography); OR
  5. Skeletal involvement (e.g., Erlenmeyer flask deformity, osteopenia, pathological fracture, radiological evidence of joint deterioration, avascular necrosis).

B. Children (< 18 years of age): Approve for 1 year in patients who meet all of the following criteria:
- Mutation of two glucocerebrosidase genome alleles for neuropathic Gaucher disease; AND
- Neurology, ophthalmology and audiology clinical findings are consistent with type III Gaucher disease; AND
- Brain imaging, electroencephalography and diagnostic brain stem evoked responses are consistent with type III Gaucher disease; AND
- At least one of the following:
  1. Abdominal or bone pain; OR
  2. Fatigue; OR
  3. Exertional limitations; OR
  4. Growth rate below normal for age and sex not associated with other conditions; OR
  5. Unintentional weight loss and muscle wasting; OR
  6. Platelet count <60,000/mm$^3$ and/or documented abnormal bleeding episode(s); OR
  7. Hemoglobin <2.0 g/dL below the lower limit of normal for age and sex; OR
  8. Skeletal involvement (e.g., Erlenmeyer flask deformity, osteopenia, pathological fracture, radiological evidence of joint deterioration, avascular necrosis).

3) Patient has been started on Cerdelga, Cerezyme, Elelyso, Vpriv, or Zavesca. Approve for an indication or condition addressed as an approval in this document and if the drug continues to provide clinical benefit for the patient (for example: improvement in symptoms, platelet count, or decrease in liver or spleen size).

DOSING:

Cerdelga (eliglustat) capsules. The recommended dosage of Cerdelga is 84 mg twice daily in CYP2D6 extensive metabolizers (EMs) and intermediate metabolizers (IMs). The recommended dosage in CYP2D6 poor metabolizers (PMs) is 84 mg once daily; appropriate adverse event monitoring is recommended.
Cerezyme (imiglucerase) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration.

Elelyso (taliglucerase alfa) is administered by intravenous infusion over 60 to 120 minutes. The recommended dosage for treatment-naïve adult and pediatric patients 4 years of age and older is 60 units per kg of body weight administered every other week.

VPRIV (velaglucerase alfa) is administered by intravenous infusion over 60 minutes. The recommended starting Vpriv dosage in naive adults and naive pediatric patients 4 years of age and older is 60 Units/kg administered every other week. The dosage can be adjusted based on achievement and maintenance of each patient’s therapeutic goals.

Zavesca (miglustat) capsules. The recommended dose is one 100 mg capsule administered orally three times a day at regular intervals. If a dose is missed, the next Zavesca capsule should be taken at the next scheduled time. 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.

CONDITIONS NOT RECOMMENDED FOR APPROVAL
Cerdelga, Cerezyme, Elelyso, Vpriv, Zavesca have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. Type II Gaucher Disease. Based upon our findings, the Company has determined enzyme replacement therapy has not been accepted in the medical community as the standard or appropriate means of treatment for type II Gaucher disease.

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.