Subject: Enzyme Replacement Therapy (ERT) for Gaucher Disease • Cerezyme (imiglucerase) • Elelyso (taliglucerase alfa) • Vpriv (velaglucerase alfa)	**Original Effective Date:** 8/3/2016
Guidance Number: MCP-276	**Revision Date(s):**
Review Date(s):	

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 OF EVIDENCE/POSITION

This policy addresses enzyme replacement therapies (ERT) **[Cerezyme (imiglucerase); Elelyso (taliglucerase alfa); Vpriv (velaglucerase alfa)]** for the treatment of Gaucher disease (GD) for when appropriate criteria are met.

The intent of the drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines, and clinical studies.

❖ The following GD therapies are NOT addressed in this policy:

- *Zavesca (miglustat)* is not included in this policy as it is substrate reduction therapy not enzyme replacement therapy. It is a competitive and reversible inhibitor of glucosyltransferase which produces glucocerebroside.
  REFER TO: Zavesca (miglustat) MCP-277

- *Cerdelga (eliglustat tartrate)* is a specific inhibitor of glucosylceramide synthase and acts as a substrate reduction therapy for Gaucher disease Type 1. Cerdelga is an oral agent approved for long term treatment of adult patients with Gaucher disease type 1 who are CHP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.
  REFER TO: Cerdelga (eliglustat) MCP-227

- *Ceredase (alglucerase)* is a modified form of the human enzyme, beta-glucocerebrosidase, prepared from a large pool of human placental tissue collected from selected donors. The quantity of the drug is based on the amount that is collected from selected donors. Due to this limit alglucerase (Ceredase) was phased out and replaced with imiglucerase (Cerezyme).
  Alglucerase has been withdrawn from the market and therefore **NOT** included in this policy.

- GD is a rare, inherited metabolic disorder in which deficiency of the enzyme glucocerebrosidase results in the accumulation of harmful quantities of certain lipids, specifically the glycolipid glucocerebroside, throughout the body especially within the spleen, liver, and bone marrow. The symptoms and physical findings associated with Gaucher disease vary greatly from case to case. Some individuals develop few or no symptoms and others may have serious complications. Common manifestations of Gaucher disease include hepatosplenomegaly, anemia, thrombocytopenia, and skeletal abnormalities.
  - Type 1 is the non-neuronopathic form and type 2 and 3 are the neuronopathic forms. Type 2 is a more severe neuronopathic form leading to mortality by 2 years of age.
  - Patients with non-neuronopathic (type 1) Gaucher disease may suffer from hepatomegaly, splenomegaly, thrombocytopenia, bleeding tendencies, anemia, hypermetabolism, skeletal pathology, growth retardation, pulmonary disease, and decreased quality of life.
  - Type III is a chronic neuronopathic form that begins any time in childhood or adulthood and exhibits slowly progressive but milder neurologic symptoms as well as organomegaly, skeletal disorders, anemia and respiratory symptoms.

- The goal of therapy is to reduce the accumulation of the toxic substrate glucocerebroside and other glycolipids to prevent progressive disease with debilitating complications. Therefore the treatment of GD consists of therapy via two mechanisms:
  - replacing the missing or defective glucosylcerebrosidase with a genetically engineered enzyme (ERT), or
  - reducing the synthesis of the glucosylceramide (SRT)

  SRT differs 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.

  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.

- **PEDIATRIC GD:**
  - **The International Collaborative Gaucher Group (ICGG)** U.S. Regional Coordinators recommend that all children with Gaucher disease be treated with ERT.[A] Children with Gaucher disease are at high-risk for irreversible, morbid complications. The diagnosis of Gaucher disease in the 1st and 2nd decades of life is indicative of a rapidly progressive course. Early intervention is necessary for these children, during the time when the skeleton is immature, to enable them to attain their peak skeletal mass by early adulthood.

  - An update to **The Pediatric Gaucher Disease in England: Guidelines for Assessment, Monitoring, and Enzyme Replacement Therapy (published 2012):**[F] All children with types I and III Gaucher disease should commence treatment with enzyme replacement therapy. Visceral disease in type III GD responds well, and so these children should be offered ERT.

    There is no evidence that the neurological features in patients with type II (neuronopathic Gaucher disease) show any response to ERT and therefore it should not be offered.

- In a study by Altarescu et al,[6] ERT with Ceredase/Cerezyme reversed the systemic manifestations (hemoglobin levels, platelet counts, liver and spleen volumes) in 19 patients with type 3 Gaucher disease. There was no evidence that improvement in the systemic disease manifestations led to early cognitive improvement or altered the neurologic course. Doses of Ceredase/Cerezyme used ranged from 120 unit/kg - 480 units/kg per month with the average being 120 units/kg every 2 weeks.

CLASSIFICATION: Metabolic Agents; Metabolic Enzymes

FDA INDICATIONS

Cerezyme (imiglucerase)[a]
Long-term enzyme replacement therapy for patients with Type 1 Gaucher disease that results in 1 or more of the following conditions: anemia, bone disease, hepatomegaly or splenomegaly, and thrombocytopenia.[a]

- *Orphan drug designation: Treatment of type I, II, and III Gaucher disease*[f]

Elelyso (taliglucerase)[b]
Treatment of adult and pediatric patients with a confirmed diagnosis of Type 1 Gaucher disease.[b]

- *Orphan drug designation: Treatment of Gaucher disease*[f]

Vpriv (velaglucerase alfa)[c]
For long-term enzyme replacement therapy for pediatric and adult patients with Type 1 Gaucher disease.[c]

Available as:

- Cerezyme (imiglucerase): 200 units and 400 units per vial
- Elelyso (taliglucerase alfa): 200 units per vial
- Vpriv (velaglucerase alfa): 400 units per vial

FDA Approved:

- Cerezyme (imiglucerase): May 23, 1994
- Elelyso (taliglucerase alfa): The FDA approved taliglucerase alfa under orphan status in May 2012
- Vpriv (velaglucerase alfa): February 26, 2010

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

REMS: *None at the time of this writing*

Type 1 (non-neuronopathic) Gaucher Disease **ONLY**

Cerezyme (imiglucerase), Elelyso (taliglucerase alfta), and Vpriv (velaglucerase alfa) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified geneticist, pediatric metabolic specialist, hematologist or physician experienced in the management of Gaucher Disease. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ONE]
Clinical documentation required for all criterion (i.e. clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis)

- ❒ Diagnosis of **Type 1** GD confirmed by either enzyme assay or DNA testing:[1-3] **[ONE]**
  - ❍ Gluocerebrosidase activity in the white blood cells or skin fibroblasts less than or equal to 30% of normal activity
  - ❍ Genotype testing indicating a mutation of two alleles of the glucocerebrosidase genome

- ❒ Clinical signs and symptoms of **Type 1** Gaucher Disease **[ADULTS (A) OR PEDIATRICS (B)]**

  A. Presentation of **the following signs and symptoms**:[I,a,b,c] **[ONE]**

  - ❒ Hematologic abnormalities **[ONE]**
    - ❍ Hemoglobin ≤ 11.5 g/dL (women) or ≤ 12.5 g/dL (men) or ≤ 1.0g/dL or more below the lower limit of normal for age and sex
    - ❍ Documented abnormal bleeding episodes
    - ❍ Symptomatic anemia
    - ❍ Thrombocytopenia, with platelet count less than 120,000/mm^3 (120 x10^9/L)
    - ❍ Transfusion dependent

  OR

  - ❒ Liver or spleen disease **[ONE]**
    - ❍ Hepatic or splenic infarcts
    - ❍ Hepatitis
    - ❍ Portal hypertension
    - ❍ Hepatomegaly[10] [BOTH]
      - o Assessed by quantitative imaging of the liver volume using magnetic resonance imaging (MRI) or computed tomography (CT)
      - o Liver mass greater than 1.25 times the normal 2.5% of total body weight in kilograms

- ❍ Splenomegaly[10] [ALL]
  - Assessed by quantitative imaging of the liver volume using MRI or CT
  - Spleen volume 5 times normal or greater

OR

- ❒ **Skeletal disease** as documented by **ONE (1)** of the following: **[ONE]**
  - ❍ Avascular necrosis
  - ❍ Lytic disease
  - ❍ Marrow infiltration
  - ❍ Osteosclerosis
  - ❍ Pathological fracture
  - ❍ Radiological evidence of joint deterioration
  - ❍ Moderate to severe osteopenia

B. PEDIATRICS ONLY [ONE]

- ❒ Evidence of skeletal involvement, *including, but not limited to,* Erlenmeyer flask deformity (failure of bone remodeling)
- ❒ Abdominal or bone pain
- ❒ Hepatosplenomegaly
- ❒ Growth failure secondary to Gaucher Disease AND not associated with other conditions
- ❒ Cachexia
- ❒ Exertional limitations
- ❒ Fatigue
- ❒ Anemia with hemoglobin less than 2.0 g/dL below lower limit of normal for age and gender
- ❒ Platelet count less than 60,000 mm^3 or documented abnormal bleeding episode(s)

3. Age/Gender/Restrictions [AS APPLICABLE]

- ❒ Cerezyme (imiglucerase): 2 years of age and older
  - ➢ *Imiglucerase has been administered to patients younger than 2 years of age, however, the safety and effectiveness in patients younger than 2 years of age have not been established.*

- ❒ Elelyso (taliglucerase alfa): 4 years or older
  - ➢ *Safety and effectiveness have not been established in children younger than 4 years of age.*

- ❒ Vpriv (velaglucerase alfa): 4 years of age or older
  - ➢ *Safety and efficacy of velaglucerase alfa have not been established in children younger than 4 years of age.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]
Clinical documentation required for all criterion (i.e. clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis)

- ❒ Prescribed as monotherapy: NOT to be used concurrently with other medications for Gaucher disease (GD) [i.e. Cerezyme, Vpriv, Elelyso, or Cerdelga]
  - ➢ *Clinical evidence supporting the combination use of enzyme replacement therapy with Zavesca (miglustat) is currently insufficient.*

5. Contraindications*/Exclusions/Discontinuations

There are no contraindications listed in the manufacturer's labeling.[a,b,c]

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

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies

Exclusions

- ❒ Type 2 Gaucher disease
- ❒ Concurrent use of velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies in conjunction with each other, or with miglustat (Zavesca)
- ❒ Member does not meet ALL of the above coverage criteria

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

Type 3 (non-neuronopathic) Gaucher Disease **ONLY**

Cerezyme (imiglucerase), Elelyso (taliglucerase alfta), and Vpriv (velaglucerase alfa) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❑ Prescribed by, or in consultation with, a board-certified geneticist, pediatric metabolic specialist, hematologist or physician experienced in the management of Gaucher Disease. Submit consultation notes if applicable.

  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ALL]
Clinical documentation required for all criterion (i.e. clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis)

- ❒ Diagnosis of **Type 3** GD confirmed by either enzyme assay or DNA testing. Documentation required:[1-3] **[ONE]**
  - ❍ Gluocerebrosidase activity in the white blood cells or skin fibroblasts less than or equal to 30% of normal activity
  - ❍ Genotype testing indicating the presence of **TWO (2)** or more alleles for neuropathic GD

- ❒ **Neurologic manifestations** consistent with Type 3 GD based on evaluation by a specialist in the following conditions. Documentation required: [ONE OR MORE]
  - ❍ Abnormal eye movement
  - ❍ Seizures, encephalopathy
  - ❍ Ophthalmoplegia
  - ❍ Progressive myoclonic epilepsy
  - ❍ Cerebellar ataxia
  - ❍ Spasticity dementia

  Note: ERT has not been shown to improve health outcomes in adult patients with Type 1 GD without clinical signs or symptoms of the disease. In addition, ERT does not provide benefit in reversing or decreasing neurologic symptoms associated with Type 2 (acute neuronopathic) or Type 3 (chronic neuronopathic) GD.

- ❒ Clinical signs and symptoms of **Type 3** Gaucher Disease **[ADULTS (A) <u>OR</u> PEDIATRICS (B)]**
  Documentation required.

  A. Presentation of **the following signs and symptoms**:[I,J,a,b,c] **[ONE]**

  - ❒ Hematologic abnormalities as documented by **ONE (1)** of the following: **[ONE]**
    - ❍ Hemoglobin $\leq$ 11.5 g/dL (women) or $\leq$ 12.5 g/dL (men) or $\leq$ 1.0g/dL or more below the lower limit of normal for age and sex
    - ❍ Documented abnormal bleeding episodes
    - ❍ Symptomatic anemia
    - ❍ Thrombocytopenia, with platelet count less than 120,000/mm^3 (120 x10^9/L)
    - ❍ Transfusion dependent

  <u>OR</u>

- ❒ Liver or spleen disease as documented by **ONE (1)** of the following: **[ONE]**
  - ❍ Hepatic or splenic infarcts
  - ❍ Hepatitis
  - ❍ Portal hypertension
  - ❍ Hepatomegaly[10] [BOTH]
    - Assessed by quantitative imaging of the liver volume using magnetic resonance imaging (MRI) or computed tomography (CT)
    - Liver mass greater than 1.25 times the normal 2.5% of total body weight in kilograms
  - ❍ Splenomegaly[10] [ALL]
    - Assessed by quantitative imaging of the liver volume using MRI or CT
    - Spleen volume 5 times normal or greater

OR

- ❒ **Skeletal disease** as documented by **ONE (1)** of the following: **[ONE]**
  - ❍ Avascular necrosis
  - ❍ Lytic disease
  - ❍ Marrow infiltration
  - ❍ Osteosclerosis
  - ❍ Pathological fracture
  - ❍ Radiological evidence of joint deterioration
  - ❍ Moderate to severe osteopenia

B. PEDIATRICS ONLY [ONE]

- ❒ Evidence of skeletal involvement, *including, but not limited to,* Erlenmeyer flask deformity (failure of bone remodeling)
- ❒ Abdominal or bone pain
- ❒ Hepatosplenomegaly
- ❒ Growth failure secondary to Gaucher Disease AND not associated with other conditions
- ❒ Cachexia
- ❒ Exertional limitations
- ❒ Fatigue
- ❒ Anemia with hemoglobin less than 2.0 g/dL below lower limit of normal for age and gender
- ❒ Platelet count less than 60,000 mm^3 or documented abnormal bleeding episode(s)

3. Age/Gender/Restrictions [AS APPLICABLE]

- ❒ Cerezyme (imiglucerase): 2 years of age and older
  - ➢ *Imiglucerase has been administered to patients younger than 2 years of age; however, the safety and effectiveness in patients younger than 2 years of age have not been established.*

- ❒ Elelyso (taliglucerase alfa): 4 years or older
  - ➢ *Safety and effectiveness have not been established in children younger than 4 years of age.*

- ❒ Vpriv (velaglucerase alfa): 4 years of age or older
  - ➢ *Safety and efficacy of velaglucerase alfa have not been established in children younger than 4 years of age.*

4. Conventional Therapy/Concurrent Therapy/Other Requirements [ALL]

- ❒ Prescribed as monotherapy: NOT to be used concurrently with other medications for Gaucher disease (GD) [i.e. Cerezyme (imiglucerase), Elelyso (taliglucerase alfta), Vpriv (velaglucerase alfa) or Cerdelga]
  - ➢ *Clinical evidence supporting the combination use of enzyme replacement therapy with Zavesca (miglustat) is currently insufficient.*

5. Contraindications*/Exclusions/Discontinuations

There are no contraindications listed in the manufacturer's labeling.[a,b,c]

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

- ❒ Non-FDA approved indications
- ❒ Known hypersensitivity to velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies

Exclusions

- ❒ Type 2 Gaucher disease **Reference 'Coverage Exclusions' section for further information*
- ❒ Concurrent use of velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies in conjunction with each other, or with miglustat (Zavesca)
- ❒ Member does not meet ALL of the above coverage criteria

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member's medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included.

NOTE: Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

CONTINUATION OF THERAPY

Cerezyme (imiglucerase), Elelyso (taliglucerase), and Vpriv (velaglucerase) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria
- ❑ Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.
- ❑ Requested ERT remains for use as monotherapy: NOT to be used concurrently with other GD drug therapy [i.e. Zavesca (miglustat) or Cerdelga (eliglustat)]

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: [ALL]
  - ❍ Adherent to the prescribed medication regimen
  - ❍ Tolerance to therapy
  - ❍ No severe adverse reactions 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

  NOTE: History of non-compliance or non-adherence as verified by member's medication fill history or prescription drug profile may result in continuation of therapy request not being authorized. [MOLINA MEDICAL/PHARMACY REVIEWER TO VERIFY

3. Labs/Reports/Documentation required [ALL]

- ❒ Documentation of **positive response or disease stability** to therapy (as compared to baseline; prior to therapy), *including but not limited to,* improvement in the following conditions: [AT LEAST ONE]
  - ❍ Anemia
    - o Increase hemoglobin levels
    - o Eliminate blood transfusion dependency
    - o Reduce fatigue, dyspnea, angina
    - o Maintain improved Hb values achieved after the first 12 to 24 months of therapy[10]
  - ❍ Thrombocytopenia
    - o Increase platelet counts sufficiently to prevent surgical, obstetrical, and spontaneous bleeding.
    - o Individuals with splenectomy: normalization of platelet count
    - o Avoidance of splenectomy (may be necessary during life-threatening hemorrhagic events)
    - o Maintain stable platelet counts to eliminate risks of bleeding after a maximal response has been achieved

- Hepatomegaly
  - Reduction or maintenance of liver volume

- Splenomegaly
  - Reduction or maintenance of spleen volume

- Skeletal/Bone disease
  - Lessen or eliminate bone pain within first or second year
  - Retain skeletal function by preventing the onset of new skeletal complications
  - Prevent bone crises or decrease frequency
  - Prevent osteonecrosis and subchondral joint collapse
  - Improve bone mineral density (BMD)

- Growth [For Pediatric members only]
  - Improvement of growth
  - Achievement towards normal onset of puberty

- Pulmonary involvement
  - Prevention or reduction of interstitial lung disease
  - Prevention of rapid deterioration of pulmonary disease and sudden death
  - Prevention of pulmonary disease by timely initiation of ERT and avoidance of splenectomy
  - Reverse hepatopulmonary syndrome and dependency on oxygen
  - Amelioration pulmonary hypertension (ERT plus other therapies)

- Functional Health and Well-being
  - Improvement or restoration of physical function for carrying out normal daily activities and fulfilling functional roles
  - Improvement scores from baseline of a validated quality of life (QOL) instrument*

    The US Regional Coordinators of the International Gaucher Collaborative Group statement: A disease-specific QOL instrument has not yet been developed that quantifies the QOL burden from patients with Gaucher disease. Thus, the recommended approach is to assess and monitor a patient's physical and mental functional health and well-being by means of one of the more common and validated generic (non-disease-specific) instruments, such as the SF-36 [Ware J et al. in SF-36 health survey manual and interpretation guide. Boston, MA: The Health Institute of New England Medical Center]

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 to therapy
  - Non-FDA approved indications
  - Known hypersensitivity to velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies

Exclusions

- ☐ Type 2 Gaucher disease ***Reference 'Coverage Exclusions' section for further information***
- ☐ Concurrent use of velaglucerase alfa (Vpriv); imiglucerase (Cerezyme); taliglucerase alfa (Elelyso) or other enzyme replacement therapies in conjunction with each other, or with miglustat (Zavesca)
- ☐ Member does not meet ALL of the above coverage criteria

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL APPLICABLE]

- ❒ **Cerezyme (imiglucerase)**
  Non-neuropathic Gaucher disease, chronic, symptomatic[a]
  - ❍ Usual dosage: Most benefits observed with doses of 30 to 60 units/kg IV every 2 weeks[a]
  - ❍ Range: 2.5 units/kg IV infusion 3 times weekly, up to 60 units/kg every 2 weeks.[a] Dose should be individualized. Dosage adjustments are made based on assessment and therapeutic goals[a]

- ❒ **Elelyso (taliglucerase alpha)**
  Gaucher disease, Type 1
  - ❍ Treatment-naive, 60 units/kg IV over 60 to 120 minutes every 2 weeks; adjust dose based on therapeutic goals[f]
  - ❍ Switching from imiglucerase (Cerezyme) therapy, use the same unit/kg dose in stable patients; adjust dose based on therapeutic goals

- ❒ **Vpriv (velaglucerase alfa)**
  Non-neuropathic Gaucher disease, chronic:
  - ❍ Treatment-naïve: 60 units/kg IV infusion over 60 minutes every other week; adjust dose based on therapeutic goals and response to therapy[f]
  - ❍ Switching from imiglucerase (Cerezyme): Initiate velaglucerase alfa (Vpriv) at previous imiglucerase (Cerezyme) dose 2 weeks following the last imiglucerase dose; infuse dose IV over 60 minutes every other week; adjust dose based on therapeutic goals and response to therapy

2. Authorization Limit [ALL]

- ❒ Quantity limit: Dose not to exceed 60 units/kg every 2 weeks
- ❒ Dispensing limit: N/A
- ❒ Duration of initial authorization: **Six (6) months**
- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **twelve (12) months** to determine continued need based on documented positive clinical response

3. Route of Administration [ALL]

- ❒ Cerezyme (imiglucerase), Elelyso (taliglucerase), and Vpriv (velaglucerase) is considered a **provider-administered** medication
- ❒ 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

This policy addresses the coverage of the following drug products, all of which are enzyme replacement therapies (ERT) [Cerezyme (imiglucerase); Elelyso (taliglucerase alfa); Vpriv (velaglucerase alfa)] for the treatment of Gaucher disease (GD) for when appropriate criteria are met.

All other uses of are enzyme replacement therapies (ERT) [Cerezyme (imiglucerase); Elelyso (taliglucerase alfa); Vpriv (velaglucerase alfa)] that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

- ❒ **Type 2 GD:** ERT may have beneficial palliative effects in Type 2 disease, however does not alter the outcome and is not generally used.

  - ❖ The Paediatric Gaucher Disease in England: Guidelines for Assessment, Monitoring, and Enzyme Replacement Therapy (2012)[D]
    - All children with types I and III Gaucher disease should commence treatment with ERT.
    - Visceral disease in type III GD responds well, and so these children should be offered ERT.
    - There is no evidence that the neurological features in patients with type II (neuronopathic Gaucher disease) show any response to ERT and therefore it should not be offered.

  - ❖ Revised Recommendations for the Management of Gaucher disease in Children (2013 Kaplan et al) [E]
    According to the recommendations, every child and adolescent with symptomatic GD should be treated with regular intravenous infusions of ERT. There is no evidence that ERT, even at high doses, can prevent or slow neurological progression in patients with type 2 or type 3 GD.
    - ERT is not recommended for type 2 GD, management should be focused on supportive care.
    - For children with type 3 GD, ERT is recommended to ameliorate the severe visceral manifestations.

  - ❖ Management of neuronopathic Gaucher disease: Revised recommendations on the management of neuronopathic GD (Vellodi et al[B])
    - There is clear evidence in most patients that ERT ameliorates systemic involvement in non-neuronopathic (Type 1) as well as chronic neuronopathic GD (Type 3); enhancing quality of life;
    - There is no evidence that ERT has reversed, stabilized or slowed the progression of neurological involvement;
    - In patients with established acute neuronopathic GD (Type 2), ERT has had little effect on the progressively downhill course. It has merely resulted in prolongation of pain and suffering.

- ❒ Prescribed for combination therapy in the treatment of GD: Concurrent use of ERTs [i.e. imiglucerase (Cerezyme), alglucerase (Ceredase), velaglucerase (Vpriv)], taliglucerase (Elelyso)] or concurrent use of SRTs [Zavesca (miglustat) or Cerdelga (eliglustat)]
  - ➢ *Insufficient evidence supporting the combination use of ERT [Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa)] with SRT [Zavesca (miglustat) or Cerdelga (eliglustat)] presently.*
  - ➢ *Combination therapy with oral miglustat and enzyme replacement has been studied. In a small active-controlled study, miglustat appeared to increase the clearance of imiglucerase (Cerezyme) by 70%; therefore, combination therapy with imiglucerase is not indicated.*

Gaucher disease (GD) is an autosomal recessive congenital disorder of lipid metabolism and is categorized as a lysosomal storage disorder. The disease is characterized by a deficiency of the lysosomal enzyme glucocerebrosidase, a necessary catalyst for the hydrolysis of glucocerebroside. Individuals with this condition have a build-up of glucocerebroside in lysosomes of phagocytic cells, which are found in storage cells of the liver, spleen, bone marrow, and other organs.

In this lysosomal storage disorder, clinical features are reflective of the accumulation of Gaucher cells in the liver, spleen, bone marrow, and other organs. The accumulation of the Gaucher cells in the liver and spleen lead to organomegaly. Presence of Gaucher cells in the bone marrow and spleen lead to anemia and thrombocytopenia. Velaglucerase, taliglucerase and imiglucerase catalyzes the hydrolysis of glucocerebroside, reducing the amount of glucocerebroside.

There are three clinical forms of GD defined by absence or presence and progression of neurologic involvement:

1) ***Type 1*** has an autosomal recessive inheritance pattern, so carriers do not have GD but can pass it along to their biological children. Type I is the most common and includes approximately 99% of the cases and is associated with enlarged liver and spleen, increased skin pigmentation, and painful bone lesions. It is estimated that there are about 1 in 50,000 to 1 in 100,000 in the general population Type I Gaucher patients and about 50% of those being symptomatic.[A] This is approximately equal to 10,000 to 15,000 Type I Gaucher patients.

   Patients with Type I experience fatigue, anemia, low blood platelets, enlargement of the liver and spleen, weakening of the skeleton, and in some instances, lung and kidney impairment. There are no signs of neurological involvement. With Type I, the onset of clinical symptoms can occur early in life, or begin in adulthood.

2) ***Type II*** involves liver and spleen enlargement and is usually apparent by 3 months of age. Type II involves progressive brain damage resulting in death by the age of two. Type II is characterized by neurologic symptoms including oculomotor apraxia, strabismus, and hypertonicity. These occur, usually in the first year of life, with death following within the first 18 months of life.

3) ***Type III*** involves variable spleen and liver enlargement and may also include seizures. Type III is similar to Type II but onset of symptoms is much later and the course is longer.

Pharmacologic Agents/Conventional Therapy

Treatment of GD consists of therapy two mechanisms: replacing the missing or defective glucosylcerebrosidase with a genetically engineered enzyme (ERT), or reducing the synthesis of the glucosylceramide (SRT).[7] 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.

- **Enzyme Replacement Therapy (ERT):** ERTs act by supplementing glucocerebrosidase, the enzyme that breaks down glucosylceramide.
  - The three ERT therapies currently available are **Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa).** ERT is currently the standard of care for treatment and is used in symptomatic patients.
  - The goal of ERT is to provide the appropriate amount of enzyme to allow excess material to be degraded. Thus, enzyme replacement therapy works by supplementing or replacing the Gaucher patient's missing or deficient enzyme. Because ERT does not cross the blood brain barrier, it does not address conditions or symptoms related to the central nervous system in Types 2 and 3 Gaucher disease.

- **Substrate Reduction Therapy (SRT):** SRT aims to restore metabolic homeostasis by limiting the amount of substrate precursor synthesized (and eventually subject to catabolism) to a level that can be effectively cleared by the mutant enzyme with residual hydrolytic activity.
    - The two SRT therapies are **Zavesca (miglustat) and Cerdelga. Zavesca (miglustat)** is only indicated in patients with mild or moderate disease who are unable to tolerate or take ERT. Therefore, it is reserved as a last line option. Both SRT regimens are administered orally. **The policy addresses the use of substrate reduction therapy (SRT), Zavesca (miglustat).**
    - The goal of SRT is to minimize the amount of production and accumulation of excess material, or a particular substrate (glucosylceramide or GL1), within cells. Thus, SRT works by reducing the amount of GL1 that a cell makes. This means that even though patients with Gaucher disease are deficient in an enzyme that breaks down GL1, with SRT, the enzyme they do have is better able to prevent GL1 from accumulating inside cells.

- Currently, the standard of care for treatment of type 1 GD is ERT with imiglucerase, a biosynthetic (recombinant DNA origin) form of human glucocerebrosidase; such therapy increases the degradation of glucocerebroside in macrophages with resultant reduction in liver and spleen size, amelioration of anemia and thrombocytopenia, and increased bone remineralization.[e]

  ERT with a recombinant glucocerebrosidase
    - Cerezyme (imiglucerase)
    - Elelyso (taliglucerase alfa)
    - Vpriv (velaglucerase alfa)

  The decision to offer ERT in patients with non-neuronopathic Gaucher disease (GD) (type 1 GD, GD1) is based upon disease severity, as determined by the initial assessment, or significant disease progression, as demonstrated through regular follow-up. Disease severity may dictate that the drug be initiated with relatively high doses or relatively frequent administration. After therapeutic response has been established, a reduction in dosage may be attempted for maintenance therapy.

Enzyme Replacement Therapy (ERT): Cerezyme (imiglucerase), Elelyso (taliglucerase), VPRIV (velaglucerase)

- **Cerezyme (imiglucerase)** is an analogue of glucocerebrosidase; it is produced by recombinant DNA technology. Imiglucerase catalyzes the hydrolysis of the glycolipid, glucocerebroside, to glucose and ceramide as part of the normal degradation pathway for membrane lipids.

- **Elelyso (taliglucerase)** was FDA-approved for long-term enzyme replacement therapy to treat Type 1 Gaucher disease on May 1, 2012. According to the FDA, due to the small number of affected patients, the effectiveness of Elelyso was evaluated in a total of 56 patients with Type 1 Gaucher disease enrolled in 2 clinical trials. Many of the study participants continued treatment on a longer-term extension study.

  Study 1: Trial of ELELYSO as Initial Therapy
  In a multi-center, double-blind, parallel-dose trial, the effectiveness of Elelyso for use as an initial therapy was evaluated in 31 adult patients with Type 1 Gaucher disease who had not previously received enzyme replacement therapy. Patients were randomly selected to receive Elelyso at a dose of either 30 or 60 units/kg. The trial was a 9-month multi-center, double blind, randomized study in patients with Gaucher disease-related enlarged spleens (>8 times normal) and thrombocytopenia (<120,000 /mm^3). Sixteen patients had enlarged livers and ten patients had anemia at baseline. All patients were naïve to ERT. Patients with severe neurological symptoms were excluded from the study. Patient age ranged from 19-74 years (mean age 36 years) and 48% were male. Patients were randomized to receive Elelyso at a dose of either 30 Units/kg (n=15) or 60 Units/kg (n=16).

  Results: At baseline, mean % body weight (%BW) and multiples of normal (MN) spleen volumes were 3.1 and 3.3 (%BW) and 15.4 and 16.7 (MN) for the 30 Units/kg and 60 Units/kg dose groups, respectively. Similarly, liver volumes were 4.2 and 3.8 (%BW) and 1.7 and 1.5 (MN). Hemoglobin concentrations were 12.2 and 11.4 g/dL and

platelet counts were 75,320 and 65,038/mm3, for the 30 Units/kg and 60 Units/kg dose groups, respectively. For all studies, liver and spleen volumes were measured by MRI. The changes in clinical parameters after nine months of treatment are shown in Table 3. The observed change from baseline in the primary endpoint, spleen volume, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Conclusion: At both doses, Elelyso was effective in reducing spleen volume, the study's primary endpoint, from baseline by an average of 29 % in patients receiving the 30 units/kg dose and by an average of 40% in patients receiving the 60 units/kg dose after 9 months of treatment. Improvements in liver volume, blood platelet counts, and red blood cell (hemoglobin) levels also were observed.

Study 2: Trial in Patients Switching from Imiglucerase to ELELYSO
The effectiveness of Elelyso was evalauted in another study of 25 patients with Type 1 Gaucher disease who were switched from imiglucerase to ELELYSO. In this multi-center, open-label, single-arm trial, patients who had been receiving treatment with imiglucerase for at least 2 years were switched to Elelyso infusions every other week at the same dose of imiglucerase. The trial was a 9-month, multi-center, open-label, single arm study in patients who had been receiving treatment with imiglucerase at doses ranging from 11 Units/kg to 60 Units/kg for a minimum of 2 years. Patients also were required to be clinically stable and to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. Patient age ranged from 13-66 years (mean age 45 years including pediatric) and 46% were male. Imiglucerase therapy was stopped, and treatment with ELELYSO was administered every other week at the same number of units as each patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed in order to maintain clinical parameters (i.e., hemoglobin, platelet count, spleen volume, and liver volume). One patient required a dose increase (from 9.5 Units/kg to 19 Units/kg at week 24) for a platelet count of 92,000/mm3 at week 22, and responded with a platelet count of 170,000mm3 at month 9.

Results: Elelyso was effective in maintaining spleen and liver volumes, blood platelet counts, and hemoglobin levels over a 9-month evaluation period. Organ volumes and hematologic values remained stable on average through 9 months of ELELYSO treatment. At baseline, spleen volume% BW was 1.1% and MN was 5.5; liver volume % BW was 2.4%and MN was 1.0; mean hemoglobin was 13.6 (± 1.57) g/dL; and mean platelet count was 160,447 (± 79,086) /mm^3. At the nine month endpoint, spleen volume %BW was 1.0% and MN was 5.1; liver volume %BW was 2.3% and MN was 0.9; mean hemoglobin was 13.4 (± 1.6) g/dL and mean platelet count was 165,654 (± 94,038) /mm^3.

❖ **VPRIV (velaglucerase alfa)[c]**
In January 2010, velaglucerase alfa (VPRIV) for the treatment of children and adults with Type I GD was FDA approved based on a priority review of data from 3 clinical studies of 82 patients aged 4 years and older, some of whom switched from imiglucerase therapy.

- Treatment-naïve: In patients aged 4 years and older, efficacy was established during 2 randomized trials (N=59) with study duration of 9 to 12 months. Velaglucerase improved platelet count, decreased liver and spleen volume, and significantly improved Hb concentration (2.4 g/dL mean change from baseline) at 12 months.[c]
- Switching from imiglucerase: In patients aged 9 years and older, velaglucerase alfa provided stable Hb and platelet counts when switched from imiglucerase therapy in a small, single-arm study (N=40).[c]
- In clinical trials in patients with type 1 GD, velaglucerase alfa produced improvements in anemia and thrombocytopenia and reductions in spleen and liver size.[c,e] In a clinical trial in patients who had been receiving imiglucerase at a stable dosage for at least 6 months, a switch to treatment with velaglucerase alfa administered every 2 weeks at a dosage equivalent to the patient's previous imiglucerase dosage resulted in stable mean hemoglobin concentrations and platelet counts, with no need for dosage adjustment during 12 months of velaglucerase alfa treatment.[c,e]
- Improvements in clinical parameters, including hemoglobin concentration, platelet count, liver volume, and spleen volume, have been observed in some patients following a switch from imiglucerase to velaglucerase alfa therapy at the same dosage every 2 weeks.[c,e]
- The recommended regimen is 60 IU/kg administered every other week as a 1-hour intravenous infusion.

- The most common adverse reactions to VPRIV are allergic reactions. Other observed adverse reactions with VPRIV are headache, dizziness, abdominal pain, back pain, joint pain, nausea, fatigue/weakness, fever, and prolongation of activated partial thromboplastin time. Pediatric patients were more likely than adults (greater than 10 % difference) to experience rash, upper respiratory tract infection, prolonged partial thromboplastin time, and pyrexia.

Studies of VPRIV as Initial Therapy

Study I was a 12-month, randomized, double-blind, parallel-dose-group, multinational study in 25 patients age 4 years and older with Gaucher disease related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease-specific therapy for at least the previous 30 months; all but one had no prior therapy. The mean age was 26 years and 60% were male. Patients were randomized to receive VPRIV at a dose of either 45 Units/kg (N=13) or 60 Units/kg (N=12) every other week. At baseline, mean hemoglobin concentration was 10.6 g/dL, mean platelet count was 97 x 10^9/L, mean liver volume was 3.6% of body weight (% BW), and mean spleen volume was 2.9% BW. For all studies, liver and spleen volumes were measured by MRI. The changes in clinical parameters after 12 months of treatment observed from baseline in the primary endpoint, hemoglobin concentration, was considered to be clinically meaningful in light of the natural history of untreated Gaucher disease.

Study II was a 9-month, randomized, double-blind, active-controlled (imiglucerase), parallel-group, multinational study in 34 patients age 3 years and older. Patients were required to have Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Patients were not allowed to have had disease-specific therapy for at least the previous 12 months. The mean age was 30 years and 53% were female; the youngest patient who received VPRIV was age 4 years. Patients were randomized to receive either 60 Units/kg of VPRIV (N=17) or 60 Units/kg of imiglucerase (N=17) every other week. At baseline, the mean hemoglobin concentration was 11.0 g/dL, mean platelet count was 171 × 10^9/L, and mean liver volume was 4.3% BW. For the patients who had not had splenectomy (7 in each group) the mean spleen volume was 3.4% BW. After 9 months of treatment, the mean absolute increase from baseline in hemoglobin concentration was 1.6 g/dL ± 0.2 (SE) for patients treated with VPRIV. The mean treatment difference in change from baseline to 9 months [VPRIV – imiglucerase] was 0.1 g/dL ± 0.4 (SE).

In Studies I and II, examination of age and gender subgroups did not identify differences in response to Vpriv among these subgroups. The number of non-Caucasian patients in these studies was too small to adequately assess any difference in effects by race.

Study in Patients Switching from Imiglucerase Treatment to VPRIV

Study III was a 12-month, open-label, single-arm, multinational study in 40 patients age 9 years and older who had been receiving treatment with imiglucerase at doses ranging between 15 Units/kg to 60 Units/kg for a minimum of 30 consecutive months. Patients also were required to have a stable biweekly dose of imiglucerase for at least 6 months prior to enrollment. The mean age was 36 years and 55% were female. Imiglucerase therapy was stopped, and treatment with VPRIV was administered every other week at the same number of units as the patient's previous imiglucerase dose. Adjustment of dosage was allowed by study criteria if needed in order to maintain clinical parameters.

Hemoglobin concentrations and platelet counts remained stable on average through 12 months of VPRIV treatment. After 12 months of treatment with VPRIV the median hemoglobin concentration was 13.5 g/dL (range: 10.8, 16.1) vs. the baseline value of 13.8 g/dL (range: 10.4, 16.5), and the median platelet count after 12 months was 174 × 109/L (range: 24, 408) vs. the baseline value of 162 × 109/L (range: 29, 399). No patient required dosage adjustment during the 12-month treatment period.

❖ **Cochrane Database of Systematic Reviews 2015**

Enzyme replacement and substrate reduction therapy for Gaucher disease[H]

Comparisons of enzyme replacement therapies in patients with Gaucher disease have limited evidence of similar efficacy

- Summarized available randomized controlled study data on the efficacy and safety of enzyme replacement therapies and substrate reduction therapy for treating Gaucher disease
  - Systematic review of 8 randomized trials evaluating enzyme replacement and substrate reduction therapies in 300 patients with Gaucher disease were evaluated
  - 6 trials evaluated enzyme replacement therapies, all patients had type 1 Gaucher disease
- No significant differences in hemoglobin level, platelet count, liver volume, or spleen volume comparing:
  - imiglucerase 60 units/kg vs. alglucerase 60 units/kg in 1 trial with 30 patients
  - imiglucerase 60 units/kg vs. velaglucerase 60 units/kg in 1 trial with 34 patients
  - different doses of taliglucerase (30 units/kg vs. 60 units/kg) in 1 trial with 32 patients
  - different doses of velaglucerase (45 units/kg vs. 60 units/kg) in 1 trial with 25 patients
  - different dosing frequencies of imiglucerase (every 2 weeks vs. every 4 weeks) in 2 trials with 113 patients
- In subgroup of 13 patients with intact spleen, imiglucerase 60 units/kg significantly reduced platelet count compared to velaglucerase 60 units/kg in 1 trial
- Conclusions:
  - The results reflect the limitations of analyzing evidence restricted to prospective randomized controlled trials, especially when dealing with chronic rare diseases. This analysis suggests that, during the first year of treatment, different recombinant glucocerebrosidases are bio-similar and non-inferior in safety and efficacy for surrogate biological response parameters.
  - ERT given at 30 to 45 units/kg body weight every two to four weeks was generally as effective as the 60 unit/kg dose for the assessed clinical outcomes. The analysis emphasizes the need to determine whether it is realistic to carry out multi-decade prospective clinical trials for rare diseases such as type 1 Gaucher disease. With large treatment effects on the classical manifestations of the disorder, therapeutic investigations in Gaucher disease mandate innovative trial designs and methodology to secure decisive data concerning long-term efficacy and safety - with the realization that knowledge about disease-modifying actions that are sustained are of crucial importance to people with this chronic condition.

PRACTICE GUIDELINES/PROFESSIONAL SOCIETIES/CONSENSUS

❖ **US Regional Coordinators for the International Collaborative Gaucher Group (ICGG)**

The International Collaborative Gaucher Group (ICGG) U.S. Regional Coordinators, a panel of independent physicians who have extensive experience in the care of Gaucher patients, concur that ERT dosing decisions should be at the discretion of the physician and tailored to individual needs. This panel which meets regularly to discuss patient management issues has reached the following conclusions concerning treatment of patients with Type 1 Gaucher's disease. The ICGG U.S. Regional Coordinators are available to address any concerns or questions regarding treatment and other issues relation to the management of patients with Gaucher disease.

The US Regional Coordinators for the International Collaborative Gaucher Group (ICGG) Registry released the **Consensus Recommendations for ERT and Monitoring for Children with Type 1 Gaucher Disease in 2004.**[C]

- Children with Gaucher disease are at high risk for irreversible, morbid complications. Early intervention with appropriate doses of ERT is necessary in childhood, when the skeleton is immature, to enable them to attain their peak skeletal mass.
- This consensus statement recommends that all children with physical signs and symptoms of Gaucher disease be treated with ERT.

- **The Paediatric Gaucher Disease in England: Guidelines for Assessment, Monitoring, and Enzyme Replacement Therapy (2012)**[F]
  - All children with types 1 and 3 Gaucher disease should commence treatment with ERT.
  - Visceral disease in type III GD responds well, and so these children should be offered ERT.
  - There is no evidence that the neurological features in patients with type II (neuronopathic Gaucher disease) show any response to ERT and therefore it should not be offered.

- **Revised Recommendations for the Management of Gaucher disease in Children (2013 Kaplan et al)** [E]
  - Every child and adolescent with symptomatic GD should be treated with regular intravenous infusions of ERT. There is no evidence that ERT, even at high doses, can prevent or slow neurological progression in patients with type 2 or type 3 GD.
  - ERT is not recommended for type 2 GD, management should be focused on supportive care.
  - For children with type 3 GD, ERT is recommended to ameliorate the severe visceral manifestations.

- **Guidelines for Diagnosis, Treatment, and Monitoring of Gaucher Disease (2004)**[D]
  The Belgian Working Group on Gaucher Disease
  - ERT is the standard of care for patients who require treatment for type I and type III Gaucher disease.
  - Substrate inhibition is indicated for the treatment of mild to moderate type I Gaucher patients, but it may be used only in the treatment of adult patients for whom ERT is unsuitable.
  - ERT is unsuccessful in the treatment of the neurological deficiencies which occur in the acute neuronopathic form of Gaucher disease. In these cases, particularly if there is severe bulbar involvement, ERT can be considered only as a palliative measure for visceral symptoms.
  - ERT is an effective and safe treatment for the non-neurological symptoms in the chronic neuronopathic form. The effect of ERT on neurological symptoms is unclear.

- **Treatment of Gaucher Disease by Enzyme Replacement with Imiglucerase or Velaglucerase, or Substrate Reduction Therapy (SRT) with Miglustat** (2011)[E]
  The Ontario Guidelines
  - ERT and SRT are effective in reversing the visceral manifestations of Gaucher disease. However, data do not suggest that either ERT or SRT is effective in improving central nervous system involvement in patients with Type 2 and 3 diseases.
  - Treatment with ERT or SRT in patients at risk of neuronopathic disease should therefore be guided by the non-neurological manifestations of their disease but not initiated in asymptomatic patients who have a genotype which increases their risk of neuronopathic involvement.

- **South African Guidelines for the Management of Gaucher Diagnosis 2011 and Gaucher Disease. European Medicine Agency 2014**
  These guidelines are consensus statements. There are no double blind, placebo controlled trials for these drugs as they are considered unethical. Therefore more reports are large case series or non-inferiority studies comparing one agent to another. Most agencies have agreed to combine data. They have also agreed that extrapolation of adult data to children is acceptable with the exception of growth. Patient registers are needed. [Per AMR Reviewer, July 2016]

DEFINITIONS

N/A

APPENDIX

Appendix A: Therapeutic goals in the treatment of Gaucher disease

- *Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol 2004; 41:4.*
- *Baldellou A, Andria G, Campbell PE, et al. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr 2004; 163:67.*

Appendix B: Severity Score System for Adults With Type 1 Gaucher Disease (GD1)

DS3 is a method of expressing an integrated assessment of the burden of disease in a given patient. It can be used to monitor patient status, determine endpoints in clinical studies, classify disease phenotypes and compare patients with the same disease. Although frequently referred to as 'disease severity indices,' DS3 instruments may also include measures of disease activity and damage. DS3s utilize a minimal data set to score the patient in a comprehensive manner. They usually are structured as a group of domains (often according to organ system) that are populated with non-redundant items that are valid, reliable, use feasible, standardized methods of assessment, and that are variably weighted based on associated morbidity and mortality. A DS3 for adult GD1 patients was recently developed and subjected to successful preliminary testing for validity, reliability and feasibility4. With respect to changes over time, a minimal clinically important difference was defined. Construct validity has been partially demonstrated.

Reference: Weinreb NJ, Finegold DN, Feingold E, Zeng Z, Rosenbloom BE, Shankar SP, Amato D. Evaluation of disease burden and response to treatment in adults with type 1 Gaucher disease using a validated disease severity scoring system (DS3). Orphanet J Rare Dis. 2015 May 22;10:64. doi: 10.1186/s13023-015-0280-3.

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
NA	

HCPCS	Description
J1786	Injection, imiglucerase, 10 units
J3060	Injection, taliglucerase alfa, 10 units
J3385	Injection, velaglucerase alfa, 100 units

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

REFERENCES

Package Insert, FDA, Drug Compendia

a. Cerezyme (imiglucerase) [prescribing information]. Cambridge, MA: Genzyme Corporation; November 2011.
b. Elelyso [prescribing information]. New York, NY: Pfizer Labs; May 2014.
c. Vpriv [prescribing information]. Lexington, MA: Shire Human Genetic Therapies, Inc. April 2015.
Product Information: VPRIV(R) intravenous injection, velaglucerase alfa intravenous injection. Shire Human Genetic Therapies, Inc. (per FDA), Lexington, MA, 2015.
d. Zavesca (miglustat) [prescribing information]. South San Francisco, CA: Actelion Pharmaceuticals US Inc; February 2014.
e. American Hospital Formulary Service (AHFS). Drug Information 2016. Velaglucerase Alfa [STAT!Ref Web site]. Available via subscription only.
f. Micromedex Healthcare Series. DrugDex. [Micromedex Web site]; 2016. Available via subscription only.
g. Drug Facts and Comparisons. Drug Facts and Comparisons 4.0 [online]. 2016. Available from Wolters Kluwer Health, Inc.
h. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2016. URL: http://www.clinicalpharmacology.com.
i. Lexi-Comp Online. (2016). AHFS DI. Alglucosidase alfa. Retrieved January 2016 from Lexi-Comp Online with UpToDate Online.

Clinical Trials, Definitions, Peer-Reviewed Publications

1. Charrow J, Esplin JA, Gribble TJ, et al. Gaucher disease: recommendations on diagnosis, evaluation, and monitoring. Arch Intern Med. 1998; 158(16):1754-1760.
2. Martins AM, Valadares ER, Porta G, et al. Recommendations on diagnosis, treatment, and monitoring for Gaucher disease. J Pediatr. 2009; 155(4):10-18.
3. NIH Technology Assessment Panel on Gaucher Disease. Gaucher Disease. Current issues in diagnosis and treatment. NIH technology assessment panel on Gaucher disease. JAMA. 1996; 275(7):548-553. Available at: http://consensus.nih.gov/1995/1995GaucherDiseaseta016html.htm
4. Charrow J, Andersson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with type 1 Gaucher disease: consensus recommendations. J Pediatr. 2004;144(1):112-120.
5. Hughes, D. Gaucher disease: Treatment. **In: UpToDate,** Hanh, S (Ed), UpToDate, Waltham, MA, 2016.Available at www.uptodate.com. Accessed June 2016.
6. Altarescu G, Hill S, Wiggs E, et al. The efficacy of enzyme replacement therapy in patients with chronic neuronopathic Gaucher`s disease. J Pediatr. 2001;138:539-547.
7. Bennett LL, Mohan D. Gaucher Disease and its treatment options. Ann Pharmacother. 2013 Sep;47(9):1182-93. Doi: 10.1177/1060028013500469.
8. Sidransky, E., Steiner, R., Windle, M., Youssoufian, H., Descartes, M., & Petry, P. (2014, October 6). Gaucher Disease Treatment & Management. Available at: http://emedicine.medscape.com/article/944157-treatment Accessed June 2016.
9. Hughes, D. Gaucher disease: Pathogenesis, clinical manifestations, and diagnosis. **In: UpToDate,** Hanh, S (Ed), UpToDate, Waltham, MA, 2016. Accessed June 2016.
10. Pastores, G.M., Weinreb, N.J., Aerts, H., Andria, G., Cox, T.M., Giralt, M., Grabowski, G.A., Mistry, P.K. & Tylki-Szymanska, A. (2004) Therapeutic goals in the treatment of Gaucher disease. Seminars in Hematology, 41, 4–14. Available at: http://williams.medicine.wisc.edu/gaucher2.pdf Accessed June 2016.
11. Pastores GM, Weinreb NJ, Aerts H, et al. Therapeutic goals in the treatment of Gaucher disease. Semin Hematol 2004; 41:4.
12. Baldellou A, Andria G, Campbell PE, et al. Paediatric non-neuronopathic Gaucher disease: recommendations for treatment and monitoring. Eur J Pediatr 2004; 163:67.
13. Pastores GM, Hughes DA. Gaucher Disease. NCBI Bookshelf 2015. www.ncbi.nlm.nih.gov.

Government Agencies, Professional Societies, and Other Authoritative Publications

A. International Collaborative Gaucher Group (ICGG), U.S. Regional Coordinators. Guidelines on Management of Gaucher Disease. Cambridge, MA: ICGG; 1998.
B. Vellodi A, Tylki-Szymanska A, Davies EH, Kolodny E, Bembi B, Collin-Histed T, Mengel E, Erikson A, Schiffmann R. Management of neuronopathic Gaucher disease: revised recommendations. Journal of Inheritable Metabolic Disease 2009, 32: 660-664.
C. Charrow J, Anderson HC, Kaplan P, et al. Enzyme replacement therapy and monitoring for children with Type 1 Gaucher disease: consensus recommendations. *J Pediatr* 2004;144(1):112-20.
D. Abramowicz MJ, Carton D, De Meirleir L, et al. Guidelines for diagnosis, treatment, and monitoring of Gaucher disease.
E. Ontario guidelines for treatment of Gaucher disease by enzyme replacement with imiglucerase or velaglucerase, or substrate reduction therapy with miglustat. Version 9; August 2011.
F. Vellodi A, Wraith JE, Collin-Histed T, Chakrapani A. Pediatric Gaucher Disease in England: Guidelines for Assessment, Monitoring, and Enzyme Replacement Therapy. Issued March 2012. Available at http://www.specialisedservices.nhs.uk/library/23/Guidelines_for_paediatric_ _Gauchers_Disease.pdf. Accessed June 2016
G. Kaplan P, Baris H, De Meirleir L, et al. Revised recommendations for the treatment of Gaucher disease in children. *Eur J Pediatr* 2013;172:447-458.
H. Shemesh E, Deroma L, Bembi B, Deegan P, Hollak C, Weinreb NJ, Cox TM. Enzyme replacement and substrate reduction therapy for Gaucher disease**. Cochrane Database of Systematic Reviews 2015,** Issue 3. Art. No.: CD010324. DOI: 10.1002/14651858.CD010324.pub2.
I. Baris HN, Cohen IJ, Mistry PK. Gaucher Disease: The Metabolic Defect, Pathophysiology, Phenotypes And Natural History. Pediatric endocrinology reviews : PER. 2014;12(0 1):72-81. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4520262/ Accessed: June 2016
J. Bhenghu L. South African Guidelines for the Management of Gaucher Diagnosis 2011. S Afr Med J.2012;102(8):697-702.
K. Gaucher Disease. European Medicine Agency. 2014.www.eq.europ.eu.