

# Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

Policy Number: CS2021D0048M  
Effective Date: July 1, 2021

[Instructions for Use](#)

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## Commercial Policy

- [Intravenous Enzyme Replacement Therapy \(ERT\) for Gaucher Disease](#)

## Application

This Medical Benefit Drug Policy does not apply to the states listed below; refer to the state-specific policy/guideline, if noted:

| State          | Policy/Guideline  |
|----------------|---|
| Florida        | None  |
| Indiana        | <a href="#">Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease (for Indiana Only)</a>   |
| Kansas         | None  |
| Kentucky       | <a href="#">Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease (for Kentucky Only)</a>  |
| Louisiana      | <a href="#">Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease (for Louisiana Only)</a> |
| North Carolina | None  |
| Pennsylvania   | Refer to the state's Medicaid clinical policy   |

## 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:<sup>1-6,10-15</sup>

- For initial therapy, all of the following:
  - Diagnosis of Type 1 Gaucher disease; and
  - Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and

- Dosing is in accordance with United States Food and Drug Administration (FDA) approved labeling; and
- Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Diagnosis of Type 1 Gaucher disease; and
  - Documentation of positive clinical response to therapy (e.g., reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
  - Dosing is in accordance with FDA approved labeling; and
  - Continuation authorization will be for no more than 12 months

\*VPRIV is the preferred enzyme replacement therapy.

Enzyme replacement therapy with Eleyso is medically necessary for the treatment of Type 1 Gaucher disease when all of the following criteria are met:

- For initial therapy, all 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; or
    - History of failure of VPRIV due to hypersensitivity to VPRIV therapy and
  - Dosing is in accordance with FDA approved labeling; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Diagnosis of Type 1 Gaucher disease; and
  - Documentation of positive clinical response to therapy (e.g., reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
  - Dosing is in accordance with FDA approved labeling; and
  - Continuation authorization will be for no more than 12 months

Enzyme replacement therapy with Cerezyme is medically necessary for the treatment of Type 1 Gaucher disease when all of the following criteria are met:

- For initial therapy, all 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; or
    - History of failure of VPRIV due to hypersensitivity to VPRIV therapy and
  - Dosing is in accordance with FDA approved labeling; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Diagnosis of Type 1 Gaucher disease; and
  - Documentation of positive clinical response to therapy (e.g., reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
  - Dosing is in accordance with FDA approved labeling; and
  - Continuation authorization will be for no more than 12 months

Enzyme replacement therapy with VPRIV is medically necessary for the treatment of Type 3 Gaucher disease when all of the following criteria are met:

- For initial therapy, all of the following:
  - 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; and
  - Initial authorization will be for no more than 12 months

- For continuation of therapy, all of the following:
  - Diagnosis of Type 3 Gaucher disease; and
  - Documentation of positive clinical response to therapy (e.g., reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
  - Dose does not exceed 60 units/kg every 2 weeks; and
  - Continuation authorization will be for no more than 12 months

Enzyme replacement therapy with Cerezyme is proven and medically necessary for the treatment of Type 3 Gaucher disease when all of the following criteria are met:<sup>4,11-15</sup>

- For initial therapy, all of the following:
  - Diagnosis of Type 3 Gaucher disease; and
  - Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); 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; or
    - History of failure of VPRIV due to hypersensitivity to VPRIV therapy and
  - Dose does not exceed 60 units/kg every 2 weeks; and
  - Initial authorization will be for no more than 12 months
- For continuation of therapy, all of the following:
  - Diagnosis of Type 3 Gaucher disease; and
  - Documentation of positive clinical response to therapy (e.g., reduced severity or resolution of anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly); and
  - Dose does not exceed 60 units/kg every 2 weeks; and
  - Continuation authorization will be for no more than 12 months

## 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 federal, state, or contractual requirements 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 and Guidelines may apply.

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

| Diagnosis Code | Description     |
|----------------|-----------------|
| E75.22         | Gaucher Disease |

## 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.<sup>4</sup>

## Proven

### *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.<sup>1-3</sup>

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.<sup>18</sup> 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, (some requiring dose reduction) during the extension study. Nineteen of 57 patients completed the extension study. The other patients (34) were discontinued from the trial due to the termination of the trial by the sponsor. Almost all patients in the extension study experienced an adverse event (AE). Sixteen of 57 patients experienced AEs that were deemed possibly or probably related to treatment. Of the 56 drug-related AEs, only events that were experienced by more than one patient were hypertension (infusion related), and headache. Six patients experienced infusion related AEs. Nineteen serious AEs were reported including a spontaneous 1<sup>st</sup> trimester abortion (patient had history of miscarriages and anti-phospholipid syndrome) and one patient death after a convulsion. No serious AEs were considered to be related to treatment. One patient tested positive for IgG anti-velaglucerase alfa antibodies. The mean increase in hemoglobin concentration was 2.75 g/dL (26%) in the overall velaglucerase alfa group, and there was a 120% mean increase in the platelet count compared with base-line; a 64% mean decrease in spleen volume and a 27% mean decrease in liver volume were also observed. The results of the analysis of efficacy parameters also indicated that there were significant clinical improvements in the first 24 months, which were either maintained or continued at a declining rate over longer term treatment. The authors concluded that Velaglucerase alfa had a good long-term safety and tolerability profile, and patients continued to respond clinically, which is consistent with the results of the extension study to the phase I/II trial of velaglucerase alfa.

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.<sup>8</sup> 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<sup>9</sup>/L (p=0.002); 45 units/kg: +66.4%; +40.9 × 10<sup>9</sup>/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.<sup>16</sup> 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 naïve or had been receiving imiglucerase. Patients received intravenous velaglucerase alfa every other week at a dose of 60 U/kg (treatment naïve) or 15-60 U/kg (previously treated).<sup>7</sup> Safety data outcomes included physical examination, vital sign monitoring, clinical laboratory evaluation (hematology and clinical

chemistry), assessment for anti-velaglycerase alfa antibodies, and monitoring for adverse events (AEs). A total of 211 (including six treatment-naïve) patients were enrolled. Among the 205 previously treated patients, 35 (17.1%) experienced an AE considered related to study drug. Among the six treatment-naïve 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-velaglycerase alfa antibodies developed during treatment in one (<1.0%) previously treated patient and none of the treatment-naïve patients. Researchers concluded that the data supports the safety of initiating treatment with velaglycerase alfa 60 U/kg EOW in patients with GD1 who are naïve to enzyme replacement therapy, in addition to showing the safety of transitioning patients from imiglycerase to velaglycerase alfa at the same dose as their previous imiglycerase dose. The safety profile of velaglycerase 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 velaglycerase alfa in patients with Type 1 Gaucher disease who were previously stable on imiglycerase therapy.<sup>9</sup> Eligible patients (n=40) ≥2 years old were switched to velaglycerase alfa at a dose equal to their prior imiglycerase dose. Velaglycerase 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 velaglycerase alfa.

The effects of a switch to velaglycerase 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 imiglycerase shortage, were described in a recent paper.<sup>15</sup> Thirty-two patients from two large European Gaucher centers switched to treatment with velaglycerase 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 velaglycerase and after up to one year of treatment with velaglycerase. 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 imiglycerase were quickly restored on treatment with velaglycerase 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 velaglycerase treatment, which was reversible in 3. Most patients received infusions at home and no important side effects were observed. Velaglycerase alfa appears to be a safe and effective alternative for imiglycerase.

## ***Pregnancy***

In order to ascertain pregnancy outcome in women receiving velaglycerase alfa, the medical records of women exposed to this therapy since 2004 were collected from six multinational clinical sites for evaluation.<sup>17</sup> 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 velaglycerase 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.<sup>10</sup> All randomized and quasi-randomized controlled studies (including open-label studies and cross-over studies) assessing enzyme replacement therapy or substrate reduction therapy, or both, in all types of Gaucher disease were included. The authors concluded that the results reflect the limitations of analysing 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 were last updated in 2011.<sup>12</sup> 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.<sup>13</sup> 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.<sup>14</sup> 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)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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.<sup>1</sup>

Elelyso is a hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for the treatment of patients 4 years and older with a confirmed diagnosis of Type 1 Gaucher disease.<sup>2</sup>

VPRIV is a hydrolytic lysosomal glucocerebrosidase-specific enzyme indicated for long-term enzyme replacement therapy (ERT) for patients with Type 1 Gaucher disease.<sup>3</sup>

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## Policy History/Revision Information

| Date       | Summary of Changes   |
|------------|--|
| 08/01/2021 | <p><b>Application</b></p> <ul style="list-style-type: none"> <li>Added language to indicate this policy does not apply to the state of North Carolina</li> </ul>   |
| 07/01/2021 | <p><b>Application</b></p> <p><i>Pennsylvania</i></p> <ul style="list-style-type: none"> <li>Added instruction to refer to the state's Medicaid clinical policy</li> </ul> <p><b>Supporting Information</b></p> <ul style="list-style-type: none"> <li>Archived previous policy version CS2021D0048L</li> </ul> |

## Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the federal, state or contractual requirements for benefit plan coverage must be referenced as the terms of the federal, state or contractual requirements for benefit plan coverage may differ from the standard benefit plan. In the event of a conflict, the federal, state or contractual requirements for benefit plan coverage govern. Before using this policy, please check the federal, state or contractual requirements for benefit plan coverage. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit 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 InterQual® criteria, to assist us in administering health benefits. The UnitedHealthcare Medical Benefit Drug Policies 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.