Subject: Cerdelga (eliglustat)	Original Effective Date: 12/5/2014
Policy Number: MCP-227	Revision Date(s): 12/15/2016; 6/22/2017
Review Dates:	

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of Cerdelga (eliglustat) for the treatment of Gaucher disease **Type 1** when appropriate criteria are met.

Cerdelga (eliglustat) is indicated for the long-term treatment of adult patients with Type 1 Gaucher disease. Some individuals with Type 1 Gaucher disease will not be eligible for Cerdelga (eliglustat) therapy based on the CYP2D6 genotype determined by a companion diagnostic which measures the individual's metabolism the drug. Cerdelga (eliglustat) is a capsule for oral administration twice daily. The current standard of treatment for Gaucher disease is Enzyme Replacement Therapy which is infused bi-weekly. Cerdelga (eliglustat) is the first oral front-line therapy for Gaucher disease.

Gaucher's disease is one of the most prevalent lysosomal storage disorders (LSDs) and is caused by decreased activity of the lysosomal enzyme acid, ß-glucosidase. Gaucher disease is inherited as an autosomal recessive disorder. ß-glucosidase (glucocerebrosidase, GBA1) results in the accumulation of glucocerebroside within the lysosomal compartment of macrophages. Systemic accumulation of these glycolipid-lipid engorged cells referred to as "Gaucher cells." This enzyme deficiency also causes lipids to collect in the spleen, liver, and bone marrow. Symptoms of Gaucher disease are caused by the accumulation of glucosylceramide, a type of lipid, in cells and tissues leading to abnormal blood counts, enlarged liver or spleen, and destructive bone disease. In summary, individuals with Gaucher disease do not produce enough of an enzyme called glucocerebrosidase. Without this enzyme, a fatty substance called glucocerebrosidase builds up in cells called macrophages. These cells can accumulate in the liver and spleen, causing the organs to become enlarged. Macrophages can also build up in the bone marrow, causing anemia and thrombocytopenia. The primary goals of therapy are elimination or improvement of symptoms, prevention of irreversible damage, and improvement in the overall health and quality of life. An additional goal in pediatric patients is optimization of growth.

Cerdelga (eliglustat) is a specific inhibitor of glucosylceramide synthase and acts as a **substrate reduction therapy** for Gaucher disease Type 1.

Based on characteristic patterns of clinical signs and age of onset, GD is subdivided into three main disease variants: type 1 (non-neuronopathic), type 2 (acute neuronopathic), and type 3 (subacute neuronopathic).[6]

Non-neuronopathic disease

Type 1 Gaucher disease (non-neuronopathic)

- Type 1 Gaucher disease is the *most common form* of the disease, accounting for more than 90% of all cases, and does not involve the central nervous system; therefore, it is also called non-neuronopathic.
- By definition, there is no impairment of the CNS through storage, and all neurological symptoms observed are secondary to the systemic complications of the disease.[2]
- Patients with Type 1 (non neuronopathic) Gaucher disease may suffer from hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life. There is no neurologic involvement with this type. Commonly seen symptoms include fatigue, growth delay in childhood and easy bruising or bleeding.
- Current treatment options available for type 1 Gaucher disease are ERT, SRT, and in rare circumstances, bone marrow or hematopoietic stem cell transplantation.

Neuronopathic Gaucher disease

NOTE: Type 2 and 3 are not addressed in this policy.

Type 2 (neuropathic Gaucher syndrome)

- Type 2 Gaucher disease, the rarest form of this disease, is characterized by severe early neurologic manifestations (acute neuronopathic) with death usually occurring before 2 years of age.
- Type 2 Gaucher disease is the most severe form of the disease. It is characterized by the presence of early onset, very rapidly progressing neurological signs. This type includes serious and rapidly progressive neurologic deterioration with less severe visceral involvement than seen in individuals with type 1 Gaucher disease.
- The neurologic involvement primarily involves the brain, and widespread dysfunction leading to severe seizures, rigidity and other motor dysfunction is common. There is currently no treatment for this type of Gaucher disease which slows the progression and individuals with this condition rarely live past the age of two years.

Type 3

- Type 3 is characterized by a slowly progressive brain involvement, in addition to severe disease of the other organs typically affected by Gaucher disease. A less severe neuropathic form of Gaucher disease, compared to type 2.
- The age of onset may occur anywhere from early childhood to late adulthood and the course of the disease is much more variable than type 1 Gaucher disease. This form of Gaucher disease also involves neurologic dysfunction, including poor coordination, paralysis of the eye muscles, and dementia. However, the severity of these conditions is much less severe than with type 2 Gaucher disease.

Pharmacologic Agents/Conventional Therapy

Previously, patient care and therapy for Type 1 Gaucher disease was primarily aimed at managing or relieving symptoms. Treatments included various pain reduction therapies, blood transfusions, orthopedic surgery for bones and joints, and possible splenectomy. Although many of these measures still have a place in the management of Type 1 Gaucher disease, the focus of disease management shifted in the early 1990s with the advent of disease-specific therapy. The goals of treatment are elimination or improvement of symptoms, prevention of irreversible damage, and improvement in the overall health and quality of life. An additional goal in children is optimization of growth.

Two major approaches to disease-specific therapies for Type 1 Gaucher disease:

1. Enzyme Replacement Therapy: Supplying exogenous glucocerebrosidase enzyme
2. Substrate Reduction Therapy: Inhibiting upstream components of the glucosylceramide biosynthetic pathway (i.e., substrate reduction)

These therapeutic approaches are also used in other lysosomal storage diseases and the descriptions below are intended to give you a general overview of these approaches.

Currently available therapies for Gaucher disease Type 1 include intravenous enzyme replacement therapies (Cerezyme®, VPRIV™, and Elelyso™) and oral substrate reduction therapy (Zavesca™).

Enzyme replacement therapy (ERT)
ERT (e.g., imiglucerase, taliglucerase alfa) is the standard first-line treatment for Gaucher's disease.[4]

The goal of ERT is to replace the deficient enzyme with the appropriate amount of artificial enzyme to allow waste material to be processed. Thus, enzyme replacement therapy works by supplementing or replacing the Gaucher patient's missing or deficient enzyme. With ERT, smaller components of waste can be removed from cells by natural processes. Treatment is typically administered once every other week at a high dose, but, in some patients, treatment is administered every week at a medium dose or as many as 3 times per week at low doses.

ERT for **Type 1** Gaucher disease includes (list may not be all-inclusive, as new agents may receive FDA approval):

- Cerezyme (imiglucerase for injection) is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of **Type 1** Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly.[f]
- Elelyso (taliglucerase alfa) is indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of **Type 1** Gaucher disease.[g]
- VPRIV (velaglucerase alfa) is indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with **Type 1** Gaucher disease.[h]

ERT does not currently address conditions or symptoms related to the central nervous system of **Types 2 and 3** Gaucher disease.

- There is no evidence that ERT, even at high doses, can prevent or slow neurological progression in patients with type 2 or type 3 Gaucher disease.[3,B] Enzyme replacement therapy is not recommended for type 2 Gaucher disease, thus management should be focused on supportive care. For children with type 3 Gaucher disease, enzyme replacement therapy is recommended to ameliorate the severe visceral manifestations.
- The use of ERT for the treatment of individuals with type 2 Gaucher disease has been described in only a few case series studies due to its relative rarity. As with type 3 Gaucher disease, these studies demonstrated the use of ERT reduces visceral, bone and hematologic symptoms while providing little to no impact on neurological symptoms. In these individuals, the progression of neurological symptoms is very rapid. The use of ERT in these individuals provides little real benefit in clinical outcomes or quality of life with the exception of some very limited circumstances.

Substrate reduction therapy (SRT)
The goal of SRT is to minimize the amount of production and accumulation of waste material, or substrate, within cells. Thus, substrate reduction therapy (SRT) works by reducing the amount of waste that a cell makes. Substrate reduction therapy is different from ERT as it does not attempt to replace absent or impaired enzyme function. Instead, SRT interrupts the function of glucosylceramide synthase, an enzyme responsible for the production of glucosylceramide, the substance that accumulates in the body and results in symptoms of Gaucher disease.

- SRT may be an option for individuals who are unable to tolerate ERT due to excessive side effects or allergies, inadequate access to blood vessels for infusion therapy, as well as those for whom ERT is unsuccessful. SRT is for Type 1 Gaucher patients for whom ERT is not an option.
- **Zavesca (miglustat)** is an oral drug approved for the disorder; however it is not available as first-line treatment. Oral miglustat therapy for type 1 Gaucher's disease is approved for use only by patients who are ineligible for ERT.[5] Miglustat frequently causes side effects, such as diarrhea, abdominal swelling, tremor, and weight loss, that affect patient acceptance. The associated clinical improvements are reported to be less effective and slower than that of ERT.[4]
- **Cerdelga (eliglustat)** is the only first-line oral therapy for Gaucher disease type 1 at the time of FDA approval in August 2014.

CLASSIFICATION: Glucosylceramide Synthase Inhibitor

FDA INDICATIONS

Gaucher disease: Treatment of adult patients with Gaucher disease type 1 (GD1) who are cytochrome P450 (CYP-450) 2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.[a]

Limitations of use: Patients who are CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of eliglustat to achieve a therapeutic effect. A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).[a]

Available as: 84 mg hard gelatin capsule

FDA Approved: August 19, 2014**.** Cerdelga (eliglustat) received orphan drug designation from the FDA.

Black Box Warnings: *None at the time of this writing*

RECOMMENDATIONS/COVERAGE CRITERIA

Cerdelga (eliglustat) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by a board-certified physician specializing in the treatment of Gaucher disease, such as geneticists, hematologists, and genetic counselors

2. Diagnosis/Indication [ALL]

- ❒ Diagnosis of **Type 1 (non neuronopathic)** Gaucher disease[a]

- ❒ Diagnosis of Type 1 Gaucher disease confirmed by ONE (1) of the following laboratory test results:[7-9] [ONE]
  - ❍ Biochemical assay of beta-glucocerebrosidase activity (in leukocytes or skin fibroblasts) of less than 30% of normal values
    OR
  - ❍ Deoxyribonucleic acid (DNA) testing (mutations in the glucocerebrosidase gene)

- ❒ **Symptomatic** manifestations of Type 1 Gaucher disease defined by ANY of the following signs and symptoms: [ONE OR MORE]
  - ❍ Moderate to severe anemia [defined as: hemoglobin less than or equal to 11.5 g/dL (adult women) or 12.5 g/dL (adult men) or less than or equal to 1.0 g/dL or more below the lower limit of normal for age and sex)]
  - ❍ Significant hepatomegaly [defined as liver size 1.25 or more times normal (1,750 cc in adults)] or splenomegaly [defined as spleen size 5 or more times normal (875 cc in adults)]
  - ❍ Skeletal disease demonstrated by objective/radiological evidence [i.e. MRI, bone scan, X-ray (or the expert opinion of a rheumatologist or orthopedist)] of joint deterioration, pathological fracture, osteopenia, avascular necrosis, osteosclerosis, marrow infiltration, lytic lesions, or Erlenmeyer flask deformity
  - ❍ Symptomatic disease, including abdominal or bone pain, fatigue, exertional limitation, weakness, or cachexia
  - ❍ Thrombocytopenia [defined as: platelet count less than or equal to 120,000/mm^3]

- ❒ Genotype established using an **FDA-cleared test** for determining CYP2D6 genotype as:[a] [ONE]
  - ❍ Extensive metabolizers (EMs)
  - ❍ Intermediate metabolizers (IMs)
  - ❍ Poor metabolizers (PMs)

NOTE: A CYP2D6 genotyping program is available through LabCorp, using an FDA-cleared test. This Genzyme-funded program can help physicians identify patients who are eligible for treatment with Cerdelga (eliglustat) through an FDA-cleared test. Physicians enroll with LabCorp then complete a Test Request form for each patient requiring genotyping. For more information call 1-800-745-4447, option #2.

NOTE: A small number of adult patients who metabolize Cerdelga (eliglustat) more quickly or at an undetermined rate, as detected by an established genetic laboratory test, will not met this criterion and will not be authorized for Cerdelga (eliglustat) treatment.

- ➢ Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga (eliglustat) to achieve a therapeutic effect.
- ➢ A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).

3. Age/Gender/Other restrictions [ALL]

- ❒ 18 years of age and older
  - ➢ *Safety and effectiveness in pediatric patients have not been established in Cerdelga (eliglustat).*

4. Step/Conservative Therapy/Other condition Requirements [ALL: A, B]

- ❒ Cerdelga (eliglustat) is not prescribed for concurrent use with other medications for Type 1 Gaucher diseases

5. Contraindications/Exclusions/Discontinuations

Authorization will not be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to Cerdelga (eliglustat) or any of its components
- ❒ CYP2D6 EMs or IMs taking a *strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [*Examples of strong or moderate CYP2D6 inhibitors include paroxetine, fluoxetine, bupropion, quinidine, cinacalcet and terbinafine]
  - ➢ *Due to the risk of significantly increased Cerdelga (eliglustat) plasma concentrations which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias*
- ❒ CYP2D6 IMs or PMs taking a *strong CYP3A inhibitor [*Examples of strong CYP3A inhibitors include ketoconazole, itraconazole, clarithromycin, nefazodone, HIV protease inhibitors. Examples of moderate CYP3A inhibitors include fluconazole, ciprofloxacin, diltiazem, verapamil and erythromycin]
  - ➢ *Cerdelga (eliglustat) is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to Cerdelga (eliglustat) and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias.*
- ❒ Cardiovascular disease:
  - ❍ Preexisting cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia)
  - ❍ Long QT syndrome
  - ❍ Concomitant use with Class IA (e.g. quinidine, procainamide) and Class III (eg. amiodarone, sotalol) antiarrhythmic medications (has not been studied) [a]
- ❒ Renal function impairment: Moderate to severe renal impairment or end-stage renal disease (use with caution in patients with mild renal impairment)[a]
- ❒ Hepatic function impairment or cirrhosis (has not been studied). [a]

CONTINUATION OF THERAPY

Cerdelga (eliglustat) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria

- ❑ Member currently meets ALL initial coverage criteria

2. Compliance [ALL]

- ❑ Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history (review Rx history for compliance), including:
  - ❍ Compliance in taking the medication as prescribed
  - ❍ No intolerable adverse effects or drug toxicity

  NOTE: Therapy may be discontinued due to poor adherence upon recommendation of the Molina Medical Director when adherence < 85% has been demonstrated in at least two months during the course of therapy

- ❑ History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY]

3. Labs/Reports/Documentation required [ALL APPLICABLE]

- ❒ Documentation of positive response or disease stability, which may include but not limited to: hematologic indices, MRI of spine/femurs, quality of life, and/or plain films of skeleton; measurements of spleen volume, hemoglobin levels, platelet counts and liver volume

- ❒ Documentation to confirm member is <u>not</u> on strong or moderate CYP2D6/3A inhibitors which results in contraindications to Cerdelga (eliglustat) therapy. Prescriber submit documentation to confirm that a review of member's current medication has been completed to meet this criterion.

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- ❑ Intolerable adverse effects or drug toxicity
- ❑ Persistent and uncorrectable problems with adherence to treatment
- ❑ Poor response to treatment as evidenced by physical findings and/or clinical symptoms
- ❑ Contraindications/Exclusions to therapy
- ❒ Non-FDA approved indications

- Hypersensitivity to Cerdelga (eliglustat) or any of its components
- CYP2D6 EMs or IMs taking a *strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor [*Examples of strong or moderate CYP2D6 inhibitors include paroxetine, fluoxetine, bupropion, quinidine, cinacalcet and terbinafine]
    - *Cerdelga (eliglustat) is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to Cerdelga (eliglustat) and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias.*
- CYP2D6 IMs or PMs on a *strong CYP3A inhibitor [*Examples of strong CYP3A inhibitors include ketoconazole, itraconazole, clarithromycin, nefazodone, HIV protease inhibitors. Examples of moderate CYP3A inhibitors include fluconazole, ciprofloxacin, diltiazem, verapamil and erythromycin]
    - *Cerdelga (eliglustat) is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to Cerdelga (eliglustat) and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias.*
- Cardiovascular disease:
    - Preexisting cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia)
    - Long QT syndrome
    - Concomitant use with Class IA (e.g. quinidine, procainamide) and Class III (eg. amiodarone, sotalol) antiarrhythmic medications (has not been studied) [a]
- Renal function impairment: Moderate to severe renal impairment or end-stage renal disease (use with caution in patients with mild renal impairment)[a]
- Hepatic function impairment or cirrhosis (has not been studied). [a]

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

Dosage is based on patient CYP2D6 metabolizer status (extensive, intermediate, poor metabolizers) determined by an FDA-cleared test. Once patients have been selected using an FDA-cleared test for determining CYP2D6 genotype, the recommended dose is as follows:

- ❒ CYP2D6 EMs or IMs: 84 mg orally twice daily
  - ➢ *To reduce the risk of potentially significant adverse reactions, the dose of Cerdelga (eliglustat) should be reduced to 84 mg orally once daily for CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors OR CYP2D6 EMs taking strong or moderate CYP3A inhibitors.*
- ❒ CYP2D6 PMs: 84 mg orally once daily
- ❒ CYP2D6 ultra-rapid metabolizers (URM) and CYP2D6 indeterminate metabolizers are **excluded** from coverage.
  - ➢ CYP2D6 URMs may not achieve adequate concentrations of Cerdelga (eliglustat) to achieve a therapeutic effect
  - ➢ A specific dosage cannot be recommended for those patients whose CYP2D6 indeterminate

Swallow capsules whole, do not crush, dissolve or open capsules. Avoid eating grapefruit or drinking grapefruit juice.

2. Authorization Limit [ALL]

- ❒ Quantity limit: Two capsules per day dosing (60 capsules per month)
- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time
- ❒ Duration of initial authorization: 3 months
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

- ❒ Cerdelga (eliglustat) is considered a **self-administered** medication (oral capsules).
- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

All other uses of the mentioned drugs that are not an FDA-approved indication or included in 'Coverage Criteria' section above are considered **experimental/investigational** and is not a covered benefit. The following list is ***not*** **all-inclusive** and is subject to change based on research and medical literature:

Cerdelga is considered investigational in patients with any diagnosis other than type 1 Gaucher disease or for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).

SUMMARY OF EVIDENCE/POSITION STATEMENTS

- The FDA approval was based on two phase III trials, ENGAGE and ENCORE, which demonstrated the safety and effectiveness of Cerdelga (eliglustat) were evaluated in two clinical trials with 199 participants with Type 1 Gaucher disease. ENGAGE included patients new to therapy and ENCORE evaluated patients switching from approved enzyme replacement therapies. The most commonly observed side effects in the clinical trials of eliglustat were fatigue, headache, nausea, diarrhea, back pain, pain in the extremities, and upper abdominal pain.

- Treatment-Naïve Gaucher disease Type 1 Patients: ENGAGE Trial
  - A double-blind, placebo-controlled trial evaluated 40 treatment-naïve patients with Gaucher disease type 1 who had not previously received enzyme replacement therapy (ERT).
  - Subjects (patients 16 years of age or older with pre-existing splenomegaly and hematological abnormalities) were randomized to eliglustat twice daily or to placebo.
    - Patients were stratified according to baseline spleen volume (≤ 20 or > 20 multiples of normal [MN]) 400 and randomized to receive eliglustat or placebo for the duration of the 9-month blinded primary analysis period. The eliglustat treatment group was comprised of IM (5%), EM (90%) and URM (5%) patients.
    - Subjects who received eliglustat started with a dosage of 42 mg twice a day (BID), with most receiving a dosage of 84 mg BID after 4 weeks. The subjects continued the drug for 9 months.
  - Compared with placebo, treatment with eliglustat resulted in a greater reduction in spleen volume from baseline to the end of the study (by week 39) — the trial's primary endpoint. Treatment with eliglustat also resulted in greater improvement in liver volume, blood platelet count, and hemoglobin level compared with placebo.
  - Improvements were seen across the following endpoints after 9 months on eliglustat: spleen size, platelet levels, hemoglobin levels, and liver volume. Patients continue to receive eliglustat in the extension period, and the majority of patients have been on treatment for over eighteen months.
  - The primary endpoint of the trial was the percent change in spleen volume from baseline to 39 weeks of treatment. Spleen volume in patients treated with eliglustat decreased from baseline by a mean of 28 percent compared with a mean increase of two percent in placebo patients, for an absolute difference of 30 percent. At the end of the trial, patients who received placebo were switched to treatment with eliglustat. The most common side effects reported in this trial were headache, joint pain and diarrhea.

- Patients Switching from Enzyme Replacement Therapy to Cerdelga (eliglustat): ENCORE Trial
  - This randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluated the efficacy and safety of eliglustat compared with imiglucerase in 159 treated Gaucher disease Type 1 patients ***previously treated*** with enzyme replacement therapy who met pre-specified therapeutic goals at baseline. This trial evaluated the safety and efficacy of eliglustat compared with that of ERT in subjects with type-1 Gaucher disease previously treated with and stabilized on ERT.
  - In the trial, 159 patients who had been receiving enzyme replacement therapy for at least three years and reached therapeutic goals were randomized (2:1) to receive either Cerdelga (eliglustat) or Cerezyme (imiglucerase) for one year. Patients were randomized to receive eliglustat or imiglucerase for the duration of the 12-month primary analysis period. The eliglustat treatment group was comprised of PM (4%), IM 446

(10%), EM (80%) and URM (4%) patients. Seventy-five percent of patients randomized to eliglustat were previously treated with imiglucerase; 21% with velaglucerase alfa and 4% were unreported.

- Patients randomized to eliglustat treatment received a starting dose of 42 mg twice daily, with dose increases to 84 mg twice daily and 127 mg twice daily possible at Weeks 4 and 8 based on plasma trough concentrations of eliglustat at Weeks 2 and 6, respectively. The percentage of patients receiving the 3 possible eliglustat doses was: 42 mg twice daily (20%), 84 mg twice daily (32%) and 127 mg twice daily (48%).
- The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume, and spleen volume) based on changes between baseline and 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. Eliglustat met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint was 84.8% for the eliglustat group compared to 93.6% for the imiglucerase group
- Conclusion: The trial demonstrated that treatment with eliglustat resulted in similar stabilization of hemoglobin level, platelet count and spleen and liver volume compared to imiglucerase (Cerezyme). Eliglustat was found to be non-inferior to imiglucerase, with the majority of patients in both groups remaining stable one year after randomization (84 percent in the eliglustat group and 94 percent in the imiglucerase group).

DEFINITIONS

N/A

APPENDIX

Appendix 1: The Gaucher Registry (www.gaucherregistry.com)

The International Collaborative Gaucher Group (ICGG) Gaucher Registry, sponsored by Genzyme, is the largest cooperative, observational registry on Gaucher disease. Many medical professionals agree that since Gaucher disease is rare, accurate and complete information on the disease is especially important. The Gaucher Registry was established in 1991 in order to better understand the natural history and progression of Gaucher disease. Today, the Registry includes more than 4,000 patients and is open to all patients worldwide, irrespective of treatment status.

Through the Gaucher Registry, healthcare providers and disease specialists can share clinical information about Gaucher disease. This may ultimately contribute to earlier diagnosis, earlier intervention, and better disease management for you and other people living with Gaucher disease.

In addition to helping understand the natural history progression of Gaucher disease, the Gaucher Registry is designed to:

- study trends and address specific questions about Gaucher disease
- provide the Gaucher medical community with information about the Gaucher disease population around the world
- help physicians evaluate the long-term effects of treatment

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CPT	Description
	NA--oral administration

HCPCS	Description
J8499	Prescription drug, oral, nonchemotherapuetic, NOS

ICD-9	Description [For dates of service prior to 10/01/2015]

272.7	Disorders of lipoid metabolism

ICD-10	Description [For dates of service on or after 10/01/2015]
E75.22	Gaucher Disease

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