Pharmacotherapy for Gaucher Disease

Medicare Advantage Medical Policy # 081
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Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider imiglucerase (Cerezyme®)‡, velaglucerase (Vpriv®)‡, and taliglucerase (Elelyso®)‡ for the treatment of Gaucher disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for imiglucerase (Cerezyme), velaglucerase (Vpriv), and taliglucerase (Elelyso) will be considered when the following criteria are met for the requested drug:

- For imiglucerase (Cerezyme) requests:
  - Patient has a diagnosis of Gaucher disease type 1; AND
  - Patient has one or more of the following conditions caused by the Gaucher disease:
    - Anemia
    - Thrombocytopenia
    - Bone disease
    - Hepatomegaly
    - Splenomegaly; OR
  - Patient has a diagnosis of Gaucher disease type 3 and has severe visceral symptoms or is at risk of neuronopathic disease
- For velaglucerase (Vpriv) requests:
  - Patient has a diagnosis of Gaucher disease type 1
- For taliglucerase (Elelyso) requests
  - Patient has a diagnosis of Gaucher disease type 1

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of imiglucerase (Cerezyme), velaglucerase (Vpriv), and taliglucerase (Elelyso) when patient selection criteria are not met (except those considered not medically necessary**) to be **investigational.***

Background/Overview

Gaucher disease is a rare autosomal recessive lysosomal storage disorder caused by a deficiency of glucocerebrosidase, the enzyme responsible for the breakdown of glucosylceramide into glucose and ceramide. This deficiency results in excessive accumulation of glucosylceramide in the visceral organs such as the liver, spleen, and bone marrow. Glucosylceramide also remains stored within lysosomes causing enlarged lipid-laden macrophages called "Gaucher cells." Gaucher disease has a wide range of clinical presentations and is classified into three phenotypes (types 1 through 3). Gaucher disease type 1 is a non-neuropathic variant with asymptomatic or symptomatic clinical manifestations of splenomegaly, hepatomegaly, anemia, thrombocytopenia, skeletal complications, and occasional lung involvement. Type 2 is an acute neuropathic form characterized by an early onset (3 to 6 months of age) of rapidly progressive neurological disease with visceral manifestations; death generally occurs by the time patients reach 1 to 2 years of age. Type 3 is characterized by neurological symptoms and visceral symptoms with a later onset and includes abnormal eye movements, ataxia, seizures, and dementia.

Treatment of Gaucher disease is tailored to the individual patient because of the variability in the manifestations, severity, and progression of disease. There are two treatment options available: ERT in which the deficient enzyme is replaced and substrate reduction therapy which inhibits the glucosylceramide synthase enzyme to reduce the production of glucosylceramide. The available enzyme replacement therapies are all administered via intravenous infusion and include imiglucerase (Cerezyme), velaglucerase (Vpriv), and taliglucerase (Elelyso). These products all contain the same enzyme, but it is produced using different methods (i.e., recombinant deoxyribonucleic acid [DNA] technology in Chinese hamster ovary cell system, gene activation technology in a human cell line, or plant cell-based protein expression system) The dosing of these agents varies based on product used and patient characteristics, but the starting dose with the most data is 60 units per kilogram every 2 weeks. Available substrate reduction therapies are orally administered and include eliglustat (Cerdelga) and miglustat (Zavesca, Yargesa). The dosing of eliglustat depends on the patient's CYP2D6 metabolizer status and ranges from 84 mg twice daily to 84 mg once daily. Miglustat should be dosed at 100 mg by mouth three times per day.

Enzyme replacement or substrate reduction therapy with eliglustat are the preferred treatments for patients with clinically significant manifestations of non-neuronopathic Gaucher disease. Substrate reduction therapy with miglustat is reserved for patients who are medically unable to receive ERT due to hypersensitivity or inability to receive intravenous infusion. According to the European Working Group on Gaucher Disease, imiglucerase (Cerezyme) may be considered for patients with Gaucher disease type 3 who have severe visceral symptoms or who are at risk for neuronopathic disease due to genotype or family history who are identified before the onset of neurologic signs or symptoms. ERT does not alter the fatal neurologic outcome of Gaucher disease type 2 and is therefore generally not used. An additional substrate reduction therapy, miglustat (Zavesca, Yargesa), is indicated for patients with Gaucher disease type 1 who are medically unable to receive ERT.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Cerezyme (imiglucerase) is approved as long-term ERT for pediatric and adult patients with a confirmed diagnosis of Gaucher disease type 1 that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.
Vpriv (velaglucerase) is approved as long term ERT for patients with Gaucher disease type 1.

Elelyso (taliglucerase) is approved for treatment of patients with a confirmed diagnosis of Gaucher disease type 1.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Cerezyme

The efficacy of Cerezyme was established in two clinical studies. The first study was a 9 month, double-blind, randomized, parallel trial conducted in 30 patients ≥ 12 years of age with Type 1 Gaucher disease. Patients were randomly assigned to receive Ceredase 60 U/kg (n = 15) or Cerezyme 60 U/kg (n = 15). No significant differences were detected in the rate or extent of improvement in hemoglobin (Hgb) levels, platelet counts, hepatic or splenic volumes between either treatment groups. The development of antibodies to glucocerebrosidase occurred in 40% of patients receiving Ceredase compared to 20% of patients receiving Cerezyme; however, the study authors noted that the antibody development did not affect therapeutic efficacy.

The second study was an unblinded Cerezyme dosing schedule comparison study involving 10 patients with Type 1 Gaucher disease. The study compared the safety and effectiveness of administration at two dosing schedules: 15 U/kg once every 2 weeks (Schedule A) or 2.5 U/kg three times a week (Schedule B). At 12 months the mean Hgb increase was 14.2% and 13%, and the mean increase in platelet count was 18% and 33.4% for Schedules A and B, respectively. The mean spleen volume reduction was 38% and 35% and the mean reduction in liver volume was 14% and 15%, in Schedules A and B, respectively. All reductions in spleen volumes and most changes in liver volumes were statistically significant.

Vpriv

The efficacy of Vpriv was evaluated in a 12 month, randomized, double-blind, parallel-dose, international study involving 25 patients ≥ 4 years of age. Patients were required to be ERT-naïve or to not have received treatment for a minimum of 30 months prior to enrollment. Patients were randomized to receive Vpriv 45 U/kg (n = 13) or 60 U/kg (n = 12) every other week. The primary outcome of the study was the change from baseline to 12 months in Hgb concentration for the 60 U/kg treatment group. The mean Hgb concentration increased by 2.4 g/dL from baseline ($P \leq 0.0001$)

in both treatment groups. In both the 60 U/kg and 45 U/kg treatment groups, mean platelet counts increased from baseline by 51 x 10^9/L (P = 0.0016) and 41 x 10^9/L (P = 0.0111), respectively, and the mean spleen volume decreased from baseline by 50% (P = 0.0032) and 40% (P = 0.0085), respectively. Mean liver volume decreased from baseline but was not statistically significant.

Elelyso
The clinical efficacy and safety of Elelyso were assessed in three studies. The first study was a 9 month, double-blind comparison dose study that randomized 31 treatment-naïve patients with Type 1 Gaucher disease to one of two doses of Elelyso (30 U/kg [n = 15] or 60 U/kg [n = 16]). Statistically significant reduction in spleen volume, the primary endpoint, was achieved by all patients in both treatment groups at Month 9: 26.9% with Elelyso 30 U/kg (95% CI: -31.9, -21.8) and by 38.0% with Elelyso 60 U/kg (95% CI: -43.4, -32.8) [P < 0.0001 for both groups]. Statistical significance in liver volume reduction and an increase in Hgb concentration were also noted. An improvement in platelet count was reported for both dose groups; however, only improvement in the higher dose group achieved statistical significance. In the extension phase of the trial (n = 23), the mean spleen volume, liver volume, and platelet count improved continuously through 36 months of treatment for patients receiving Elelyso 30 U/kg and 60 U/kg. For the 30 U/kg and 60 U/kg groups, respectively, the spleen volume decreased by 50.1% and 64.6%; liver volume decreased by 25.6% and 24.4%; hemoglobin concentrations increased by 16.0% and 35.8%; and the platelet count increased by 45.7% and 114.0%, respectively. In the continuation of the extension study for 60 months (n = 17), the mean spleen and liver volumes showed continuous decreases.38 Overall, Elelyso was well tolerated over the 5 years, with nasopharygitis and arthralgia as the most common adverse events (AEs).

The second study was an unpublished extension study of the double-blind study with 26 of the 31 patients that continued treatment with Elelyso in a blinded manner for a total duration of treatment of 24 months. For the respective 30 U/Kg and 60 U/kg groups, mean (± standard deviation [SD]) spleen volume (reported as % body weight) decreased -1.4 ± 0.65% and by -2.0 ± 2.0%, Hgb increased by 1.3 ± 1.7 g/dL and 2.4 ± 2.3 g/dL, liver volume decreased by -1.1 ± 0.5% and -1.0 ±0.7%, and platelet count increased by 28,433 ± 31,996/mm3 and 72,029 ± 68,157/mm3, respectively.

The third study was a 9 month, multicenter, open label switchover study in 25 patients. This study assessed the safety and efficacy of switching to Elelyso in adult and pediatric patients with Gaucher disease, who had been previously treated with Cerezyme for at least the previous 2 years. A total of 26 adult patients and 5 pediatric patients participated in the trial. Enrolled patients had been receiving treatment with Cerezyme at doses ranging from 9 U/kg to 60 U/kg for a minimum of 2 years. On average, all efficacy parameters (Hgb, platelet count, spleen and liver volume) remained stable when switching from Cerezyme to Elelyso for the three treatment groups based on dose (≤ 15 units/kg dose, > 15 to ≤ 30 units/kg dose, and > 30 units/kg dose). At baseline, spleen volume (as % body weight) was 1.1%, liver volume was 2.4%, mean Hgb was 13.6 ± 1.57 g/dL and the mean platelet count was 160,447 ± 79,086/mm^3. At the 9 month endpoint, spleen volume was 1.0%, liver volume was 2.3%, mean Hgb was 13.4 ± 1.6 g/dL and the mean platelet count was 165,654 ± 94,038/mm^3. One adult patient had an increase in spleen volume from baseline to Month 9; however, no other

clinically relevant deterioration in other efficacy endpoints were noted. Similarly, one adult and one pediatric patient had an increase in liver volume, which were not clinically meaningful. One patient did have deterioration due to decreased platelet count and this was attributed to treatment interruption due to Cerezyme shortage. The platelet levels increased after an increase in Elelyso dose from the previously administered lower Cerezyme dose. There were a total of 10 patients who continued on to the extension phase of the study and completed 36 months of therapy with Elelyso. The mean percent changes from the time of switch to Elelyso to 36 months were as follows: mean hemoglobin concentration was unchanged through 36 months (-1.0%); the mean platelet count was +9.3%; the spleen volume decreased by -19.8%; and the liver volume was mostly unchanged at 0.9%. All treatment-related AEs were mild or moderate.

References

1. Cerdelga [package insert].Waterford, Ireland. Genzyme. August 2014.
2. Zavesca [package insert]. South San Francisco, CA. Actelion Pharmaceuticals US Inc. February 2014.
3. Cerezyme [package insert]. Waterford, Ireland. Genzyme. April 2018
4. Vpriv [package insert]. Lexington, MA. Shire. November 2017
5. Elelyso [package insert]. New York, NY. Pfizer. January 2017
6. Gaucher disease substrate reduction therapy class summary. Express Scripts. Updated November 2016.
7. Gaucher disease enzyme replacement therapy class summary. Express Scripts. Updated November 2016.
8. Gaucher disease: Treatment. UpToDate. April 2018.
9. Yargesa [package insert]. Parsippany, New Jersey. Edenbridge Pharmaceuticals, LLC. October 2023.

Policy History

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01/21/2025 UM Committee review. New policy
Next Scheduled Review Date: 01/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	No codes
HCPCS	J1786, J3060, J3385
ICD-10 Diagnosis	E75.22

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;

B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.