Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

Policy Number: 2016D0048D
Effective Date: October 1, 2016

Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSTRUCTIONS FOR USE</td>
<td>1</td>
</tr>
<tr>
<td>BENEFIT CONSIDERATIONS</td>
<td>1</td>
</tr>
<tr>
<td>COVERAGE RATIONALE</td>
<td>2</td>
</tr>
<tr>
<td>U.S. FOOD AND DRUG ADMINISTRATION</td>
<td>2</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>3</td>
</tr>
<tr>
<td>APPLICABLE CODES</td>
<td>3</td>
</tr>
<tr>
<td>CLINICAL EVIDENCE</td>
<td>3</td>
</tr>
<tr>
<td>CENTERS FOR MEDICARE AND MEDICAID SERVICES</td>
<td>5</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>6</td>
</tr>
<tr>
<td>POLICY HISTORY/REVISION INFORMATION</td>
<td>6</td>
</tr>
</tbody>
</table>

INSTRUCTIONS FOR USE

This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. 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 Drug Policy is based. In the event of a conflict, the member specific benefit plan document supersedes this Drug 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 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.

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for 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.

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.
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

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

*VPRIV is the preferred enzyme replacement therapy.

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

1. Diagnosis of Type 3 Gaucher disease
   AND
2. Symptomatic disease (e.g., moderate to severe anemia, thrombocytopenia, bone disease, hepatomegaly, splenomegaly)
   AND
3. 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:

1. Both of the following:
   A. Diagnosis of Type 1 Gaucher disease
   AND
   B. 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
      • Patient is attempting to become pregnant
   OR
2. 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

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 glucocerebroside-specific enzyme indicated for the treatment of long- patients 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
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 and Coverage Determination Guidelines may apply.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J1786</td>
<td>Injection, imiglucerase, 10 units</td>
</tr>
<tr>
<td>J3060</td>
<td>Injection, taliglucerase alfa, 10 units</td>
</tr>
<tr>
<td>J3385</td>
<td>Injection, velaglucerase alfa, 100 units</td>
</tr>
</tbody>
</table>

ICD-10 Codes

ICD-10-CM (diagnoses) and ICD-10-PCS (inpatient procedures) must be used to report services provided on or after October 1, 2015.

<table>
<thead>
<tr>
<th>ICD-10 Diagnosis Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E75.22</td>
<td>Gaucher Disease</td>
</tr>
</tbody>
</table>

CLINICAL EVIDENCE

Proven
Type 1 Gaucher Disease

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, (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 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.5 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. 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-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-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, nonneutralizing, anti-velaglucerase 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 velaglucerase 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 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. 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 greater in children with GD3 than in those with GD1.

**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
Intravenous Enzyme Replacement Therapy (ERT) for Gaucher Disease

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. (Accessed June 8, 2016)
REFERENCES


POLICY HISTORY/REVISION INFORMATION

<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<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>
</tr>
<tr>
<td>2/1/2014</td>
<td>New policy 2014D0048A. Approved by the National Pharmacy and Therapeutics Committee 7/9/2013.</td>
</tr>
</tbody>
</table>