**Enzyme Replacement Therapy for Gaucher Disease**

**Policy Number:** 2014D0048B  
**Effective Date:** 9/1/2014

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**INSTRUCTIONS FOR USE**

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

**COVERAGE RATIONALE**

This policy refers to the following drug products, all of which are enzyme replacement therapies used in the treatment of Gaucher disease:

- Imiglucerase (Cerezyme®)
- Taliglucerase (Elelyso™)
- Velaglucerase (VPRIV®)

*Imiglucerase, taliglucerase and velaglucerase are proven for the treatment of Type 1 Gaucher disease when all of the following criteria are met:

A. Diagnosis of Type 1 Gaucher disease
AND
B. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)
AND
C. Dose does not exceed 60 units/kg every 2 weeks

*VPRIV* is the preferred enzyme replacement therapy.

Imiglucerase is proven for the treatment of Type 3 Gaucher disease when all of the following criteria are met:

A. Diagnosis of Type 3 Gaucher disease

AND

B. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)

AND

C. Dose does not exceed 60 units/kg every 2 weeks

Enzyme replacement therapy with Cerezyme is medically necessary for the treatment of Gaucher disease when one of the following criteria is met:

A. Both of the following:
   1. Diagnosis of Type 1 Gaucher disease
   2. One of the following:
      a. History of failure of VPRIV due to failure to meet clinical goals (e.g., persistent anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly) despite VPRIV therapy
      b. History of failure of VPRIV due to hypersensitivity to VPRIV therapy
      c. Patient is pregnant or breastfeeding
      d. Patient is attempting to become pregnant

OR

B. Diagnosis of Type 3 Gaucher disease

Enzyme replacement therapy with Elelyso is medically necessary for the treatment of Gaucher disease when both of the following criteria are met:

A. Diagnosis of Type 1 Gaucher disease

AND

B. One of the following:
   1. History of failure of VPRIV due to failure to meet clinical goals (e.g., persistent anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly) despite VPRIV therapy
   2. History of failure of VPRIV due to hypersensitivity to VPRIV therapy

Centers for Medicare and Medicaid Services (CMS):
Medicare covers outpatient (Part B) drugs that are furnished “incident to” a physician’s service provided that the drugs are not usually self-administered by the patients who take them. Refer to the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals at [http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf](http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf).

Medicare does not have a National Coverage Determination (NCD) specifically for imiglucerase (Cerezyme®) when used to treat Gaucher’s disease. Local Coverage Determinations (LCDs) do exist, refer to the LCDs for Ceredase/Cerezyme.

Medicare does not have a NCD specifically for taliglucerase (Elelyso™) when used to treat Gaucher’s disease. LCDs or Local Articles do not exist at this time.

Medicare does not have a NCD specifically for velaglucerase (VPRIV®) when used to treat Gaucher’s disease. LCDs or Local Articles do not exist at this time.

(Accessed May 2, 2014)

**BENEFIT CONSIDERATIONS**
Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases.

**BACKGROUND**

Gaucher disease is an inherited autosomal recessive disease characterized by deficient glucocerebrosidase and consequent accumulation of glucocerebroside in the reticuloendothelial cells of the liver, spleen, bone marrow, and other tissues. Type 1 Gaucher disease is the most common subtype, accounting for more than 90% of all cases, and is characterized by systemic manifestations without primary central nervous system involvement (nonneuronopathic). Type 2 Gaucher disease is characterized by severe early neurologic manifestations (acute neuronopathic) with death usually occurring before 2 years of age. Type 3 Gaucher disease is characterized by subacute neurologic symptoms (chronic neuronopathic) and systemic manifestations.4

**CLINICAL EVIDENCE**

Using data from the International Collaborative Gaucher Group (ICGG) Gaucher Registry, Weinreb et al. published a benchmark analysis of achievement of quantifiable, clinically meaningful therapeutic outcomes for Type 1 Gaucher disease in patients treated with imiglucerase.7 The pathologic parameters studied were anemia, thrombocytopenia, hepatomegaly, splenomegaly, bone pain and bone crises. The evaluation included one hundred and ninety-five patients with data available for these parameters at first infusion and after 4 years of therapy. The proportion of patients who met all six therapeutic goals increased from 2.1% at first infusion to 41.5% at 4 years; ≥5 goals from 12.8% to 76.9%; ≥4 goals from 37.4% to 92.8%; ≥3 goals from 70.8% to 99.0%; and ≥2 goals from 95.4% to 99.5%. All patients met at least one goal at first infusion and after 4 years of treatment. The proportion of patients meeting specific therapeutic goals increased for all parameters between first infusion and 4 years of therapy: platelet count (24.6%-79.5%), spleen volume (25.6%-78.5%), liver volume (45.6%-90.8%), bone pain (62.6-70.3%), hemoglobin (68.2-91.8%), and bone crises (91.8-99.0%). On average, patients who received higher doses of imiglucerase achieved a greater number of therapeutic goals.

A 9-month multicenter, double-blind, randomized study of 31 adult patients with Type 1 Gaucher disease naïve to enzyme replacement therapy was conducted to assess the safety and efficacy of taliglucerase.2 For the respective 30 and 60 units/kg groups, mean (±SD) spleen volume (%BW) decreased -0.9 (±0.4) and -1.3 (±1.1); hemoglobin increased 1.6 (±1.4) g/dL and 2.2 (±1.4) g/dL; liver volume (%BW) decreased -0.6 (±0.5) and -0.6 (±0.4); and platelet count increased 11,427 (±20,214)/mm3 and 41,494 (±47,063)/mm3 for the respective 30 and 60 units/kg groups. Twenty-six previously treatment naïve patients continued to be treated with taliglucerase in an extension of this study. After 24 months of blinded therapy, mean (±SD) spleen volume (%BW) decreased -1.4 (±0.6) and -2.0 (±2.0); hemoglobin increased 1.3 (±1.7) g/dL and 2.4 (±2.3) g/dL; liver volume (%BW) decreased -1.1 (±0.5) and -1.0 (±0.7); and platelet count increased 28,433 (±31,996)/mm3 and 72,029 (±68,157)/mm3 for the respective 30 and 60 units/kg groups.

The safety and efficacy of taliglucerase was assessed in 25 patients with Type 1 Gaucher disease who were switched from imiglucerase therapy.2 The 9-month, multi-center, open-label,
single arm study enrolled 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 taliglucerase 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). Organ volumes and hematologic values remained stable on average through 9 months of taliglucerase treatment. At baseline, spleen volume %BW was 1.1% and multiples of normal (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) /mm3. 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) /mm3.

A multinational, phase 3 trial was conducted to evaluate the efficacy and safety of two doses of velaglucerase alfa in 25 treatment-naïve anemic patients with Type 1 Gaucher disease. Subjects were randomized to intravenous velaglucerase alfa 60 units/kg (n=12) or 45 units/kg body weight (n=13) every other week for 12 months. The primary endpoint was change from baseline in hemoglobin concentration in the 60 units/kg arm. At 12 months, mean hemoglobin concentrations increased from baseline [60 units/kg: +23.3%; +2.43 g/dL (p<0.001); 45 units/kg: +23.8%; +2.44 g/dL (p<0.001)], as did mean platelet counts [60 units/kg: +65.9%; +50.9 × 10^9/L (p=0.002); 45 units/kg: +66.4%; +40.9 × 10^9/L(p=0.01)]. Mean splenic volume decreased from baseline [60 units/kg: -50.4%, from 14.0 to 5.8 multiples of normal (MN) (p=0.003); 45 units/kg: -39.9%, from 14.5 to 9.5 MN (p=0.009)]. No drug-related serious adverse events or withdrawals were observed. Velaglucerase alfa was generally well tolerated and effective for adults and children with Type 1 Gaucher disease in this study. All disease-specific parameters measured demonstrated clinically meaningful improvements after 12 months.

A randomized, double-blind, active-controlled (imiglucerase), parallel-group, multinational study was conducted in patients with Gaucher disease-related anemia and either thrombocytopenia or organomegaly. Thirty four patients aged 3 years and older were equally divided to receive either 60 units/kg of velaglucerase or 60 units/kg of imiglucerase every other week for 9 months. Participants were not allowed to have had disease-related therapy in the 12 months prior to the study. At baseline, the mean hemoglobin concentration was 11.0 g/dL, mean platelet count was 171 x 10^9/L, and mean liver volume was 4.3% BW. At the completion of the study period, the mean absolute increase from baseline in hemoglobin concentration was 1.6 g/dL ± 0.2 for those patients who had received velaglucerase.

A multicenter, open-label, 12-month study examined the safety and efficacy of velaglucerase alfa in patients with Type 1 Gaucher disease who were previously stable on imiglucerase therapy. Eligible patients (n=40) ≥ 2 years old were switched to velaglucerase alfa at a dose equal to their prior imiglucerase dose. Velaglucerase alfa infused for one hour every other week was generally well tolerated with most adverse events of mild or moderate severity. Hemoglobin concentrations, platelet counts, and spleen and liver volumes remained stable through 12 months. Investigators concluded that adult and pediatric patients with Type 1 Gaucher disease may be successfully transitioned to velaglucerase alfa.

The effects of a switch to velaglucerase alfa in a group of adult patients with type 1 Gaucher disease, all of whom had previously had their dose reduced as a consequence of the worldwide imiglucerase shortage, were described in a recent paper. Thirty-two patients from two large European Gaucher centers switched to treatment with velaglucerase alfa after 1 to 8.5 months of dose reduction. The course of important Gaucher disease parameters was studied at four time points: one year before the shortage, just before the shortage, before a switch to velaglucerase and after up to one year of treatment with velaglucerase. These parameters included hemoglobin concentration, platelet count, plasma chitotriosidase activity in all patients, and spleen and liver volumes (as well as bone marrow fat fraction images) in 10 patients. Decreases in platelet counts...
as a result of reduced treatment with imiglucerase were quickly restored on treatment with velaglucerase alfa. Chitotriosidase activity declined overall after switching. Five out of 10 patients had an increase in liver volume of at least 10% after six months of velaglucerase treatment, which was reversible in 3. Most patients received infusions at home and no important side effects were observed. Velaglucerase alfa appears to be a safe and effective alternative for imiglucerase.

The effectiveness of enzyme replacement therapies (ERT) for children with Type 1 and Type 3 Gaucher disease (GD) were determined in a longitudinal cohort study including prospective and retrospective clinical data. The investigators estimated age- and gender-adjusted treatment effects using generalized linear mixed models. Children (n=25, aged 1.1 to 15.6 years) with a diagnosis of GD (14 with Type 1 and 11 with Type 3 GD) who attended a specialist treatment center in England were enrolled in this study. At recruitment, 24 patients were receiving ERT (mean treatment duration, 5.57 years; range 0-13.7 years). Children on treatment contributed data before and during treatment, while the child not on treatment contributed natural history data. Platelet count, hemoglobin, and absence/presence of bone pain were the clinical outcomes chosen to reflect disease progression. The investigators found that duration of ERT was associated with statistically significant improvements in platelet count (p<0.001), hemoglobin (p<0.001), and reported bone pain (p = 0.02). They noted that the magnitude of effect on hematological parameters was greater in children with GD3 than in those with GD1.

In order to ascertain pregnancy outcome in women receiving velaglucerase alfa, the medical records of women exposed to this therapy since 2004 were collected from six multinational clinical sites for evaluation. In all, 25 singleton pregnancies (mean gravidity, 2.7; mean parity, 2.0; mean months on ERT, 31.2) were reported in 21 women (mean age, 32.0 years). Two primiparous women suffered three first trimester abortions and one missed abortion occurred in a multigravida female. Live birth rate was 84% (mean gestational age, 39.7 weeks). Mean birthweight was 3234.4 g, with APGAR scores above 9. All but three were vaginal deliveries; elective cesarean sections were performed in two patients with hip arthroplasty and one after previous cesarean. Nine patients received regional analgesia/anesthesia. Post-partum complications were rare, with only one post-partum (placental) bleed which resolved without intervention. Mean hemoglobin and platelet counts improved during pregnancy (9.45% and 26.0%, respectively). Based upon their evaluation of this postmarketing surveillance data collected over an approximate period of 8 years, the evaluators concluded that velaglucerase alfa is safe for conception and pregnancy with good maternal and neonatal outcomes.

The French Gaucher Disease Registry is comprised of all patients with known Gaucher disease (GD) living in France with at least one consultation between the years of 1980 and 2010. Patients in the registry were divided into four groups: the entire cohort, with clinical description; and its subgroups: patients with ≥ 1 follow-up visits, to investigate complications; recently followed (2009-2010) patients; and patients treated during 2009-2010. These groups were examined to determine complications before and during treatment. Among the 562 registry patients, 265 (49.6%) were females; 454 (85.0%) had type 1, 22 (4.1%) type 2, 37 (6.9%) perinatal-lethal type and 21 (3.9%) type 3. Median ages at first GD symptoms and diagnosis, respectively, were 15 (0-77) and 22 (0-84) years for all types. The first symptom diagnosing GD was splenomegaly and/or thrombocytopenia (37.6% and 26.3%, respectively). Bone-marrow aspiration and/or biopsy yielded the diagnosis for 54.7% of the patients, with enzyme deficiency confirming GD for all patients. Birth incidence rate was estimated at 1/50,000 and prevalence at 1/136,000. For the 378 followed patients, median follow-up was 16.2 (0.1-67.6) years. Major clinical complications were bone events (BE; avascular necrosis, bone infarct or pathological fracture) for 109 patients, splenectomy for 104, and Parkinson's disease for 14; 38 patients died (neurological complications for fifteen type 2 and three type 3 patients, GD complications for eleven type 1 and another disease for nine type 1 patients). Forty-six had monoclonal gammopathy. Among 283 recently followed patients, 36 were untreated and 247 had been treated during 2009-2010; 216 patients received treatment in December 2010 (126 with imiglucerase, 45 velaglucerase, 24 taliglucerase, 21 miglustat). BE occurred before (130 in 67 patients) and under treatment (60 in 41 patients) with respective estimated frequencies (95% CI) of first BE at 10 years of 20.3% (14.1%-26.5%) and 19.8% (13.5%-26.1%). This registry enabled
the epidemiological description of GD in France and showed that BE occur even during treatment.

Bone mineral density (BMD) was evaluated in adults receiving velaglucerase alfa in a seminal Phase I/II and extension trial.\textsuperscript{19} Ten treatment-naive symptomatic patients with GD1 (four men, six women; median age 35 years, range 18-62 years) were included; of these, four patients were receiving bisphosphonates at enrollment. Using WHO criteria to classify the lumbar spine (LS) and femoral neck (FN) BMD T-scores, respectively, one (10%) and four (40%) patients had osteoporosis; eight (80%) and five (50%) had osteopenia; and one each (10%) was in the normal range, at baseline. By Month 69, two LS and one FN osteopenic patients normalized and one FN osteoporotic patient became osteopenic; change was seen only in patients not receiving bisphosphonates. Significant improvements in BMD Z-scores were seen at the LS by Month 24 and at the FN by Month 33 and were continuous thereafter. In linear mixed models, Z-scores were significantly lower than the reference population at baseline and improved significantly with treatment (LS and FN both \( p < 0.01 \)); analysis of the subgroup of patients not receiving bisphosphonates showed similar results. In conclusion, in this small cohort, velaglucerase alfa was associated with clinically meaningful and statistically significant LS and FN BMD improvements as early as Month 24 (LS) and 33 (FN), despite dose reduction and significant baseline skeletal pathology. These results suggest that velaglucerase alfa may hold promise in the management of skeletal pathology associated with GD1.

**Professional Societies**

The US Regional Coordinators for the International Collaborative Gaucher Group (ICGG) Registry released Consensus Recommendations for ERT and Monitoring for Children with Type 1 Gaucher Disease in 2004.\textsuperscript{10} 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 Belgian Working Group on Gaucher Disease published Guidelines for Diagnosis, Treatment, and Monitoring of Gaucher’s Disease in 2004.\textsuperscript{11} 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 nonneurological symptoms in the chronic neuronopathic form. The effect of ERT on neurological symptoms is unclear.

The Ontario Guidelines for Treatment of Gaucher Disease by Enzyme Replacement with Imiglucerase or Velaglucerase, or Substrate Reduction Therapy (SRT) with Miglustat were last updated in 2011.\textsuperscript{12} The guidelines state that 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 disease. 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.

An update to The Paediatric Gaucher Disease in England: Guidelines for Assessment, Monitoring, and Enzyme Replacement Therapy was released in 2012.\textsuperscript{13} 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.
Kaplan et al. published Revised Recommendations for the Management of Gaucher disease in Children in 2013. According to the recommendations, every child and adolescent with symptomatic Gaucher disease should be treated with regular intravenous infusions of enzyme replacement therapy. There is no evidence that enzyme replacement therapy, even at high doses, can prevent or slow neurological progression in patients with type 2 or type 3 Gaucher disease. Because enzyme replacement therapy is not recommended for type 2 Gaucher disease, 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.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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.¹

Elelyso (taliglucerase alfa) is indicated for long-term enzyme replacement therapy (ERT) for adults with a confirmed diagnosis of Type 1 Gaucher disease.²

VPRIV (velaglucerase alfa) is indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with Type 1 Gaucher disease.³

APPLICABLE CODES

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] 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 health service. Coverage is determined by the benefit document.

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<td>J3060</td>
<td>Injection, taliglucerase alfa, 10 units</td>
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<td>J3385</td>
<td>Injection, velaglucerase alfa, 100 units</td>
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ICD-10 Codes (Preview Draft)

In preparation for the transition from ICD-9 to ICD-10 medical coding on October 1, 2015*, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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REFERENCES


**POLICY HISTORY/REVISION INFORMATION**

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<td>9/1/2014</td>
<td>Annual review of policy. Revised to list Type 3 Gaucher disease as a proven use of imiglucerase. Revised medical necessity criteria for Cerezyme and Elelyso. Updated clinical evidence and references. Approved by the National Pharmacy &amp; Therapeutics Committee on 7/8/2014. Policy 2014D0048A archived.</td>
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<tr>
<td>2/1/2014</td>
<td>New policy 2014D0048A. Approved by the National Pharmacy and Therapeutics Committee 7/9/2013.</td>
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