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Horizons

A Newsletter for the Gaucher Community *From the Genzyme Corporation*

Sarah and David

Happy couple

Getting married in the Spring

Planning for children…someday

Preparing for their future together

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Patient Story

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Let us know how we can make *Horizons* even better.

Please send us your feedback by filling out the enclosed business reply card or emailing our publisher (petercis1@yahoo.com).

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Foreword

Kathleen Coolidge

Welcome to this issue of *Horizons*. My name is Kathleen Coolidge and I am the Associate Director of Patient Advocacy at Genzyme.

I hope you find this resource issue of *Horizons* magazine informative and useful.

All of us at Genzyme know the critical importance of keeping you updated on the status of Cerezyme® (imiglucerase for injection) supply, not just in the near term, but also in the long term, for your treatment and care.

Genzyme continues our commitment to updating you on our progress in overcoming the current Cerezyme® supply situation. In addition to the Gaucher Town Halls we've held, and the support and education from the Genzyme field and case management staff, we'd also like to encourage you to visit our supply website for updates at http://supplyupdate.genzyme.com.

We also want to hear from you. If you have questions or feedback of any kind please contact me at Kathleen.Coolidge@genzyme.com.

Thank you and we look forward to hearing from you.

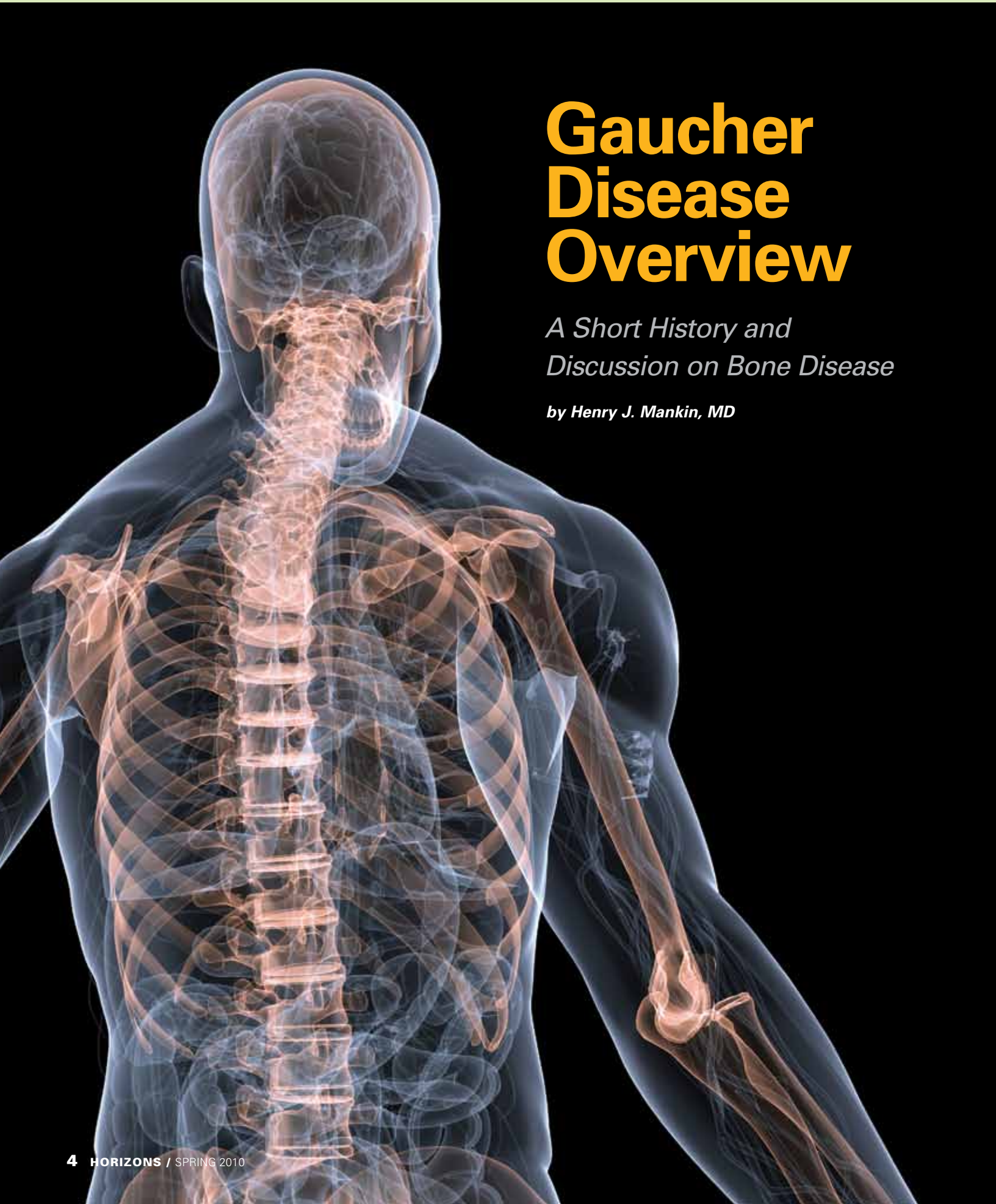
Kathleen Coolidge

Cerezyme® (imiglucerase for injection) 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, splenomegaly.

Important Safety Information

Side effects related to Cerezyme (imiglucerase for injection) administration have been reported in less than 15% of patients. Each of the following events occurred in less than 2% of the total patient population. Reported side effects include nausea, vomiting, abdominal pain, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and rapid heart rate. Because Cerezyme therapy is administered by intravenous infusion, reactions at the site of injection may occur: discomfort, itching, burning, swelling or uninfected abscess. Symptoms suggestive of allergic reaction include anaphylactoid reaction (a serious allergic reaction), itching, flushing, hives, an accumulation of fluid under the skin, chest discomfort, shortness of breath, coughing, cyanosis (a bluish discoloration of the skin due to diminished oxygen), and low blood pressure. Approximately 15% of patients have developed immune responses (antibodies); periodic monitoring by your physician is suggested. Patients should notify their physician immediately if they experience any side effects with treatment. For more information, consult your physician. Please see accompanying full Prescribing Information.

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit FDA.gov/medwatch, or call 1-800-FDA-1088.



Gaucher Disease Overview

A Short History and Discussion on Bone Disease

by Henry J. Mankin, MD

Genetic disorders are a major problem in science and in orthopedic practice. Not very long ago, there was limited information available on the genetic error that caused many diseases and therefore no therapies existed to treat them. With advancing science as well as biological studies of such rare disorders, it has now become possible to not only define the characteristics of the clinical entities, but to also describe the causes of the findings, discover the gene errors, and introduce treatments that could treat patients with these disorders. Such a systematic and spectacular series of discoveries has been made for type 1 Gaucher disease over 100 years after it was first described, which has not only helped patients with that disease, but has now opened the gates for similar approaches to many other genetic diseases.

History of Gaucher Disease

The syndrome called Gaucher disease was first described in 1882 by Phillipe Charles Ernest Gaucher[1], a French dermatologist, after conducting a postmortem evaluation of a 32-year-old woman with an enlarged spleen. At the time, Dr. Gaucher thought it was a form of cancer; however, it wasn't until many years later that the true nature of Gaucher disease was understood. In 1965, Roscoe Brady[2] discovered Gaucher disease is a lysosomal storage disorder involving a deficiency of the enzyme (glucocerebrosidase) responsible for the breakdown of a fatty molecule in the body.

The Biologic Cause and Three Types of Gaucher Disease

Affecting about 10,000 people worldwide, Gaucher disease is an inherited genetic condition that causes fatty deposits to build up in the cells of certain organs and bones. The signs and symptoms of the disease are a result of the progressive build-up of these cells (called Gaucher cells) in the body. Whereas Gaucher cells typically accumulate in the spleen, liver, and bone marrow, they may also collect in other tissues, including the lymphatic system, lungs, skin, eyes, kidney, heart, and in rare instances, the nervous system. Gaucher disease has a wide variety of signs and symptoms, including enlarged liver or spleen, easy bleeding or bruising, excessive fatigue, anemia, bone and joint pain, and weak bones that fracture too easily.

Dr. Mankin is senior research consultant for the Orthopedic Oncology Service at Massachusetts General Hospital and Edith M. Ashley Professor Emeritus of Orthopedics at Harvard Medical School, both in Boston, and is a member of the National Gaucher Foundation Medical Board headquartered in Tucker, Georgia.

Type 1 Gaucher disease is most common in the United States, Europe, and Israel. It is classified as mild to moderately severe, appears in childhood or early adulthood, and is slowly progressive and non-neuronopathic (i.e., does not involve the brain or central nervous system). It is most common in people of Ashkenazi Jewish heritage and is characterized by enlarged spleen, hematologic complications, and skeletal abnormalities.[3]

Type 2 Gaucher disease is a very rare, rapidly progressive form of the disorder that affects the brain as well as the organs affected by type 1 Gaucher disease. Skeletal malformation is uncommon in infants with type 2 disease, who typically appear normal during the first few months of life, but shortly thereafter develop the neurological signs of the disease.

Type 3 Gaucher disease is also very rare. It is characterized by slowly progressive brain involvement, in addition to severe disease of the other organs of the body. Type 3 is not limited to any particular ethnic group, but a concentrated number of cases has been reported in Sweden, and a higher number of cases than in the general population have been reported in Japan. The signs and symptoms of type 3 Gaucher disease appear in early childhood and—other than the central nervous system involvement—many are the same as in type 1.

The Type 1 Gaucher Disease Clinical Syndrome

As a result of Gaucher cells building up in various organs and in the bone marrow, type 1 Gaucher disease affects the body in many ways, especially the following:

- **Enlarged liver and/or spleen.** Patients with type 1 Gaucher disease may have distended abdomens, caused by the liver and/or spleen swelling to unusual sizes because of built-up Gaucher cells. Such swelling can suppress a patient's appetite because of the pressure placed on the stomach, creating a full feeling after eating very little.

- **Anemia.** This red blood cell deficiency causes people to feel tired because the body is not getting enough oxygen. It is often responsible for fatigue and low stamina in patients with type 1 Gaucher disease.

- **Infection.** Patients with type 1 Gaucher disease may have a reduced resistance to infection both of soft tissues and the bones.

- **Bone crisis.** Patients with type 1 Gaucher disease may experience severe bone pain (also called "bone crisis"). The pain can be intense, often accompanied by fever, and can last from a few hours to a few days or even weeks, usually causing patients to be bedridden during this time. According to one study, painful bone crises occur in 42% of patients under 10 years of age and in 24% of patients 10 years of age or older.[4]

- **Bone mineral density.** Type 1 Gaucher disease causes reduced mass and density of bone tissue, causing the bones to weaken.

Testing for Bone Disease

The disease's bone-related symptoms can be particularly painful and debilitating, impairing a patient's mobility. The severity of bone disease in patients with type 1 Gaucher disease varies in several ways: according to age, whether or not the patient has had their spleen removed, how long they have been receiving enzyme therapy, among others. Some patients with type 1 Gaucher disease have few complaints about their bones, while others may have severe symptoms that require them to be wheelchair-bound.

It's a good idea for people with type 1 Gaucher disease to check the health of their bones on a regular basis by gathering information and taking certain tests. Some of these include the patient history (growth pattern, bone pain and crises, family connection); physical examination (height and growth, stature, deformities, range of motion, gait, stability); x-rays; computed tomography (CT scans); magnetic resonance imaging (MRI) scans; and dual-energy x-ray absorptiometry (DXA or DEXA) tests.

A CT scan, which uses a small amount of radiation, is a bit more intense than an x-ray, but provides much more detailed images. A patient may have a bit of dye injected into them, lies still in the scanner for just a few minutes, and 3-D images of the patient's insides are produced, which a radiologist will later examine.

Unlike the CT scan, an MRI machine uses no radiation. Rather, magnets and radio waves send signals to a nearby computer. The computer then instantly creates a three-dimensional picture of whichever part of the body is being tested. Like the CT scan, a patient may have a dye injection, but all the patient needs to do is lie back and relax for about 45 minutes.

A DXA (pronounced "dexa") test is the best way to measure the density or hardness of one's bones. At the end of a DXA test, the patient will know how their bone health compares with other men or women who are the same age. Since DXA technology uses only a very low level of radiation, it is an extremely safe test. Results from each of these tests provide one's health care team with information to guide treatment decisions so bones and the marrow inside them stay as healthy as possible.

Treatment of Patients With Type 1 Gaucher Disease

Aside from the enlarged spleen, the major issues for untreated patients with type 1 Gaucher disease are the bony lesions, fractures, and bone crises. In the past, removal of the spleen was the major approach for many patients, which eliminated the abdominal enlargement, but it carried a greater risk of liver disease and bone problems. Today, many of the patients with type 1 Gaucher disease receive Cerezyme® (imiglucerase for injection) infusions every two weeks. Once treatment begins, the spleen and liver usually reduce in size, the number of red blood cells rises, and the bone crises may become less frequent. The problem with osteoporosis and weakening of the bone sometimes responds to the administration of bisphosphonates.

Generally speaking, patients with Gaucher disease should be monitored every six months and continue to have imaging studies done. Their skeletal systems should be monitored in terms of bone strength on a regular basis. Even asymptomatic patients not requiring treatment should have regular checkups, just to be certain. ■

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Cerezyme®

(imiglucerase for injection)

200 UNITS **400 UNITS**

DESCRIPTION

Cerezyme® (imiglucerase for injection) is an analogue of the human enzyme ß-glucocerebrosidase, produced by recombinant DNA technology. ß-Glucocerebrosidase (ß-D-glucosyl-N-acylsphingosine glucohydrolase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glycolipid glucocerebroside to glucose and ceramide.

Cerezyme® is produced by recombinant DNA technology using mammalian cell culture (Chinese hamster ovary). Purified imiglucerase is a monomeric glycoprotein of 497 amino acids, containing 4 N-linked glycosylation sites (Mr = 60,430). Imiglucerase differs from placental glucocerebrosidase by one amino acid at position 495, where histidine is substituted for arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are somewhat different from those on placental glucocerebrosidase. These mannose-terminated oligosaccharide chains of imiglucerase are specifically recognized by endocytic carbohydrate receptors on macrophages, the cells that accumulate lipid in Gaucher disease.

Cerezyme® is supplied as a sterile, non-pyrogenic, white to off-white lyophilized product. The quantitative composition of the lyophilized drug is provided in the following table:

Ingredient	200 Unit Vial	400 Unit Vial
Imiglucerase (total amount)*	212 units	424 units
Mannitol	170 mg	340 mg
Sodium Citrates	70 mg	140 mg
(Trisodium Citrate) (Disodium Hydrogen Citrate)	(52 mg) (18 mg)	(104 mg) (36 mg)
Polysorbate 80, NF	0.53 mg	1.06 mg
Citric Acid and/or Sodium Hydroxide may have been added at the time of manufacture to adjust pH.		

*This provides a respective withdrawal dose of 200 and 400 units of imiglucerase.

An enzyme unit (U) is defined as the amount of enzyme that catalyzes the hydrolysis of 1 micromole of the synthetic substrate para-nitrophenyl-ß-D-glucopyranoside (pNP-Glc) per minute at 37°C. The product is stored at 2-8°C (36-46°F). After reconstitution with Sterile Water for Injection, USP, the imiglucerase concentration is 40 U/mL (see **DOSAGE AND ADMINISTRATION** for final concentrations and volumes). Reconstituted solutions have a pH of approximately 6.1.

CLINICAL PHARMACOLOGY

Mechanism of Action/Pharmacodynamics

Gaucher disease is characterized by a deficiency of ß-glucocerebrosidase activity, resulting in accumulation of glucocerebroside in tissue macrophages which become engorged and are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic sequelae include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures. **Cerezyme®** (imiglucerase for injection) catalyzes the hydrolysis of glucocerebroside to glucose and ceramide. In clinical trials, **Cerezyme®** improved anemia and thrombocytopenia, reduced spleen and liver size, and decreased cachexia to a degree similar to that observed with Ceredase® (alglucerase injection).

Pharmacokinetics

During one-hour intravenous infusions of four doses (7.5, 15, 30, 60 U/kg) of **Cerezyme®** (imiglucerase for injection), steady-state enzymatic activity was achieved by 30 minutes. Following infusion, plasma enzymatic activity declined rapidly with a half-life ranging from 3.6 to 10.4 minutes. Plasma clearance ranged from 9.8 to 20.3 mL/min/kg (mean ± S.D., 14.5 ± 4.0 mL/min/kg). The volume of distribution corrected for weight ranged from 0.09 to 0.15 L/kg (0.12 ± 0.02 L/kg). These variables do not appear to be influenced by dose or duration of infusion. However, only one or two patients were studied at each dose level and infusion rate. The pharmacokinetics of **Cerezyme®** do not appear to be different from placental-derived alglucerase (Ceredase®).

In patients who developed IgG antibody to **Cerezyme®**, an apparent effect on serum enzyme levels resulted in diminished volume of distribution and clearance and increased elimination half-life compared to patients without antibody (see **WARNINGS**).

INDICATIONS AND USAGE

Cerezyme® (imiglucerase for injection) 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:

a. anemia
b. thrombocytopenia
c. bone disease
d. hepatomegaly or splenomegaly

CONTRAINDICATIONS

There are no known contraindications to the use of **Cerezyme®** (imiglucerase for injection). Treatment with **Cerezyme®** should be carefully re-evaluated if there is significant clinical evidence of hypersensitivity to the product.

WARNINGS

Approximately 15% of patients treated and tested to date have developed IgG antibody to **Cerezyme®** (imiglucerase for injection) during the first year of therapy. Patients who developed IgG antibody did so largely within 6 months of treatment and rarely developed antibodies to **Cerezyme®** after 12 months of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity.

Patients with antibody to **Cerezyme®** have a higher risk of hypersensitivity reaction. Conversely, not all patients with symptoms of hypersensitivity have detectable IgG antibody. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Treatment with **Cerezyme®** should be approached with caution in patients who have exhibited symptoms of hypersensitivity to the product.

Anaphylactoid reaction has been reported in less than 1% of the patient population. Further treatment with imiglucerase should be conducted with caution. Most patients have successfully continued therapy after a reduction in rate of infusion and pretreatment with antihistamines and/or corticosteroids.

PRECAUTIONS

General

In less than 1% of the patient population, pulmonary hypertension and pneumonia have also been observed during treatment with **Cerezyme®** (imiglucerase for injection). Pulmonary hypertension and pneumonia are known complications of Gaucher disease and have been observed both in patients receiving and not receiving **Cerezyme®**. No causal relationship with **Cerezyme®** has been established. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

Therapy with **Cerezyme®** should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Caution may be advisable in administration of **Cerezyme®** to patients previously treated with Ceredase® (alglucerase injection) and who have developed antibody to Ceredase® or who have exhibited symptoms of hypersensitivity to Ceredase®.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies have not been conducted in either animals or humans to assess the potential effects of **Cerezyme®** (imiglucerase for injection) on carcinogenesis, mutagenesis, or impairment of fertility.

Teratogenic Effects: Pregnancy Category C
Animal reproduction studies have not been conducted with **Cerezyme®** (imiglucerase for injection). It is also not known whether **Cerezyme®** can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. **Cerezyme®** should not be administered during pregnancy except when the indication and need are clear and the potential benefit is judged by the physician to substantially justify the risk.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when **Cerezyme®** (imiglucerase for injection) is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of **Cerezyme®** (imiglucerase for injection) have been established in patients between 2 and 16 years of age. Use of **Cerezyme®** in this age group is supported by evidence from adequate and well-controlled studies of **Cerezyme®** and Ceredase® (alglucerase injection) in adults and pediatric patients, with additional data obtained from the medical literature and from long-term post-marketing experience. **Cerezyme®** has been administered to patients younger than 2 years of age, however the safety and effectiveness in patients younger than 2 have not been established.

ADVERSE REACTIONS
Since the approval of **Cerezyme®** (imiglucerase for injection) in May 1994, Genzyme has maintained a worldwide post-marketing database of spontaneously reported adverse events and adverse events discussed in the medical literature. The percentage of events for each reported adverse reaction term has been calculated using the number of patients from these sources as the denominator for total patient exposure to **Cerezyme®** since 1994. Actual patient exposure is difficult to obtain due to the voluntary nature of the database and the continuous accrual and loss of patients over that span of time. The actual number of patients exposed to **Cerezyme®** since 1994 is likely to be greater than estimated from these voluntary sources and, therefore, the percentages calculated for the frequencies of adverse reactions are most likely greater than the actual incidences.

Experience in patients treated with **Cerezyme®** has revealed that approximately 13.8% of patients experienced adverse events which were judged to be related to **Cerezyme®** administration and which occurred with an increase in frequency. Some of the adverse events were related to the route of administration. These include discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture. Each of these events was found to occur in < 1% of the total patient population.

Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of patients. Onset of such symptoms has occurred during or shortly after infusions; these symptoms include pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. Anaphylactoid reaction has also been reported (see **WARNINGS**). Each of these events was found to occur in < 1.5% of the total patient population. Pre-treatment with antihistamines and/or corticosteroids and reduced rate of infusion have allowed continued use of **Cerezyme®** in most patients.

Additional adverse reactions that have been reported in approximately 6.5% of patients treated with **Cerezyme®** include: nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia. Each of these events was found to occur in < 1.5% of the total patient population.

Incidence rates cannot be calculated from the spontaneously reported adverse events in the post-marketing database. From this database, the most commonly reported adverse events in children (defined as ages 2 – 12 years) included dyspnea, fever, nausea, flushing, vomiting, and coughing, whereas in adolescents (>12 – 16 years) and in adults (>16 years) the most commonly reported events included headache, pruritis, and rash.

In addition to the adverse reactions that have been observed in patients treated with **Cerezyme®**, transient peripheral edema has been reported for this therapeutic class of drug.

OVERDOSE

Experience with doses up to 240 U/kg every 2 weeks have been reported. At that dose there have been no reports of obvious toxicity.

DOSAGE AND ADMINISTRATION

Cerezyme® (imiglucerase for injection) is administered by intravenous infusion over 1-2 hours. Dosage should be individualized to each patient. Initial dosages range from 2.5 U/kg of body weight 3 times a week to 60 U/kg once every 2 weeks. 60 U/kg every 2 weeks is the dosage for which the most data are available. Disease severity may dictate that treatment be initiated at a relatively high dose or relatively frequent administration. Dosage adjustments should be made on an individual basis and may increase or decrease, based on achievement of therapeutic goals as assessed by routine comprehensive evaluations of the patient's clinical manifestations.

Cerezyme® should be stored at 2-8°C (36-46°F). After reconstitution, **Cerezyme®** should be inspected visually before use. Because this is a protein solution, slight flocculation (described as thin translucent fibers) occurs occasionally after dilution. The diluted solution may be filtered through an in-line low protein-binding 0.2 µm filter during administration. Any vials exhibiting opaque particles or discoloration should not be used. DO NOT USE **Cerezyme®** after the expiration date on the vial.

On the day of use, after the correct amount of **Cerezyme®** to be administered to the patient has been determined, the appropriate number of vials are each reconstituted with Sterile Water for Injection, USP. The final concentrations and administration volumes are provided in the following table:

	200 Unit Vial	400 Unit Vial
Sterile water for reconstitution	5.1 mL	10.2 mL
Final volume of reconstituted product	5.3 mL	10.6 mL
Concentration after reconstitution	40 U/mL	40 U/mL
Withdrawal volume	5.0 mL	10.0 mL
Units of enzyme within final volume	200 units	400 units

A nominal 5.0 mL for the 200 unit vial (10.0 mL for the 400 unit vial) is withdrawn from each vial. The appropriate amount of **Cerezyme®** for each patient is diluted with 0.9% Sodium Chloride Injection, USP, to a final volume of 100 – 200 mL. **Cerezyme®** is administered by intravenous infusion over 1-2 hours. Aseptic techniques should be used when diluting the dose. Since **Cerezyme®** does not contain any preservative, after reconstitution, vials should be promptly diluted and not stored for subsequent use. **Cerezyme®**, after reconstitution, has been shown to be stable for up to 12 hours when stored at room temperature (25°C) and at 2-8°C. **Cerezyme®**, when diluted, has been shown to be stable for up to 24 hours when stored at 2-8°C.

Relatively low toxicity, combined with the extended time course of response, allows small dosage adjustments to be made occasionally to avoid discarding partially used bottles. Thus, the dosage administered in individual infusions may be slightly increased or decreased to utilize fully each vial as long as the monthly administered dosage remains substantially unaltered.

HOW SUPPLIED

Cerezyme® (imiglucerase for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available as follows:

200 Units per Vial NDC 58468-1983-1
400 Units per Vial NDC 58468-4663-1

Store at 2-8°C (36-46°F).

Rx only

U.S. Patent Numbers: 5,236,838
5,549,892

Cerezyme® (imiglucerase for injection) is manufactured by:
Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142 USA

Certain manufacturing operations may have been performed by other firms.

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Genzyme's Research and Development in Type 1 Gaucher Disease

Quest to Improve Therapy for This Rare Illness

A Discussion With Edward M. Kaye, MD

Edward M. Kaye, MD, is Vice President of Clinical Research at Genzyme, where he supervises the clinical research in the lysosomal storage disease programs and in the genetic neurological disorders. Dr. Kaye spoke to *Horizons* about Genzyme's research and development efforts, the company's small-molecule program and continued research efforts for an oral therapy for type 1 Gaucher disease, and the Gaucher disease registry.

Research and Development Efforts

Genzyme is one of the world's leading biotechnology companies and is dedicated to making a major positive impact on the lives of people with serious diseases. With many established products and services helping patients in nearly 100 countries, Genzyme is a leader in the effort to develop and apply the most advanced technologies in the life sciences. The company's products and services are focused on rare inherited disorders, kidney disease, orthopedics, cancer, transplant and immune disease, and diagnostic testing. Genzyme's commitment to innovation continues today with a substantial development program focused on these fields, as well as cardiovascular disease, neurodegenerative diseases, and other areas of unmet medical need.

In recent years, Genzyme has studied the difference between administering Cerezyme® (imiglucerase for injection) at the same dose once a month versus every 2 weeks.

A Possible Oral Therapy for Type 1 Gaucher Disease on the Horizon

More than a decade ago, explained Dr. Kaye, Genzyme began researching a drug therapy that would hopefully work as well as Cerezyme® but be delivered as an oral pill. "There was an enormous amount of research and development efforts in animal models that has allowed us to gradually bring this product into phase III testing in patients," said Dr. Kaye. "There were many hurdles along the way, one of which was aiming for a drug that would have minimal side effects."

Having just completed a phase II study and with three phase III studies just beginning, Genzyme will be testing the new molecule in more than 300 patients worldwide. Dr. Kaye declared that if patients with type 1 Gaucher disease could "take a medication orally twice a day and respond appropriately without having to have infusion therapy every 2 weeks, it could well be a big breakthrough for convenience." Depending on the trials and collecting the clinical data, this oral therapy could potentially come to the market in the next few years, he said.

Whereas current trials only study adults, Genzyme has a commitment to research the new drug in children as well. In what's called a "pediatric investigational plan," the study will look at various age groups, including a 12-to-18-year-old group, as well as a younger population. As it is "usually easier to pick up safety concerns in adults," said Dr. Kaye, "once we know the drug is safe in adults, then we'll administer it to the children—starting with the oldest children first and then bringing it to the younger children."

Gaucher Disease Registry

The International Collaborative Gaucher Group (ICGG) Registry is the largest cooperative, observational registry on Gaucher disease. Sponsored by Genzyme, it was established in 1991 as a longitudinal database tracking outcomes of routine clinical practice. By January 2010, data from more than 5700 patients with Gaucher disease have been collected from physicians in more than 60 countries. The Registry's goal is to significantly contribute to the medical understanding of Gaucher disease and to improve the quality of care for Gaucher patients worldwide through active publication of Registry findings and disease management approaches. The objectives of the Registry are to enhance the under-

"We've realized that certain regions of the world have a slightly different type of Gaucher disease. For instance, in Japan and China, we see a much higher incidence of neurologic complications such as the type 2 or type 3 Gaucher disease."

standing of the variability, progression, and natural history of Gaucher disease with the ultimate goal of better guiding and assessing therapeutic intervention; to provide the Gaucher medical community with recommendations for monitoring patients and provide reports on patient outcomes to help optimize patient care; and to evaluate the long-term effectiveness of therapy.

The ICGG Registry has been extremely helpful to physicians learning about the disease. "We've also been able to demonstrate through our Registries that there is an effect on bone" (bone pain, bone crisis and bone mineral density) said Dr. Kaye. "On average, it takes about 8 years of Cerezyme® therapy before patients notice an improvement in the bone mineralization.

Dr. Kaye pointed to how "from the beginning of their research in type 1 Gaucher disease, Genzyme decided to study the disease rather than just the drug." The number of patients worldwide affected by this disease is so small in comparison to other illnesses, explained Dr. Kaye, "So it was really important for us to understand the natural history of type 1 Gaucher disease and also to understand what the effect of therapy was on this small patient population."

Genzyme's ICGG Registry has helped the entire medical community learn about type 1 Gaucher disease, which has allowed physicians to understand how Cerezyme® works, understand more about the disease, as well as which subsets of patients with type 1 Gaucher disease are more likely to have serious complications. Furthermore, said Dr. Kaye, "it's a continuous learning tool that physicians and health care advocates can use that provides information to the physicians and even to the patients knowing about the prevalence of the disease and the location in certain countries. People can have a better understanding of type 1 Gaucher disease in general."

The ICGG Registry is a *disease* registry, so it is open to everyone, including patients taking products made by Genzyme's competitors. Companies enroll their patients in the same Registry and follow them in the same way whether the patient is taking Cerezyme®, another drug, or nothing at all. "In fact," said Dr. Kaye, "the Registry has been used by a number of countries for continuing registration of Cerezyme® in the country itself. Canada requires it." Physicians can compare their patients with others in different countries around the world, which helps physicians make recommendations to the country for dose as well as make sure that patient quality of health care within that country is adequate. "It's a tool that can be used by any physician and any patient who has type 1 Gaucher disease, whatever therapy they happen to be on," Dr. Kaye said.

GAUCHER REGISTRY

I C G G

HEMATOLOGIC • VISCERAL • SKELETAL • QUALITY OF LIFE

The Registry has also been helpful in identifying other populations that seem to have a higher prevalence of type 1 Gaucher disease outside of the Jewish community. "We've realized that certain regions of the world have a slightly different type of Gaucher disease," explained Dr. Kaye. "For instance, in Japan and China, we see a much higher incidence of neurologic complications such as the type 2 or type 3 Gaucher disease. We also see type 3 patients much more commonly in the Middle East, and a particular form of type 3 patients in certain eastern European countries." According to Dr. Kaye, this information helps physicians identify specific symptoms and forms of Gaucher disease within different populations.

"The clinical research and the science staff here at Genzyme are committed to trying to improve the therapy for type 1 Gaucher disease," said Dr. Kaye. "Genzyme has been studying type 1 Gaucher disease longer than any other company, and we continually see the need to learn about the disease and make improvements in the treatment. There are still unmet medical needs that we'd like to try to address, and we're hopeful that we will continue to make better therapies available for patients with type 1 Gaucher disease." ■

Infant's Rare Gaucher Defies Classification, Intrigues Experts, May Spur Research

Hannah's Story

Hannah Ostrea was born on July 25, 2008 with a rare form of Gaucher disease – at the time, physicians were unsure whether to classify it in the Type 2 or Type 3 category. In fact, some medical professionals have speculated that Hannah may have a hybrid version of both conditions, or even a wholly new form of the malady. Hannah's mother, Carrie Ostrea, explained how "at birth [Hannah] presented with an enlarged spleen, an enlarged liver [at her 2-mo hematology appointment], and low platelets (6000)." Her daughter's Gaucher disease (which actually presented but remained undetected *in utero* when an ultrasound image revealed Gaucher-related abdominal swelling) has "never been documented or seen before." In fact, said Carrie, "we just thought she had a big stomach."

Finding a Diagnosis

Hannah spent the first two weeks of her life in the intensive care unit. For the next 5 months, Carrie and her husband were consumed with trying to discover the root cause of their child's symptoms. Her search led to the Texas Children's Hospital, Houston, where after a skin biopsy, Hannah was diagnosed with Gaucher disease. Having researched the disease, Carrie recalled the fearful uncertainty she felt at that juncture. She "hoped that it was type 1" knowing it had better odds and outcomes and can often be effectively treated with Cerezyme® (imiglucerase), an enzyme replacement therapy (ERT).

Unfortunately, type 1 Gaucher disease was soon ruled out as a possibility. Carrie explained, "We were referred to Dr. Schiffmann who was at the NIH for many years studying Gaucher disease and who moved to Dallas shortly before Hannah was diagnosed. He was referred to us by Dr. Neal Weinreb, another Gaucher expert and scientific board member of the National Gaucher Foundation." According to Carrie, Dr. Schiffmann "noticed the presence of abnormal eye movements; so at that point, we knew that Hannah had type 2 or 3 Gaucher disease."

Types of Gaucher Disease

Gaucher disease is divided into types (1, 2, and 3), with varying degrees of prevalence, central nervous system (CNS) involvement, and symptom onset (**Figure**). In non-neuronopathic disease (type 1) multiple organs and tissues can be involved, but not the brain. In neuronopathic disease (types 2 and 3) the brain is also involved. Typically, when Gaucher disease is mentioned within the pages of *Horizons*, the text is referring to type 1 disease, since the overwhelming majority of those afflicted with the disease (approximately 90% to 95%, depending on the data source), are suffering from type 1.

Type 1 is the most common form of Gaucher disease, can present at any age, and has no CNS involvement. Perhaps the most common sign of type 1 is enlargement of the spleen. This is often the initial finding and may be first recognized in childhood. Skeletal symptoms of bone involvement can occur at any time in life, are very common, and present in the majority of patients at the time of diagnosis.

Type 2 Gaucher disease is a very rare, rapidly progressive form of the disorder that affects the brain as well as the organs affected by type 1. Type 2 is characterized by severe neurological involvement in the first year of life. Fewer than 1 in 100,000 newborns have this type. These infants typically appear normal during the first few months of life before developing the neurological signs and symptoms associated with type 2. A child afflicted with type 2 Gaucher disease does not usually live past the age of two years owing to the severe CNS involvement.

Figure. Gaucher Disease Types

	Non-neuronopathic	Neuronopathic	
Type	Type 1	Type 2	Type 3
Prevalence	*General Population:* 1 in 40,000-60,000 *Ashkenazi Jews:* 1 in 850	<1 in 100,000	< 1 in 100,000
CNS involvement	None	Severe	Moderate to severe
Symptom onset	Any age	First year of life	Childhood

CNS = Central nervous system.
Types of Gaucher disease. Available at: www.gauchercare.com/en/patient/about/TypesOfGaucher.aspx. Accessed January 25, 2010.

Type 3 is also very rare, and is characterized by slowly progressive brain involvement, in addition to severe disease of the other organs of the body. Signs and symptoms of type 3 Gaucher disease appear in early childhood. Other than the CNS involvement, many of the type 3 signs and symptoms are the same as those for type 1. If brain dysfunction is still subtle at diagnosis, children with type 3 disease may appear to have type 1 Gaucher disease. A clear diagnosis may be made only after neuronopathic signs and symptoms progress and are confirmed with clinical testing. Type 3 individuals who reach adolescence may survive into their 30s.

Infant's Condition Defies Easy Classification

At just over 18 months old (at the time of this writing), Hannah Ostrea has typical and atypical symptoms and an uncharacteristic progression when compared with other children who presented with symptoms before 3 months old. For example, Hannah recently lost the involuntary reflex to blink her eyes. As Carrie pointed out, "This is not a typical Gaucher symptom." The slower-than-expected pace of disease onset has "fooled the earlier doctors . . . who predicted that Hannah would require breathing tubes and feeding tubes at this point."

Carrie said, "We went to the National Institutes of Health in July 2009 and are going back in March 2010." According to Carrie, "Dr. Goker-Alpan and Dr. Sidransky cannot classify Hannah as type 2 or type 3 either. She is called a 'puzzle of sorts.'" If Hannah were type 2, "she should be sicker because she presented at birth. She's unique. This is new." So new, in fact, that according to Carrie, "the NIH is interested in meeting with her." (Since this interview occurred, a meeting at NIH headquarters in Bethesda, MD, has been finalized.)

Hannah's Disease Progression May Unlock Gaucher Mysteries

Several experts who have treated Hannah are optimistic that the peculiar nature of her disease presentation, progression, and symptoms may yield new insights into Gaucher disease care. For example, Hannah's lack of blinking reflex would make more sense in the context of Parkinson's disease (PD), as it is a symptom that is closely associated with PD but not associated with Gaucher disease at all. This has led researchers to explore potential links between these two diseases.

Another enticing avenue currently being explored is the modification of Cerezyme® ERT so that it will be able to cross the blood-brain barrier. If Cerezyme® can be reconfigured in this manner, then it might have the potential to be an effective treatment option for type 2 and/or type 3 Gaucher disease. Researchers are currently testing alternate Cerezyme® formulations in mouse models.

A Mother on a Mission

Carrie Ostrea has become a tireless advocate on behalf of her daughter. "I'm on a mission to find a treatment for her," asserted Carrie. "I spend all day talking to researchers and scientists and working with other moms who have kids (with Gaucher disease and other similar lysosomal storage diseases). That's my day job." Aside from her own personal battle against her daughter's illness, Carrie is also fighting to raise awareness and funds for other children with neuronopathic Gaucher disease. By coordinating her efforts with other parents of children with the disease, Carrie hopes they can provide one another with a support network and fundraising infrastructure.

"I don't want any parent to feel alone out there!" said Carrie. "The more parents we have fighting for our kids, the stronger we can be. These kids (children with type 2 or type 3 Gaucher disease) need to be helped, supported, and cared for. I believe that [Neuronopathic] Gaucher disease is underfunded and under-researched . . . the individuals with this disease aren't given a chance."

Equally as troubling as the scarcity of funding, according to Carrie, is the piecemeal, uncoordinated approach that currently characterizes most neuronopathic Gaucher research. "We don't have one centralized

initiative in which all findings are shared and built upon. Researchers are investigating bits and pieces of this disease. We need to start thinking of this in terms of solving the problem, finding a treatment or a cure, not throwing together bits and pieces of research," asserted Carrie.

Special Support for Special Patients

"If you have a type 2 or type 3 child, this is a very lonely disease. You think you are out there alone," Carrie explained, but Genzyme representatives have helped mitigate those feelings of isolation. She cited Genzyme as an invaluable resource, praising the company for providing stalwart support and demonstrating a willingness "to go out of their way (for Hannah and others like her)." One particular Genzyme representative was singled out for special praise: Kathleen Coolidge, Associate Director, U.S. Patient Advocacy. "Prior to dealing with Genzyme, I had my face slammed in so many doors. Ever since I [connected] with Kathleen, she has been amazing," declared Carrie. "She's helped me contact researchers and other parents (of children with Type 2 and Type 3 Gaucher disease)."

www.littlemisshannah.com

As *Horizons* goes to press, Carrie will continue to battle for her daughter and others like her with all means at her disposal. Hannah is continuing to battle as well; each day for her is a triumph over staggering odds and expert calculations. As her caregivers continue to observe and examine Hannah's rare manifestation of Gaucher disease, they hope to gain insights that are significant enough to yield care advances. They "hope that Hannah holds some new answers," because as Carrie succinctly summarized: "She's here for a reason."

Hannah's continued and vigorous resistance against her disease has provided her mother with encouragement and hope. Carrie concluded her *Horizons* interview with an appeal to the readership, urging anyone who is interested in getting involved in any way to contact her through Hannah's website (www.littlemisshannah.com). ■

Lysosomal Disease Network Highlights Promising Research on Type 1 Gaucher Disease at the 2010 World Symposium

The Lysosomal Disease Network World Symposium 2010 was held in Miami, Florida, on February 10-12, 2010. Researchers and geneticists from all over the world met for the 3-day conference to discuss a range of lysosomal storage disorders (LSDs), including Gaucher disease, cystinosis, Niemann-Pick disease, Krabbe disease, mucopolysaccharidosis, Fabry disease, and Pompe disease. These are all rare inherited genetic disorders. In addition to discussing specific diseases, many studies were presented on how LSDs are recognized, treated, and studied.

Type 1 Gaucher disease was a prominent topic of discussion at the conference, and preliminary results were presented from trials of several new enzyme replacement therapies (ERTs) being studied in patients with type 1 Gaucher disease. Genzyme Corporation, which has manufactured Cerezyme® (imiglucerase for injection) since its approval in 1994, presented updated data from a mid-stage study of eliglustat tartrate (formerly known as Genz-112638), which is designed to be taken orally.

The study enrolled 26 patients, and 20 patients have now completed two years of treatment with eliglustat tartrate.

Genzyme is enrolling patients for the next stage of studies, which includes two global trials called ENCORE and ENGAGE. In ENCORE, patients will receive eliglustat tartrate or Cerezyme®. ENGAGE, designed for patients with type 1 Gaucher disease who have not been treated in the prior 12 months, will compare eliglustat tartrate to a placebo. More than 30 medical centers in more than 20 countries are participating in these trials. A third trial will compare taking eliglustat tartrate once a day with taking the oral drug two times a day. You can learn more about these trials at the NIH website www.clinicaltrials.gov or by contacting Genzyme Medical Information at medinfo@genzyme.com or (800) 745-4447.

www.clinicaltrials.gov

The Genzyme Gaucher Registry Update

At a presentation on the International Collaborate Gaucher Group (ICGG) Gaucher Registry by Neal Weinreb, MD, University Research Foundation for Lysosomal Storage Disorders, Coral Springs, Florida, the presenter expressed concern that short-term results might not represent what type 1 Gaucher patients would experience in practice. He also said some of the standard therapeutic goals might need to be reassessed, because the Registry suggests that most appear to have little clinical meaning, with the exception of bone health.

Dr. Weinreb said he hopes that future investigation will look more at long-term response to treatment and also focus on when to start treatment and whether earlier treatment might help reduce the risk of splenectomy. This is when the spleen is removed, and the Registry shows that it can have negative consequences for some patients with type 1 Gaucher disease even after they start enzyme replacement therapy.

Another highlight from the meeting involved continued investigation into an association between the genes responsible for type 1 Gaucher disease and Parkinson's disease. Are patients with type 1 Gaucher disease or carriers of a Gaucher gene at higher risk for Parkinson's? The research seems to be pointing more and more to yes, though the risk appears to be small. Dr. Weinreb said the ICGG hopes to publish articles on this subject later in the year.

An important message to take from this symposium is that a high level of interest remains in helping patients with type 1 Gaucher disease lead healthier lives. Genzyme continues to look for better ways to diagnose and treat this disorder and to stimulate interest among researchers to study type 1 Gaucher disease. Tremendous steps have been made in the understanding of type 1 Gaucher disease since the approval of Cerezyme® 16 years ago; Genzyme researchers continue to study the disease and investigate for improved therapies and treatment options.