

**Regence BlueCross BlueShield of Oregon • Regence BlueShield
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Medication Policy Manual

Policy No: dru002

Topic: Cerezyme[®], imiglucerase

Date of Origin: January 1996

Revised/Effective Date: January 9, 2009

Next Review Date: January 2010

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Imiglucerase (Cerezyme) is a man-made form of a naturally occurring protein called glucocerebrosidase. A deficiency of glucocerebrosidase is called Gaucher disease. This deficiency may over time lead to disease of the skeleton, bone marrow, spleen, liver and lungs.

Policy/Criteria

- I.** Most contracts require prior authorization approval of imiglucerase prior to coverage. Imiglucerase may be considered medically necessary in pediatric and adult patients with Gaucher disease when the criteria under A and B below are met.

- A.** Diagnosis of Type 1 Gaucher disease confirmed by one of the following:

- 1.** Biochemical assay of glucocerebrosidase activity in WBCs or skin fibroblasts is less than or equal to 30% of normal activity. (Note: laboratory normals may vary).

OR

- 2.** Genotyping revealing two pathogenic mutations of the glucocerebrosidase gene.

AND

- B.** Symptomatic manifestations of the disease are present, such as anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly.

II. Administration, Quantity Limitations, and Authorization Period

- A.** Regence does not consider imiglucerase to be a self-administered medication.

- B.** When prior authorization is approved, imiglucerase may be authorized as follows:

1. Initial Authorization

- a.** A dose up to 30 u/kg body weight every 2 weeks (or other equivalent dose) may be authorized when criteria are met.
- b.** Doses up to 60 u/kg every 2 weeks may be approved when the patient meets high risk dosing guidelines in Appendix 1 for adults or Appendix 2 for children.

2. Continued Authorization

- a. Documentation by chart notes of maintenance or improvement in disease must be provided. (This may include, but is not limited to, hematologic indices, MRI of spine/femurs, quality of life and/or plain films of skeleton).
 - b. Doses up to 60 u/kg every 2 weeks may be approved when the physician indicates by chart notes that the patient has not responded to lower doses over a period of 6 months.
 - C. Initial and continued authorization (after the initial 6 month period) shall be renewed at least every 6 months to confirm that current medical necessity criteria are met and that the medication is effective.
- III. Imiglucerase is considered investigational when used for all other conditions and when it is used in combination with miglustat (Zavesca[®]).

Position Statement

- Enzyme replacement therapy (ERT) with imiglucerase has been shown to be effective in halting or reversing the hematological, visceral and skeletal abnormalities associated with Type 1 Gaucher disease.^[3-5, 7-8, 11-13, 32, 33]
- Imiglucerase, manufactured by recombinant DNA production, is considered the accepted product for ERT in Type 1 Gaucher disease, in order to reduce risk of developing IgG antibodies and hypersensitivity reactions that may occur with alglucerase (derived from human placental tissue).
- ERT for Gaucher disease is considered lifelong.
 - * If left untreated, Gaucher disease can be a fatal disorder.
 - * Prolonged periods off therapy are not recommended.
 - * Interruption in therapy is associated with relapse and hematological and organ volume parameters and is presumed to also result in relapse of skeletal parameters.^[2]

Clinical Efficacy

- Alglucerase and imiglucerase are considered therapeutically equivalent in treating Type 1 Gaucher disease.^[7]
 - * The Pivotal Study confirmed the safety and efficacy of imiglucerase and alglucerase in all clinical parameters evaluated and was the basis for FDA approval of imiglucerase for the treatment of Type 1 Gaucher disease.^[7]
 - * The study further verified that patients can be safely transferred from alglucerase to imiglucerase and maintain the expected treatment effect.^[7]
- Adult patients should have a minimal level of disease severity in order to be considered for ERT, such as evidence of osteopenia or hematological manifestations.

ERT has not been shown to improve health outcomes in adult patients with Type 1 Gaucher disease without clinical signs or symptoms of the disease.

- ERT has not yet proven to provide benefit in reversing or decreasing neurologic symptoms associated with Type 2 (acute neuronopathic) or Type 3 (subacute or chronic neuronopathic) Gaucher disease.
- The U.S. Regional Coordinators of the International Collaborative Gaucher Group (ICGG), a panel of physicians who have extensive experience in the care of Gaucher patients, have made recommendations for therapy and dosing based on risk assessment for irreversible morbid complications^[1] (see Appendix 1 and 2).
 - * Initial doses of 30-60 U/kg of body weight every 2 weeks are considered safe and effective in demonstrating improvements in hepatosplenomegaly, anemia, thrombocytopenia and quality of life.^[8, 11-13, 33]
 - * Doses as low as 15 U/kg administered every 2 weeks or 2.3 U/kg three times weekly have shown improvement in some hematological and visceral parameters.^[10, 14]
 - * One small randomized trial suggested that patients could receive the usual cumulative dose of imiglucerase administered every 4 weeks. However two patients in the low-frequency group lost control of their disease. Further research is needed before this dosing schedule can be recommended.^[30]
- The ICGG U.S. Regional Coordinators recommend that all children with Gaucher disease be treated with ERT due to high risk for irreversible, morbid complications.^[1]

- * Diagnosis of Gaucher disease in the 1st and 2nd decades of life is indicative of a rapidly progressive course.
- * Early intervention is necessary for these children, during the time when the skeleton is immature, to enable them to attain their peak skeletal mass by early adulthood.
- Medical literature suggests that different organs respond differently to ERT.^[11, 17, 32]
 - * While hematologic and visceral parameters usually improve within the first year, the response of the skeletal system is slower to occur and more difficult to measure.
 - * Evidence of skeletal improvement may require up to 2-3 years of therapy and may require doses of ERT that are greater than that which is necessary to observe improvement in hematological or organ parameters.
 - * Failure of a patient to respond to therapy in 6 months typically indicates that a higher dose may be necessary.
- ERT with imiglucerase improved quality of life in patients with skeletal manifestations of Gaucher disease as measured by The Short Form-36 Health Survey.^[29]
- There is no useful evidence of additional clinical benefit using concomitant combination therapy of imiglucerase and miglustat. However, miglustat may be an effective maintenance therapy in patients with Type 1 Gaucher disease after initial stabilization with imiglucerase.^[19-26, 31]

Safety

- Approximately 15% of patients treated and tested to date have developed IgG antibody to Cerezyme (imiglucerase for injection) during the first year of therapy.^[33]
- Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity.^[33]
- Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution.^[33]
- Common adverse reactions include:^[33]
 - * Infusion related reactions – 13.8% (discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture).

- * Symptoms suggestive of hypersensitivity – 6.6% (pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension).
- * Additional adverse reactions – 6.5% (nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia).

Appendix 1: Adults with Type 1 Gaucher Disease: Risk Assessment and Dosage Recommendations ^[1]

Initial Dose	Highest Risk: 60 U/kg every 2 weeks	Lowest Risk: 30 U/kg or less every 2 weeks
Risk Criteria	<p>At least one or more of the following:</p> <ul style="list-style-type: none"> - Symptomatic skeletal disease: <ul style="list-style-type: none"> * Moderate to severe osteopenia defined as reduced Bone Mineral Density (BMD) of greater than 1 S.D. below the mean (which predicts a relative fracture risk of 2.5, using the World Health Organization criteria). * Chronic bone pain. * Bone crises. * Avascular necrosis. * Pathological fractures. * Joint replacement(s). - Cardiopulmonary disease, including pulmonary hypertension 	<ul style="list-style-type: none"> - Normal liver, cardiac, lung and renal function - Skeletal disease limited to mild osteopenia (low bone density) and Erlenmeyer flask deformity - Hemoglobin as follows: <ul style="list-style-type: none"> Males: less than or equal to 12.5 g/dL and greater than 11.5 g/dL. Females: Less than or equal to 11.5 g/dL and greater than 10.5 g/dL. (or overall not more than 2.0 g/dL below lower limit of normal for age and sex). - Platelet count less than or equal to 120,000 per mm³ and greater than 60,000 mm³ on three determinations. - Liver volume less than 2.5 x norm

	<ul style="list-style-type: none"> - Hematologic Symptoms * Platelet count less than or equal to 60,000 mm³ or documented abnormal bleeding episodes. * Symptomatic anemia or hemoglobin less than or equal to 8.0 g/dL. * Transfusion dependency. - Significant Liver Disease * Severe hepatomegaly defined as liver volume greater than or equal to 2.5 x norm. * Infarcts. * Portal hypertension. * Hepatitis. - Significant splenic disease * Severe splenomegaly defined as spleen volume greater than 15 x norm. * Infarcts. * Significant renal disease such as evidence of bilaterally reduced (less than 8.5cm) kidney size by imaging studies. 	<ul style="list-style-type: none"> - Spleen volume less than 15 x norm
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Appendix 2: Children (less than 18 years) with Type 1 Gaucher Disease: Risk Assessment and Dosage Recommendations ^[1]

Initial Dose	Highest Risk: 60 U/kg every 2 weeks	Lowest Risk: < 60 U/kg every 2 weeks
Risk Criteria	<p>Symptomatic disease, including manifestations of abdominal or bone pain, fatigue, exertional limitations, weakness and cachexia, with the addition of one or more of the following:</p> <ul style="list-style-type: none"> - Growth failure - Evidence of skeletal involvement, including Erlenmeyer flask deformity - Platelet count less than 60,000 mm³ and/or documented abnormal bleeding episode(s) - Hemoglobin less than 2.0 g/dL below lower limit of normal for age and sex 	<p>All children with relevant physical signs or manifestations of Type 1 Gaucher disease should be treated with ERT. These may include, but not limited to evidence of:</p> <ul style="list-style-type: none"> - Symptomatic disease, including manifestations of marrow infiltration, organomegaly, abdominal or bone pain, fatigue, exertional limitations, weakness and delayed growth. <p>Signs and symptoms must be due to no other cause of origin, except Gaucher Disease.</p>

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Cross References		
Zavesca [®] , miglustat dru109		

Codes	Number	Description
HCPCS	J1785	Injection, imiglucerase, per unit