Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

Policy Number: 2021D0048K
Effective Date: April 1, 2021

Related Commercial Policy
• Provider Administered Drugs – Site of Care

Community Plan Policy
• Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

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 for the treatment of Type 1 Gaucher disease when all of the following criteria are met:16,10-15

- 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 Elelyso 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 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

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Effective 04/01/2021

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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

- 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 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 and Guidelines may apply.

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<thead>
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<td>Injection, imiglucerase, 10 units</td>
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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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<table>
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<tr>
<th>Diagnosis Code</th>
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<tbody>
<tr>
<td>E75.22</td>
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### 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

### Benefit Considerations

Some Certificates of Coverage allow for 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. See the Policy and Procedure addressing the treatment of serious rare diseases.
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.\textsuperscript{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.\textsuperscript{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, (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 1st 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 baseline; 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-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.\textsuperscript{8} 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%; +23.8% (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 x 10^9/L (p=0.002); 45 units/kg: +66.4%; +40.9 x 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=0.002); 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.\textsuperscript{16} 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).\textsuperscript{7} Safety data outcomes included physical examination, vital sign monitoring, clinical laboratory evaluation (hematology and clinical...
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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. 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. 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)**

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.1

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

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

**Centers for Medicare and Medicaid Services (CMS)**

Medicare does not have National Coverage Determinations (NCDs) for the following intravenous enzyme replacement therapies used in treatment of Gaucher Disease: Cerezyme® (imiglucerase), Elelyso™ (taliglucerase) and VPRIV® (velaglucerase). Local Coverage Determinations (LCDs) do not exist at this time.

In general, 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, Chapter 15, §50 - Drugs and Biologicals. (Accessed September 9, 2020)
References

### Policy History/Revision Information

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<th>Date</th>
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<td>• Added criterion requiring one of the following:</td>
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<td>▪ History of failure of VPRIV due to hypersensitivity to VPRIV therapy</td>
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<td>• Added language to indicate enzyme replacement therapy with VPRIV is medically necessary for the treatment of Type 3 Gaucher disease when all of the following criteria are met:</td>
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<td><strong>Continuation of Therapy</strong></td>
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### Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. 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.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. 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.