INTRAVENTOUS ENZYME REPLACEMENT THERAPY (ERT) FOR GAUCHER DISEASE

Policy Number: PHARMACY 270.8 T2

Effective Date: September 1, 2017

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Related Policies

- Acquired Rare Disease Drug Therapy Exception Process
- Experimental/Investigational Treatment
- Experimental/Investigational Treatment for NJ Plans

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting Oxford benefit plans. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members. Oxford reserves the right, in its sole discretion, to modify its policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice. The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies.

When deciding coverage, the member specific benefit plan document must be referenced. The terms of the member specific benefit plan document [e.g., Certificate of Coverage (COC), Schedule of Benefits (SOB), and/or Summary Plan Description (SPD)] may differ greatly from the standard benefit plan upon which this Clinical Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Clinical Policy. All reviewers must first identify member eligibility, any federal or state regulatory requirements, and the member specific benefit plan coverage prior to use of this Clinical Policy. Other Policies may apply.

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.

CONDITIONS OF COVERAGE

Applicable Lines of Business/ Products

This policy applies to Oxford Commercial plan membership.

Benefit Type

Medical

Referral Required

No

Authorization Required

Yes¹,² (Does not apply to non-gatekeeper products)

Precertification Required

Yes¹

Applicable Site(s) of Service

Outpatient

(If site of service is not listed, Medical Director review is required)

Special Considerations

¹Providers must call Oxford’s Medical Management Department to obtain precertification, with required review by a Medical Director or their designee. Precertification is not required for velaglucerase (VPRIV®).

²Does not apply to non-gatekeeper products.
Special Considerations (continued)

New Jersey Small Members should refer to their certificate of coverage for precertification guidelines and quantity limit guidelines.

BENEFIT CONSIDERATIONS

Before using this policy, please check the member specific benefit plan document and any federal or state mandates, if applicable.

Some Certificates of Coverage allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan 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. Refer to: Acquired Rare Disease Drug Therapy Exception Process.

Essential Health Benefits for Individual and Small Group

For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs, the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this policy, it is important to refer to the member specific benefit plan document to determine benefit coverage.

COVERAGE RATIONALE

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

- Cerezyme® (imiglucerase)
- Elelyso® (taliglucerase)
- VPRIV®* (velaglucerase)

Cerezyme, Elelyso, and VPRIV* are proven and medically necessary for the treatment of Type 1 Gaucher disease when ALL of the following criteria are met:1-6,10-15

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

*VPRIV is the preferred enzyme replacement therapy and does not require precertification.

Cerezyme is proven and medically necessary for the treatment of Type 3 Gaucher disease when ALL of the following criteria are met:4,11-15

- Diagnosis of Type 3 Gaucher disease; and
- Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
- 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:

- Both of the following:
  - Diagnosis of Type 1 Gaucher Disease; and
- One of the following:
  - 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
  - History of failure of VPRIV due to hypersensitivity to VPRIV therapy
  - Patient is pregnant or breastfeeding
Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

- Patient is attempting to become pregnant
- 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:**
- Diagnosis of Type 1 Gaucher Disease; and
- One of the following:
  - 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
  - History of failure of VPRIV due to hypersensitivity to VPRIV therapy

**U.S. FOOD AND DRUG ADMINISTRATION (FDA)**

Cerezyme 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 is a hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for the treatment of patients with a confirmed diagnosis of Type 1 Gaucher disease.²

VPRIV is a hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for pediatric and adult patients with Type 1 Gaucher disease.³

**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

**APPLICABLE CODES**

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

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<td>Injection, taliglucerase alfa, 10 units (Elelyso)</td>
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<td>J3385</td>
<td>Injection, velaglucerase alfa, 100 units (VPRIV)</td>
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**CLINICAL EVIDENCE**

**Proven/Medically Necessary**

**Type 1 Gaucher Disease**

Imiglucerase, velaglucerase alfa, and taliglucerase alfa are indicated for long-term enzyme replacement therapy (ERT) in pediatric and adult patients with Type 1 Gaucher disease.¹-³

Hughes et al. published the results and the long-term data from a single extension study of two phase III trials for velaglucerase alfa treatment.¹⁸ Fifty-seven patients (25 patients from the TKT032 trial, 32 patients from the HGT-GCB-039 trial), aged 3 to 62 years were enrolled. All patients received their first 3 infusions at the clinical site. If the patient exhibited no signs of adverse events, they were able to receive infusions at an alternative site of care at the direction of the investigator. All patients received velaglucerase alfa, every other week for 1.2 to 4.8 years at 60 U/kg,
Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

Investigators concluded that adult and pediatric patients with Type 1 Gaucher disease may be successfully transitioned to velaglucerase alfa. Hemoglobin concentrations, platelet counts, and spleen and liver volumes remained stable in patients who were switched to velaglucerase alfa at a dose equal to the prior imiglucerase dose. Velaglucerase alfa infused for one hour every other week at a dose of 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. 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.

A multinational, phase 3 trial was conducted to evaluate the efficacy and safety of two doses of velaglucerase alfa in 25 treatment-naive 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 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.

**Therapy Change from Imiglucerase to Velaglucerase Alfa**

Pastores et al. conducted a multicenter open-label study which evaluated the safety of velaglucerase alfa in Type 1 Gaucher (GD1) disease patients that were treatment naive or had been receiving imiglucerase. Patients received intravenous velaglucerase alfa every other week at a dose of 60 U/kg (treatment naive) or 15-60 U/kg (previously treated). Safety data outcomes included physical examination, vital sign monitoring, clinical laboratory evaluation (hematology and clinical chemistry), assessment for anti-velaglucerase alfa antibodies, and monitoring for adverse events (AEs). A total of 211 (including six treatment-naive) patients were enrolled. Among the 205 previously treated patients, 35 (17.1%) experienced an AE considered related to study drug. Among the six treatment-naive patients, one had an AE considered related to study drug. The most frequently reported AE’s were headache, nasopharyngitis, nausea, and fatigue. Infusion-related AE’s occurred in 28 (13.3%) of the 211 patients and usually occurred during the first 3 infusions. De novo, non-neutralizing, anti-velaglucerase alfa antibodies developed during treatment in one (<1.0%) previously treated patient and none of the treatment-naive patients. Researchers concluded that the data supports the safety of initiating treatment with velaglucerase alfa 60 U/kg EOW in patients with GD1 who are naive to enzyme replacement therapy, in addition to showing the safety of transitioning patients from imiglucerase to velaglucerase alfa at the same dose as their previous imiglucerase dose. The safety profile of velaglucerase alfa observed across a broad range of patient ages is in agreement with that previously observed in controlled trials.

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.³⁵ 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.

**Pregnancy**

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-partial 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.

**Technology Assessments**

**Gaucher Disease**

A 2015 Cochrane review was published to summarize all available randomized controlled study data on the efficacy and safety of enzyme replacement therapies and substrate reduction therapy for treating Gaucher disease.¹⁰ All randomized and quasi-randomized controlled studies (including open-label studies and cross-over studies) assessing enzyme replacement therapy or substrate replacement therapy, or both, in all types of Gaucher disease were included. The authors concluded that the results reflect the limitations of analyzing evidence restricted to prospective randomized controlled trials, especially when dealing with chronic rare diseases. The analysis suggested 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. Enzyme replacement therapy 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.

**Professional Societies**

**Gaucher Disease**

The *Ontario Guidelines for Treatment of Gaucher Disease by Enzyme Replacement with Imiglucerase or Velaglucerase, or Substrate Reduction Therapy (SRT) with Miglustat* was last updated in 2011.¹² 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 2012.¹³ 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.\(^{14}\)

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.

**REFERENCES**

The foregoing Oxford policy has been adapted from an existing UnitedHealthcare Pharmacy Clinical Pharmacy Program that was researched, developed and approved by the UnitedHealth Group National Pharmacy & Therapeutics Committee [2017D0048E].

12. Ontario guidelines for treatment of Gaucher disease by enzyme replacement with imiglucerase or velaglucerase, or substrate reduction therapy with miglustat. Version 9; August 2011.

**POLICY HISTORY/REVISION INFORMATION**

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