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Gaucher HORIZONS

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ERT & SRT

Understanding the Differences in Gaucher Treatments

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Foreword

Welcome to the first issue of *Gaucher Horizons* for 2015. With the approval of Cerdelga for the treatment of certain patients with Gaucher disease type 1, some patients may be confused about the need for additional testing to determine if they are good candidates for this oral treatment option. To assist those patients, our cover story is about genotyping. We also have a story detailing the difference between substrate-reduction therapy (e.g., Cerdelga) and enzyme replacement therapy. This issue also includes our exclusive interview with one of the lead investigators from the Cerdelga clinical trials, Dr Pramod Mistry, Professor of Medicine and Pediatrics at Yale University.

This issue also has two excellent Patient Profiles, featuring Shauna Mangum and Tamara Issacs Ciocci, as well as our regular feature—Ask the Case Manager—with special contributor Kristina Woessner.

We hope you enjoy this issue of *Gaucher Horizons*. As always, we welcome your ideas.

- Your team at Genzyme

ERT & SRT: Understanding the Differences in Gaucher Treatments

By Cheryl Alkon

For a person with Gaucher disease type 1, the body does not process a fatty material that builds up in the cells. Instead of being cleared away naturally, those fatty materials build up—typically in the spleen, liver, and bones—and can cause health problems such as bone pain, enlarged organs, fatigue, and other issues. Such problems can occur anytime from childhood to adulthood for a person with Gaucher disease.

There are two approaches to treatment: *enzyme-replacement therapy* (ERT) and *substrate-reduction therapy* (SRT). What's the difference? Quite simply, ERT removes the clogged "leaves from the street" more rapidly than it would without treatment, while SRT slows down the "amount of leaves that are collecting" so the debris doesn't accumulate as quickly.

Both are effective ways to treat patients with Gaucher type 1, and patients should speak with their physicians about which kind of treatment is best for them, based on their medical history, background, and other considerations.

Gaucher Disease and Treatments: A Closer Look

Gaucher disease occurs when a genetic mutation causes the body's cells to be unable to clear out a fatty material. This material, known as *glucosylceramide*, or GL-1, builds up when the body does not have enough of the enzyme called *glucocerebrosidase*, that breaks GL-1 down into simpler materials that can be cleared by the cell.

"The synthesis, or creation, of GL-1 exceeds the body's ability to degrade it, or break it down," according to Jennifer Ibrahim, MD, the US Medical Affairs Director of Gaucher and MPS at Genzyme. "ERT replaces the deficient enzyme in the body, which increases the level of degradation so that it matches the level of synthesis of GL-1. SRT reduces the synthesis of GL-1, thereby bringing it down to the level of degradation the body can perform with available enzyme. In both scenarios, the processes of synthesis and degradation are brought into balance."

(Continued on next page)

Please see accompanying full Prescribing Information for CERDELGA and CEREZYME.

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With ERT, more waste material can be degraded than could be done by the cells through the body's own function. It's as if the wind is clearing out the leaves in the street instead of letting them accumulate. With SRT, it's as if there are not as many leaves falling on the ground in the first place.

ERT, which has been available for patients with Gaucher disease since the early 1990s, is currently available from Genzyme as Cerezyme® (imiglucerase for injection). It is administered intravenously, and patients who are on this therapy typically receive infusions every two weeks for 1-2 hours at a time. Genzyme's first SRT treatment, Cerdelga® (eliglustat) capsules was approved for patient use by the US Food and Drug Administration (FDA) in August 2014. It is an oral therapy that is recommended for adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test.

Zavesca® (miglustat) capsules are another SRT medication approved for treatment of adult patients with mild/moderate type 1 Gaucher disease for whom ERT is not a therapeutic option.

Treatment Options

Patients should speak with their doctor about the treatment that may be appropriate for them. "There are many factors that affect treatment choice, both medical and psychosocial," said Ibrahim. "Physicians are encouraged to discuss all treatment options with their patients, recognizing that there are advantages and disadvantages to any form of treatment."

"Cerdelga is appropriate for certain people who haven't received [any] therapy before and for those who are switching from another therapy," said Ibrahim. Cerdelga is not for all patients with Gaucher disease type 1. (For more details about how to find out whether you are a candidate for Cerdelga, please see story on page 6).

For some patients, one important feature with Cerdelga is that it is a once- or twice-daily capsule swallowed with water, rather than an intravenous infusion therapy received over several hours. But how effective is Cerdelga for Gaucher disease treatment? Ibrahim said that the medication "isn't inferior" to ERT treatment. "The clinical trial data showed that most patients who were stable on ERT and switched to Cerdelga maintained their medical stability." she said.

"In clinical studies involving 400 adult patients with Gaucher disease type 1 in 29 countries, Cerdelga has been shown to safely and effectively maintain the stability of the primary clinical manifestations of the disease, specifically hepatosplenomegaly [enlarged spleen and liver], low hemoglobin levels, and thrombocytopenia [low blood platelet counts]." The most common adverse events reported in the clinical trials with Cerdelga were fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain, but safety and efficacy will vary with each patient.

Just as it makes sense to clear away fallen leaves from a street so there's no debris impeding activity, both ERT and SRT therapies can work to help keep the cellular pathways clear for adults patients living with Gaucher disease type 1.

A Conversation with Dr. Pramod Mistry About Cerdelga® (eliglustat) Capsules

By James Radke

The approval of Cerdelga® (eliglustat) capsules provides an oral treatment option for certain adult patients with Gaucher disease type 1. Cerdelga's approval was based largely on two pivotal studies: One compared Cerdelga with placebo, and one compared Cerdelga with standard enzyme-replacement therapy (ERT).

A key player in the clinical studies was Dr. Pramod Mistry, professor of Medicine at Yale University and director of the Yale Lysosomal Disease Center and Gaucher Treatment Center in New Haven, CT. In an exclusive interview with *Gaucher Horizons*, Dr. Mistry talked about the clinical studies that led to Cerdelga's approval as a safe and effective medication for certain patients with Gaucher disease type 1.

Cerdelga's Pivotal Clinical Trials - Design

The design of the clinical trials for Cerdelga had to find the correct balance between providing the US Food and Drug Administration (FDA) with properly controlled clinical trials that met their standard rigorous criteria and being limited by the small patient population. The studies also had to show that since treatment options already exist for Gaucher disease type 1—and this was a new type of first line treatment option—that Cerdelga was a viable substrate reduction treatment option compared with the current standard of care (ERT). This required that two clinical trials be conducted.

According to Dr. Mistry, Study 1 "was a placebo-controlled, randomized clinical trial where 20 patients were randomized

to the active drug—eliglustat (Cerdelga)—and 20 patients were randomized to the placebo group. And the treatment period was 9 months, after which everyone switched over to the open label study."

Study 2 "was a non-inferiority trial, and the design of this trial was to show whether the maintenance of therapeutic goals was comparable in the Cerezyme® (imiglucerase for injection) (ERT) arm versus the Cerdelga arm. In this particular study, 53 patients continued on Cerezyme and 106 were started on Cerdelga, and the treatment period was 1 year," said Dr. Mistry.

Cerdelga's Pivotal Clinical Trials - Results

The results of the phase 3 clinical trials established Cerdelga to be safe and effective, and the FDA approved Cerdelga for the long-term treatment of adults with Gaucher disease type 1 who are CYP2D6 *extensive metabolizers* (EMs), *intermediate metabolizers* (IMs), or *poor metabolizers* (PMs), as detected by an FDA-cleared test.

In Study 1, Dr. Mistry noted, "the primary endpoint was reduction of spleen volume, and that was met."

Spleen volume in patients treated with Cerdelga decreased from baseline by a mean of 28%, while spleen volume increased 2% in the placebo group. Dr. Mistry added that all of the secondary endpoints were met, "using a very stringent statistical criteria" (eg, platelet levels, hemoglobin levels, and liver volume also improved in patients given Cerdelga compared with placebo; liver size decreased by a mean of 5% in the Cerdelga group and increased 1% in the placebo group; hemoglobin levels increased 0.7 g/dL in the Cerdelga group and decreased 0.5 g/dL in the placebo group; and platelet counts increased 32% and decreased 9% in the Cerdelga group and placebo group, respectively).

Dr. Mistry noted that these "endpoints are important because they form the core of the therapeutic goals that were established almost one decade ago by experts worldwide." Spleen volume, liver volume, platelet counts, and hemoglobin counts are considered meaningful clinical endpoints by both clinicians and the FDA.

In Study 2, the endpoint was a composite of all key treatment goals (hemoglobin level, platelet count, and spleen and liver volume), and Dr. Mistry stated that patients switching from ERT to Cerdelga showed similar clinical efficacy and safety. Dr. Mistry said, "the bottom line is the study showed that eliglustat is an effective drug in maintaining control of disease for certain qualified patients who might choose to switch over."

Largest Clinical Program Ever

"The eliglustat clinical trial program is probably the most ambitious and most detailed program conducted in the history of this rare disease," said Dr. Mistry, adding that it is a clinical program that has spanned nearly a decade of work, as well as a collaboration of clinical groups worldwide with patient advocacy groups to make this treatment option a reality.

"The eliglustat clinical trial program is probably the most ambitious and most detailed program conducted in the history of this rare disease."

– Pramod Mistry

"In any therapy, safety is of paramount importance. And all of these clinical trials were designed to conduct a vigorous safety analysis," noted Dr. Mistry. "None of the trials have shown evidence of any serious or life threatening events. More than 90% of patients have tolerated the treatment."

An Exciting Time

"This is an exciting moment in the history of Gaucher disease type 1," proclaimed Dr. Mistry, "because there are many options available."

Cerdelga is an effective first-line therapy. Dr. Mistry said, "Cerdelga is an oral treatment whose efficacy is similar to ERT for certain patients with Gaucher type 1 who have been screened by their physicians." Cerdelga is approved only for CYP2D6 intermediate, extensive, and poor metabolizers.

"There is a lot of interest among patients in the Gaucher community about the prospect of switching over to an oral treatment," said Dr. Mistry.

Please see accompanying full Prescribing Information for CERDELGA and CEREZYME.

Why Is Genotyping for Cerdelga® (eliglustat) Capsules Important?

By Cheryl Alkon

With the approval of Cerdelga® (eliglustat) capsules, a first-line oral treatment, Genzyme provides another option for the treatment of certain adults with Gaucher disease type 1.

But before patients can start this *substrate reduction therapy* (SRT), they must have their blood tested to determine how their bodies will process the medication properly. Through a simple blood test known as the CYP2D6 Genotyping test (done by LabCorp), the physician can learn if the patient is appropriate for Cerdelga and how it should be dosed.

"In order to determine the appropriate dose of Cerdelga, your physician must first test for your CYP2D6 activity level," said Jennifer Ibrahim, MD, the US Medical Affairs Director of Gaucher and MPS at Genzyme. "The activity level of this enzyme varies from one person to another."

It's important to note that CYP2D6 genotyping is a different test altogether from genotyping tests used to diagnose Gaucher disease. Gaucher disease occurs due to changes to the GBA (glucosidase beta acid) gene, and is associated with the accumulation of fatty waste materials in the body's cells. The GBA gene and the CYP2D6 genes have different functions, so CYP2D6 genotype testing related to Cerdelga use is entirely different from testing related to a Gaucher disease diagnosis.

What Is the CYP2D6 Test?

"CYP2D6 is one of a group of enzymes that affects the metabolism, or breakdown, of drugs," Ibrahim explained. People classified as extensive, intermediate, or poor metabolizers are appropriate candidates for Cerdelga, according to the Cerdelga product information provided by Genzyme. Depending on results from the genotyping test, the doctor will determine whether a patient should take Cerdelga at all, and if so, how often. "Most people are extensive and intermediate metabolizers and will take Cerdelga twice a day." said Ibrahim. "A small portion, about 5%, are poor metabolizers and should take Cerdelga once a day," she said.

But the medication isn't for everyone. About 2% of the Gaucher disease population has such ultra-rapid metabolism, as measured though the CYP2D6 test, that they are not good candidates for Cerdelga at all because the drug leaves their bodies too quickly. "Another 8% of those tested find that their metabolism rates are inconclusive, and therefore should not take the drug because it's unclear what would be a safe and effective dose," Ibrahim added.

And women who are pregnant or nursing, and those younger than age 18, should not take Cerdelga at all, regardless of their metabolism rates.

How Cerdelga Works

Gaucher disease is a rare but serious disease that occurs when a person does not have enough *glucocerebrosidase*, an enzyme that processes a fat molecule that is created in the body's cells (this happens due to what could be more than 200 possible mutations in the GBA gene, mentioned earlier). As a result, fatty material called *glucosylceramide* (GL-1) builds up in different parts of the body, including the spleen, liver, and bone marrow. This condition is chronic, and without proper diagnosis and treatment, these excess materials can cause many health problems. Gaucher disease symptoms can appear anytime—in childhood through late adulthood—and may be misdiagnosed for years since Gaucher is a relatively rare condition. According to the GaucherCare.com website, it is estimated that about 1 in 40,000 to 60,000 people in the world, or approximately 10,000 people worldwide, have Gaucher disease. While Jews of Eastern European descent have a higher rate of being diagnosed with the disease (about 1 in 550 people), it still affects people worldwide of any ethnic or racial background.

"Cerdelga inhibits the activity of the enzyme glucosylceramide synthase that is responsible for the formation of GL-1" said Ibrahim.

In other words, Cerdelga helps slow down the build-up of fatty material in the cells that takes place in Gaucher disease type 1.

Am I a Candidate for Cerdelga?

To find out whether Cerdelga would be appropriate, individual patients should speak with the physician that provides them with Gaucher disease care and treatment. "It seems to be, to me, that there have been physicians waiting for their patients to approach them" about the possibility of trying Cerdelga, said Ibrahim.

"Most patients with Gaucher disease type 1 get an annual evaluation. If physicians hear from their patients in advance of the annual visit, the patients can come in and talk about it. Other patients may just prefer to wait for their annual evaluation, and bring it up as part of the evaluation," she said.

The CYP2D6 genotyping blood test results that determine Cerdelga eligibility typically are reported to the physician within 7-14 days; physicians will discuss the results with patients to explain what they mean in terms of Cerdelga eligibility. Physicians can contact LabCorp or Genzyme directly for information on how to order CYP2D6 genotype testing.

If adult patients do begin taking Cerdelga to treat their Gaucher disease type 1, Ibrahim urges them to be open with their physicians about any other medications or treatments they may be taking, including vitamins and supplements.

"As is the case with many medicines, Cerdelga has the potential to interact with other medications that people are taking," said Ibrahim. "Whoever will prescribe your Cerdelga needs to know the medicines you are taking, including herbal supplements and vitamins. Depending on what drugs you are taking, it might be necessary to take Cerdelga only once a day. Or it might be contraindicated [not recommended] entirely."

"Certain antidepressants, certain anti-seizure medications, and St. Johns wort, have been found to interact poorly with Cerdelga," Ibrahim noted. "However, this is by no means a comprehensive list," she said.

In addition, physicians should be fully aware of patients' health history, particularly if it includes kidney or liver problems, heart attacks, or heart rhythm problems. In addition, as recommended on the Cerdelga website (www.cerdelga.com), "especially tell your doctor if you take medicines for fungal infections, tuberculosis, seizures, heart rhythm and rate problems, or high blood pressure. Your doctor may need to prescribe a different medicine, change your dose of other medicines, or change your dose of Cerdelga per recommendations in the Cerdelga package Insert. Tell your doctor about any new medicines before you start taking them."

Patient Profile:

Shauna Mangum

By Cheryl Alkon

Living in a small town in New Mexico, Shauna Mangum never knew anyone else with Gaucher disease type 1. Growing up in the 1970s and 1980s, there was no Internet to find answers to the questions about her lifelong symptoms of fatigue, low platelet count, and bleeding complications such as nosebleeds that would last for 2 hours. Shauna remembers having a local doctor treat the nosebleeds by "sticking these hot sticks up my nose" to cauterize them.

So when she was finally diagnosed with Gaucher disease in 1995 at age 26, after years of health issues, she never thought to question the doctor she found to oversee her disease. "There was a lot of relief that I finally had an answer," said Shauna, who had traveled to the Mayo Clinic in Scottsdale, Arizona, after several New Mexico physicians could not determine what she had. Clinic doctors could only diagnose but not treat Gaucher disease at the time.

Shauna then worked with a doctor in San Diego, who told her she had a "mild to moderate" case of Gaucher disease, an inherited disorder that occurs when a person's body cannot process *glucocerebroside*, a fatty material created in the body's cells. It builds up in the cells instead of being broken down, and without treatment to 'flush it out', the fatty material can lead to enlarged organs and bleeding disorders, among other health issues.

"You don't need treatment," the doctor told Shauna, and so she returned to New Mexico, even though she had been feeling a lot of bone pain and fatigue.

Shauna Mangum

Finding The Right Medical Care

But for Shauna, now 45, and based in the city of Farmington, New Mexico, where she lives with her husband and four children, everything changed when she learned in 1998 that a new Gaucher disease specialist was accepting new patients. She traveled across the country to New York to see him, and learned that she should be treated with medication, and that she should be followed for annual and other periodic checkups. With medication and regular medical care in place, Shauna realized that life with Gaucher disease could be so much better than it had been for her.

But first, Shauna had to contend with her health insurer, who initially agreed to cover Cerezyme® (imiglucerase for injection) but then stopped.

"It's frustrating," she said. "It was an exhausting battle because I was one little person battling this company. It was mentally exhausting. I went through a level 2 appeal and decided to keep fighting because I felt like I had a legitimate case."

Starting Cerezyme *and Cerdelga® (eliglustat) Capsules Therapy*

At that point, Shauna learned that there had been some miscommunication when her insurer was bought by a larger company, and after a year of appealing, the company agreed to cover the costs of Cerezyme for her.

Once she began Cerezyme treatment and had regular ongoing medical care for her Gaucher disease, Shauna said that the difference in how she felt was dramatic. "I had been feeling a lot of fatigue and bone pain, and that was my life, because I didn't know how bad it was until I see how well I feel now," she said

Shauna was part of the recent clinical trial to test Cerdelga, an oral treatment for Gaucher, which ended in October 2014, and has since transitioned into taking Cerdelga. "I started the clinical trial after an evaluation with Dr. Pramod Mistry, and he discussed how Cerdelga worked and explained how this medication could be a better benefit for me," she said. "After running some preliminary tests, I was approved as a participant in the clinical trial. It may be different for other people taking Cerdelga but I have not experienced any side effects from it,

and the transition [from Cerezyme] was easy. I have enjoyed the benefit of extra time that is not committed to enzyme replacement therapy every 2 weeks, and I have continued to feel good throughout my experiences with Cerdelga, which has been a good fit in my active and busy lifestyle." The most common adverse events in the Cerdelga clinical trials were fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain.

Living Life

Now that her children are older, Shauna has focused on her own career and interests. She is a school nurse in a local middle school and is completing her master's degree to become a nurse educator. "I love helping kids," she said. "I love watching them succeed despite other issues going on in their lives." Shauna said she hasn't met a child with Gaucher disease at her school, as far as she knows, but that the issues of living with chronic illness translate to others. "Particularly with kids with a chronic illness, like type 1 diabetes, sometimes the nurse is a big part of being successful, for getting accommodations for individualized care."

For her own health, Shauna runs regularly and has completed several half marathons, running the Chicago Marathon in 2009 and the New York City Marathon, with her husband Wayne, in 2010. "Running is how I appreciate how I feel," she said. "I can run and I feel good. That's my outlet to say I'm in a much better place than I used to be." The family also travels often, with New York and Hawaii as memorable destinations.

Advice for Others

Since it's now possible to access valuable research online, as opposed to 20 years ago when Shauna was first diagnosed, it's crucial to find the best medical care for yourself. "Follow your instincts, and make sure you have a good doctor who is able to make good decisions on your behalf, and that you are comfortable with those decisions," she said. "Don't be afraid to be outspoken and be an advocate for yourself."

"Do all your research, and find out everything you can about this disease. Everyone is different and has different symptoms.

– Shauna Mangum

Once she began Cerezyme treatment and had regular ongoing medical care for her Gaucher disease, Shauna said that the difference in how she felt was incredible. "I had been feeling a lot of fatigue and bone pain, and that was my life, because I didn't know how bad it was until I see how well I feel now," she said.

Being an educated patient helps you to know when things aren't right. "Do all your research, and find out everything you can about this disease," she said. "Everyone is different and has different symptoms. Know what works for you. Follow your doctor's advice, but if you're not comfortable with your doctor, it's okay to get a second opinion. You never know when there will be a point when you might go downhill, and knowledge is everything. We have so much more access to information now, so there's no reason not to be an advocate for yourself." ●

Patient Profile:

Tamara Isaacs Ciocci

By Cheryl Alkon

From just about the day she was born, Tamara Isaacs Ciocci has always known sickness.

Chicken pox as an infant. A broken hip from a simple fall as a toddler. Sore throats, fevers, ongoing bone pain, and abnormal lab work. And anxiety about it all. No matter what it was, "there was an accumulation of odd things going on," said Tamara, now 50, and a kitchen and bath interior designer based in Duxbury, Massachusetts. The daughter of an anesthesiologist in California, and one of five kids in the household that included her three siblings and a cousin, Tamara said she "seemed to attract a lot of strange childhood illnesses that would latch on and never go away."

But no one could connect the dots, she said, despite having "no lack of access to medical care." Many different doctors, including her father's colleagues, thought she had either rheumatoid arthritis at age 8, leukemia at age 12, and other autoimmune diseases at age 21. By the time she was 12, she had missed an entire school year due to her symptoms. She was too ill to leave her house, so medical specialists from various children's hospitals—more of her father's colleagues— would stop by her home to try to figure out what was wrong.

At age 14, with her spleen and liver 20 times the normal size, Tamara was diagnosed with lupus, and began taking steroids. Unfortunately, the medications caused bone loss and brought further pain. Tamara says that it was simply a sign of the times. At that point in the 1970s and 1980s, no one even knew what Gaucher disease was.

"With all the medical access we had, at every fine hospital, no one diagnosed me" [correctly]. So Tamara see-sawed between feeling terrible and feeling okay.

By age 21, Tamara was a student at the University of California at Irvine studying English Literature and in a sorority. When she felt well, she remembers, "I had big plans that I wanted to be an architect and write in New York City. When I was really sick, I thought, 'I couldn't live another day like this. Maybe these things aren't going to happen for me.'"

That year, a rheumatologist told her she didn't have lupus, but possibly leukemia. After a bone marrow test a day later, that doctor called and told her she had Gaucher disease type 1.

"Here we go again with another label," she said. "I just didn't know what to think."

Uncovering the Sickness Source

Gaucher disease, a chronic rare disease where people do not properly process fatty materials in their cells, at the time had no treatment. Because there was no available treatment, Tamara did what she could when she felt sick, and when she felt well, she threw herself into her studies, her social life, and later, her work.

Tamara Isaacs Ciocci with her husband

After graduating from U.C. Irvine, she studied fashion illustration, and later, interior design at the Fashion Institute of Design & Merchandising in Los Angeles. She worked as a visual merchandising stylist on display sets and with architects, and eventually designed for STOR, a precursor to the IKEA furniture store chain, in California. It was physical work, setting up display windows, doing kitchen and bath licensing, and Tamara loved it—until her health intervened.

"My problem was that I loved to work 40-50 hours a week until I got sick," she said. "I have this need to be very creative, and I'd be fine…until I wasn't." Her blood platelet count dipped below 40,000 (normal is 250,000-500,000), and she felt very tired. A cough and sneeze would turn into 4 months of bronchitis or pneumonia, and Tamara would need to take medical leave.

By the end of the 1980s, a clinical trial to evaluate Ceredase® (alglucerase injection), Genzyme's (and the world's) first intravenous treatment for Gaucher disease, was beginning. And while Tamara qualified for one of the 40 openings for that first trial, she was too ill to travel from California to the National Institutes of Health (NIH) in Bethesda, Maryland. "Weekly flying from California to the NIH was too much for me," she said. "Going into the kitchen was too much—that's how tired I was."

Finally, a Gaucher Treatment

When Ceredase was approved by the Food and Drug Administration (FDA) in 1991, Tamara was one of the first patients to be given it, through an oncologist colleague of her father's. There were many steps that followed. "It was a long day, trying to figure out dosing and protocol," she said. "I was monitored very closely."

That first day, she became sick immediately, with nausea, vomiting, and other stomach issues. "At the same time, it was kind of exciting," she admitted. Standing at five feet tall, and weighing 100 pounds, Tamara's enlarged liver and spleen gave her a 42-inch waist—her midsection was about three-quarters as big around as she was tall. "There was a piece of me that felt, 'Maybe I'll get my life back.'"

All of her life, Tamara had heard that she wouldn't live to be 30, and then when she passed that in 1994, that she wouldn't see her 40th birthday. At the same time, when she felt well, "I was trying to establish myself in design, and going either full speed ahead or not at all," she said. By 1993, she was able to receive the medication, then known as Cerezyme® (imiglucerase for injection), in her primary care physician's office every other week. After about 6-12 months on the medication, Tamara noticed a physical difference.

"My organs were still large, but the swelling around my waist was almost like water weight—it just seemed to slowly melt away after about a year," she said. "Physically, I looked very different. There were other benefits, too. My labs weren't so dangerously strange, and my platelet count started to climb."

For what she gained in health, though, she lost in time.

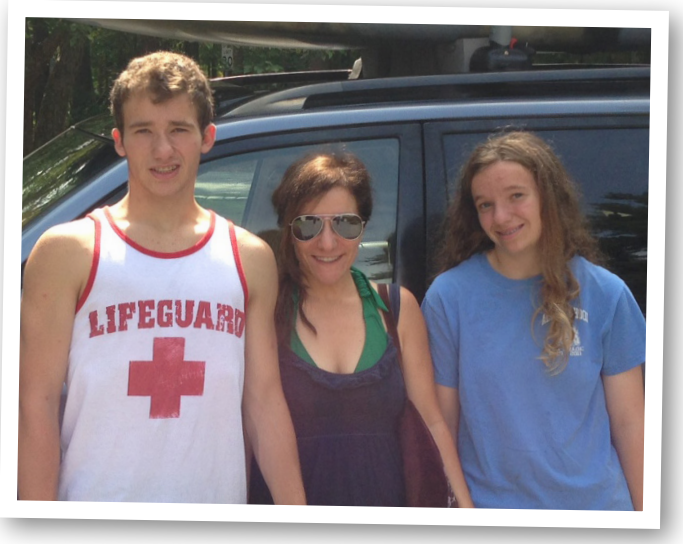
"A lot of people thought infusions were only an hour out of my day, once or twice a month," she said. But it required so much more attention. "I had to speak to a specialty pharmacy daily to order the medications. Plus, because it is such an expensive medication, I had to answer follow-up questions from our insurer about whether I refrigerated it properly. There were all these phone calls, and I never felt like my week was free from Gaucher arrangements. There are critical timing and dosing issues, so following protocol was very important."

When Tamara went to her doctor's office for treatment, she sometimes spent an hour commuting back and forth from her home, and longer if there was traffic. In addition, years of blood tests had sclerosed her veins, making it difficult to access them to administer the drug. "That really adds up for time, and you really couldn't plan a work day on those days, so it was a [full] day out of my work schedule," she said.

Tamara's insurance eventually agreed to have a visiting nurse administer her medication at her home in New Jersey, where she had moved after marrying her husband Rich, who works as an advocate for rare orphan diseases, and having two children, Matthew, now 16, and Lillian, 13. They share their home with Snoopers, the family dog.

Even when receiving treatment at home, which began when her children were young, Tamara explained that it was still a significant time investment: "I'd clean the house, get a babysitter for the toddler and baby, put on a pot of coffee. It doesn't sound like a big deal, but when you are doing this every week, it becomes a nuisance," she said. "It's like my whole life is revolving around my infusions."

Tamara Isaacs Ciocci with her two children



The Cerdelga Years

For 20 years, Tamara took Cerezyme, except for a 2007-2008 medication shortage, when only the most critically ill people took the medication and Tamara took it sporadically. Going without Cerezyme showed Tamara just how dependent on it she was. "Without it, it became very clear that my health went into a downward spiral," she said. "I was sleeping more than I was awake, and I'd call myself a 'sleep-at-home mom.' I hired every 12-year-old in the neighborhood to play with my kids because I was sleeping and dealing with bone pain."

Her physician, Dr. Pramod Mistry, was heading up a new clinical trial for Cerdelga® (eliglustat) capsules, an oral medication to treat Gaucher disease type 1, and he thought Tamara would be an excellent candidate for it. "It was getting harder and harder to find a vein for me to take Cerezyme, and I had pretty much gotten as far as I could on it," Tamara said. She was evaluated in 2010 and entered the trial in 2011, undergoing assorted medical testing and taking the new drug twice a day. Initially, she travelled twice a month to the trial's location in New Haven, Connecticut. Later, it was every 6 weeks, and then to every 12 weeks.

After 6 months, Tamara noticed a difference.

"I was functioning at a much higher level than I was without the drugs," she said. "My lab work returned to more stable numbers. My platelets were at the highest number ever in my life, and the active disease in my bone marrow started to disappear."

Her other illnesses are better, too. "Now, when I get sick, I bounce back much quicker, and my immune system is much more tolerant than it has ever been," she added. Feeling bet-

Please see accompanying full Prescribing Information for CERDELGA and CEREZYME.

(Continued from previous page)

ter has helped her to move forward with her career, too: Tamara plans to begin a master's program at Boston Architectural College in January 2015.

The Cerdelga trial that Tamara participated in ended in October 2014, and she is now working with her insurance company and a Genzyme case manager to determine how her insurance will handle coverage. "For me, Cerdelga has been a huge part of stabilizing my disease, and I'm very confident I will stay on it. I'm not a candidate for going back on infusion therapy."

Advice for Others

What has Tamara learned after having lived with Gaucher disease for half a century? Don't compare yourself to others.

"Learning to accept that maybe your path in life might differ from those around you, but you can't compare success," she said. "You really need to stay your course and learn *not* to say to yourself, 'What a loser—my girlfriend just ran 6 miles and I can't even get out of bed.' Instead, I learned to measure myself against a different standard."

When she is not working or receiving treatment, Tamara says she likes to fill her time with everything she enjoys, and not use it as an excuse to not do things. She has pursued drawing, painting, quilting, and cooking, and tries to eat a whole-food, clean diet. "Things that don't require me to run a marathon or row in the Hudson River," she said.

Eating well is within her control, and it helps her—along with avoiding smoking and drinking very little alcohol—to feel better. "I use a lot of common sense for the types of foods I eat and my family eats because I know it can't hurt me," she said.

Sharing her story has become something Tamara does even more as a "Gaucher Patient Partner," a Genzyme program in which individuals with Gaucher disease speak to others about their experiences. It's something she certainly has the background for.

"In spite of it all, I feel like I've had a very positive journey," Tamara shared. "I wouldn't trade it for anyone else's journey. Now that I am more stable healthwise, I can be very sensitive to families who are new to the disease or are uncertain about it. I can offer a lot in terms of perspective. It's kind of a privilege to meet others and maybe share my experience." ●

Ask Your Case Manager
Kristina Woessner

Kristina Woessner, senior case manager with Genzyme, assists patients in finding solutions to treatment barriers and helps advocate for access to treatment and disease-specific resources at local, state, and federal levels. Here, she answers some commonly asked questions about insurance coverage for Gaucher disease therapy.

Question: How do I know which medical plan will be the best for my Gaucher disease therapy?

Answer: For commercial plans, or plans through the Health Insurance Marketplace (http://www.hhs.gov/healthcare), I often ask the patient to send me the plan overviews or the summaries of coverage and benefits. The plan summaries can often be lengthy and confusing. I then review the plans based on the needs of patients and their families. I point out the positive and negative aspects of each plan, but the final choice is up to each patient.

For Medicare Part D Plans, I help patients review the plan options by entering all of their medications into the Plan Finder on Medicare.gov. I then assist patients in narrowing down their options (usually 3 plans that are the best value and best meet their needs). Again, the final decision on plan choice is up to the individual, but we assist him/her in making informed decisions. Both commercial and Medicare plans can seem overwhelming when first looking at them, but by systematically going over the plans, it can be fairly easy for the patient to decide on the plan that is best for them and their family.

We encourage you to send us your questions for future columns by filling out the postcard in the centerfold of this issue of ***Gaucher Horizons***.

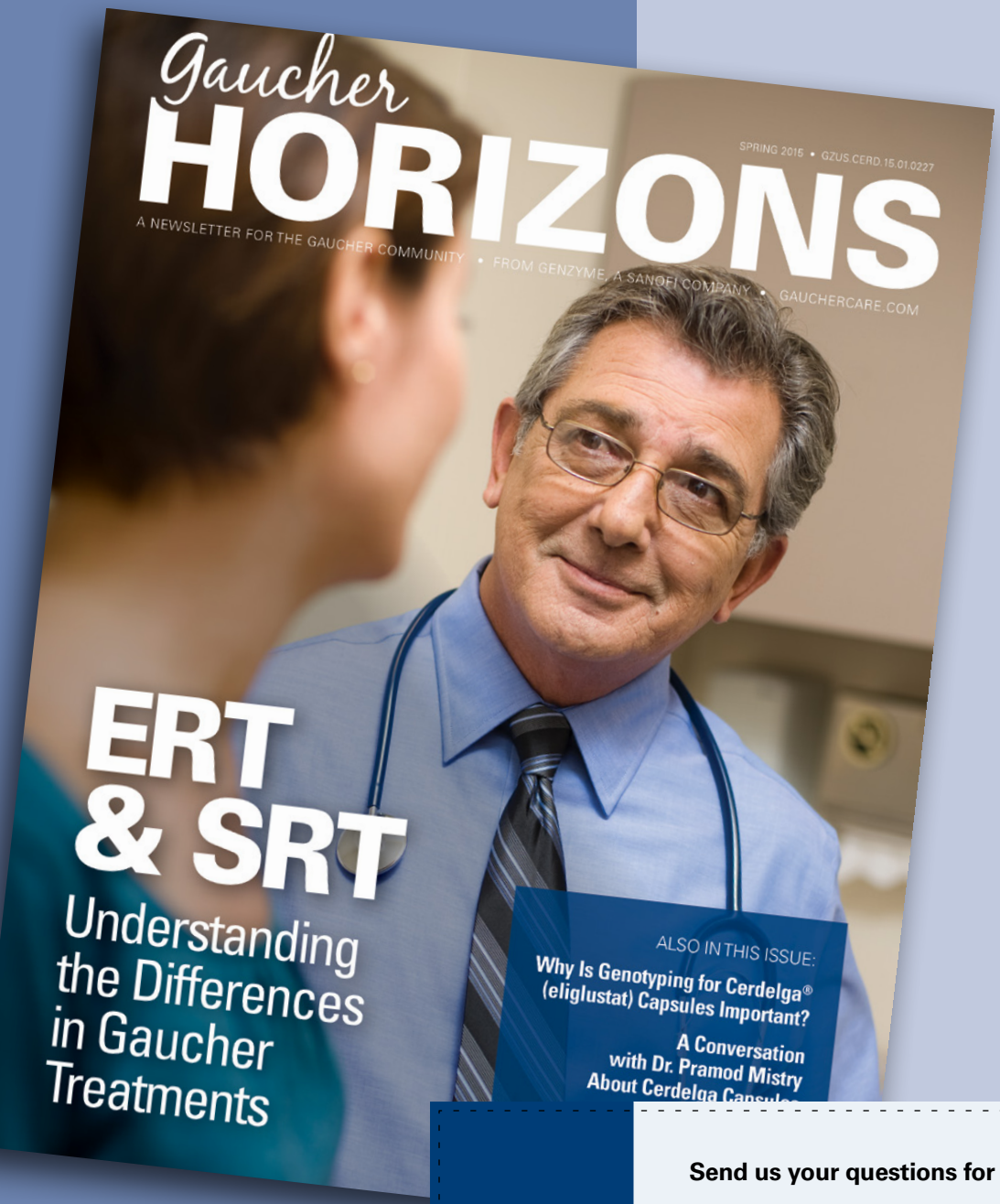
What if Cerdelga (eliglustat) is not included in my health plan?

If an insurance company is blocking a patient's access to Cerdelga following appropriate screening by the patient's physician, patients shouldn't be afraid to call or write the company and let them know what the patient would like to see changed.

Genzyme has a Co-Pay Assistance Program available to assist with co-payments for Cerdelga, as well as for Cerezyme® (imiglucerase for injection) for people with commercial plans not funded by state or federal government, military, Medicaid, Medicare, etc). Patients should call their case manager to discuss eligibility if they have questions.

Although there are barriers to getting Cerdelga covered by insurance—mostly due to Cerdelga not being on formulary with certain insurers—many patients have been able to transition to Cerdelga from other medications.

Kristina Woessner has a Master of Science degree in social work and is currently completing her master's degree in bioethics.



If you have enjoyed this issue of *Gaucher Horizons*, please let us know by completing and returning the postage-paid Business Reply Card below.

Gaucher HORIZONS

Send us your questions for our "Ask the Case Manager" column!

What questions would you like to see answered in an upcoming issue of *Gaucher Horizons*:

_____

_____

☐ **Check here if you would like to receive *Gaucher Horizons* by email.**

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Would you be interested in sharing your story of living with Gaucher disease?
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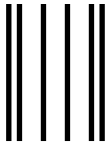

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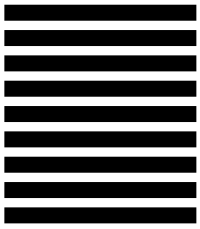

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CERDELGA™ safely and effectively. See full prescribing information for CERDELGA.

CERDELGA™ (eliglustat) capsules, for oral use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

CERDELGA is a glucosylceramide synthase inhibitor indicated for the long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test. (1)

Limitations of Use:
- CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect (1)
- A specific dosage cannot be recommended for CYP2D6 indeterminate metabolizers (1)

DOSAGE AND ADMINISTRATION

- Select patients using an FDA-cleared test for determining CYP2D6 genotype (2.1)
- CYP2D6 EMs or IMs: 84 mg orally twice daily (2.2)
- CYP2D6 PMs: 84 mg orally once daily (2.2)
- Swallow capsules whole, do not crush, dissolve or open capsules (2.3)
- Avoid eating grapefruit or drinking grapefruit juice (2.3)

DOSAGE FORMS AND STRENGTHS

- 84 mg capsules (3)

CONTRAINDICATIONS

- CYP2D6 EMs and IMs taking a strong or moderate CYP2D6 inhibitor with a strong or moderate CYP3A inhibitor (4, 5.1, 7.1, 12.2)
- CYP2D6 IMs and PMs taking a strong CYP3A inhibitor (4, 5.1, 7.1, 12.2)

WARNINGS AND PRECAUTIONS

- ECG Changes and Potential for Cardiac Arrhythmias: Not recommended in patients with pre-existing cardiac disease, long QT syndrome, and concomitant use of Class IA and Class III antiarrhythmics (5.2)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are: fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme Corporation at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Eliglustat is a CYP2D6 and CYP3A substrate. Co-administration of CERDELGA with drugs that inhibit CYP2D6 and CYP3A may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval, which could result in cardiac arrhythmias. Consider potential drug interactions prior to and during therapy (5.1, 7.1)
- CYP2D6 IMs and PMs taking moderate CYP3A inhibitors: not recommended (7.1)
- CYP2D6 PMs taking weak CYP3A inhibitors: not recommended (7.1)
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors and CYP2D6 EMs taking strong or moderate CYP3A inhibitors: reduce the dosage to 84 mg once daily (2.2, 7.1)
- Eliglustat is an inhibitor of P-gp and CYP2D6. Co-administration with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the other drug (7.2)
- See Full Prescribing Information for a list of clinically significant drug interactions (7.1, 7.2)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Only administer if the potential benefit justifies the potential risk. Based on animal data, may cause fetal harm (8.1)
- Nursing mothers: Discontinue drug or nursing based on importance of drug to mother (8.3)
- Renal impairment: Not recommended in moderate to severe impairment (8.6)
- Hepatic impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CERDELGA is indicated for the long-term treatment of adult patients with Gaucher disease type 1 (GD1) who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test *[see Dosage and Administration (2.1)]*.

Limitations of Use:
- Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of CERDELGA to achieve a therapeutic effect *[see Clinical Studies (14)]*.
- A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers) *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients with Gaucher disease type 1 based on their CYP2D6 metabolizer status. It is recommended patient genotypes be established using an FDA-cleared test for determining CYP2D6 genotype *[see Indications and Usage (1)]*.

2.2 Recommended Adult Dosage

The recommended dosage of CERDELGA is 84 mg twice daily in CYP2D6 EMs and IMs. The recommended dosage in CYP2D6 PMs is 84 mg once daily; appropriate adverse event monitoring is recommended *[see Adverse Reactions (6.1)]*. The predicted exposures with 84 mg once daily in patients who are CYP2D6 PMs are expected to be similar to exposures observed with 84 mg twice daily in CYP2D6 IMs *[see Clinical Pharmacology (12.3)]*.

Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's metabolizer status *[see Contraindications (4)]*. Co-administration of CERDELGA with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potentially significant adverse reactions *[see* Table 3 *and* Table 4 *in Drug Interactions (7.1)]*.

Reduce the dosage of CERDELGA to 84 mg once daily for:
- CYP2D6 EMs and IMs taking strong or moderate CYP2D6 inhibitors
- CYP2D6 EMs taking strong or moderate CYP3A inhibitors

2.3 Important Administration Instructions

- Swallow capsules whole, preferably with water, and do not crush, dissolve, or open the capsules.
- CERDELGA can be taken with or without food.
- Avoid the consumption of grapefruit or grapefruit juice with CERDELGA because grapefruit is a strong CYP3A inhibitor *[see Drug Interactions (7.1)]*.
- If a dose of CERDELGA is missed, take the prescribed dose at the next scheduled time; do not double the next dose.
- For patients currently treated with imiglucerase, velaglucerase alfa, or taliglucerase alfa, CERDELGA may be administered 24 hours after the last dose of the previous enzyme replacement therapy (ERT).

3 DOSAGE FORMS AND STRENGTHS

CERDELGA is supplied as 84 mg hard gelatin capsules, with a pearl blue-green opaque cap and pearl white opaque body imprinted with "GZ02" in black. Each capsule contains 100 mg eliglustat tartrate, which is equivalent to 84 mg of eliglustat.

4 CONTRAINDICATIONS

CERDELGA is contraindicated in the following patients due to the risk of significantly increased eliglustat plasma concentrations which may result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias. See Table 3 and Table 4 for examples of drugs in each of the categories described *[see Drug Interactions (7.1)]*:
- EMs or IMs taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor.
- IMs or PMs taking a strong CYP3A inhibitor.

5 WARNINGS AND PRECAUTIONS

5.1 Drug-Drug Interactions

Eliglustat is a CYP2D6 and CYP3A substrate. Drugs that inhibit CYP2D6 and CYP3A metabolism pathways may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac intervals that could result in cardiac arrhythmias *[see Clinical Pharmacology (12.2)]*. Some drugs that are inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's CYP2D6 metabolizer status *[see Contraindications (4)]*. See Table 3 and Table 4 for other potentially significant drug interactions *[see Drug Interactions (7.1)]*.

5.2 ECG Changes and Potential for Cardiac Arrhythmias

Use of CERDELGA in patients with pre-existing cardiac conditions has not been studied during clinical trials. Because CERDELGA is predicted to cause increases in ECG intervals (PR, QTc, and QRS) at substantially elevated eliglustat plasma concentrations, use of CERDELGA is not recommended in patients with pre-existing cardiac disease (congestive heart failure, recent acute myocardial infarction, bradycardia, heart block, ventricular arrhythmia), long QT syndrome, and in combination with Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most common adverse reactions to CERDELGA (occurring in ≥10% of the 126 GD1 patients treated with CERDELGA across Trials 1 and 2) were fatigue, headache, nausea, diarrhea, back pain, pain in extremities, and upper abdominal pain.

The adverse reaction profile of CERDELGA is based on two controlled studies, Trials 1 and 2. Table 1 presents the profile from the 9-month double-blind, randomized, placebo-controlled trial of 40 treatment-naive patients (Trial 1). Patients were between the ages of 16 and 63 on the date of the first dose of study drug, and included 20 males and 20 females.

Table 1: Adverse Reactions Occurring in ≥10% of Treatment-Naïve GD1 Patients and More Frequently than Placebo (Trial 1)

Adverse Reaction	CERDELGA (N=20) Patients n (%)	Placebo (N=20) Patients n (%)
Arthralgia	9 (45)	2 (10)
Headache	8 (40)	6 (30)
Migraine	2 (10)	0 (0)
Flatulence	2 (10)	1 (5)
Nausea	2 (10)	1 (5)
Oropharyngeal pain	2 (10)	1 (5)

Table 2 presents the profile from the 12-month open-label, randomized, imiglucerase-controlled trial of 159 treated patients switching from enzyme replacement therapy (ERT) (Trial 2). Patients were between the ages of 18 and 69 on the date of the first dose of CERDELGA, and included 87 females and 72 males.

Table 2: Adverse Reactions Occurring in ≥5% of GD1 Patients Switching from Enzyme Replacement Therapy to CERDELGA and More Frequently than Imiglucerase (Trial 2)*

Adverse Reaction	CERDELGA (N=106) Patients n (%)	Imiglucerase (N=53) Patients n (%)
Fatigue	15 (14)	1 (2)
Headache	14 (13)	1 (2)
Nausea	13 (12)	0 (0)
Diarrhea	13 (12)	2 (4)
Back pain	13 (12)	3 (6)
Pain in extremity	12 (11)	1 (2)
Upper abdominal pain	11 (10)	0 (0)
Dizziness	9 (8)	0 (0)
Asthenia	9 (8)	0 (0)
Cough	7 (7)	2 (4)
Dyspepsia	7 (7)	1 (2)
Gastroesophageal reflux disease	7 (7)	0 (0)
Constipation	5 (5)	0 (0)
Palpitations	5 (5)	0 (0)
Rash	5 (5)	0 (0)

*Trial 2 was not designed to support comparative claims for CERDELGA for the adverse reactions reported in this table.

In an uncontrolled study, with up to 4 years of treatment, in 26 patients, the types and incidences of adverse reactions were similar to Trials 1 and 2.

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect CERDELGA

Eliglustat is a CYP2D6 and CYP3A substrate.

CYP2D6 and CYP3A Inhibitors

Drugs that inhibit CYP2D6 and CYP3A pathways may significantly increase the exposure to eliglustat and result in prolongation of the PR, QTc, and/or QRS cardiac interval which could result in cardiac arrhythmias:
- Some inhibitors of CYP2D6 and CYP3A are contraindicated with CERDELGA depending on the patient's CYP2D6 metabolizer status *[see Contraindications (4)]*.
- Co-administration of CERDELGA with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the patient's CYP2D6 metabolizer status to reduce the risk of potential significant adverse reactions (see Table 3 and Table 4).

Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Drug Interaction Studies or on Predicted Interaction in EMs and IMs

	Recommended CERDELGA Dosage, by CYP2D6 Metabolizer Status	
CYP450 Inhibitors	**EM**	**IM**
Strong or Moderate CYP2D6 inhibitors concomitantly with Strong or Moderate CYP3A inhibitors	Contraindicated	Contraindicated
Strong CYP2D6 inhibitors e.g., paroxetine	84 mg once daily	84 mg once daily
Moderate CYP2D6 inhibitors e.g., terbinafine	84 mg once daily	84 mg once daily
Strong CYP3A inhibitors e.g., ketoconazole	84 mg once daily	Contraindicated
Moderate CYP3A inhibitors e.g., fluconazole	84 mg once daily	Not recommended

Table 4: Established and Other Potentially Significant Drug Interactions: Alteration in CERDELGA Dosage May Be Recommended Based on Predicted Interaction in PMs

CYP450 Inhibitors	Recommended CERDELGA Dosage for PMs
Strong CYP3A inhibitors e.g., ketoconazole	Contraindicated
Moderate CYP3A inhibitors e.g., fluconazole	Not recommended
Weak CYP3A inhibitors e.g., ranitidine	Not recommended

CYP3A Inducers

Co-administration of CERDELGA with strong CYP3A inducers significantly decreases eliglustat exposure. Use of CERDELGA with strong CYP3A inducers (e.g., rifampin, carbamazepine, phenobarbital, phenytoin, and St. John's Wort) is not recommended in EMs, IMs, and PMs.

7.2 Potential for CERDELGA to Affect Other Drugs

Eliglustat is an inhibitor of P-gp and CYP2D6. Co-administration of CERDELGA with drugs that are substrates for P-gp or CYP2D6 may result in increased concentrations of the concomitant drug as shown in Table 5.

Table 5: Drug Interactions that Result in Increased Concentrations of the Concomitant Drug

Drug Class or Drug Name	Clinical Recommendations
Digoxin (P-gp substrate)	Measure serum digoxin concentrations before initiating CERDELGA. Reduce digoxin dose by 30% and continue monitoring.
Other P-gp substrates (e.g., phenytoin, colchicine, dabigatran etexilate)	Monitor therapeutic drug concentrations, as indicated, or consider reducing the dosage of the concomitant drug and titrate to clinical effect.
CYP2D6 substrates • Metoprolol; • tricyclic antidepressants (e.g., nortriptyline, amitriptyline, imipramine); • phenothiazines (e.g., perphenazine, chloropromazine).	

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate or well-controlled studies with CERDELGA in pregnant women. However, animal reproduction studies have been conducted for eliglustat. In these animal studies, a spectrum of anomalies at doses 6 times the recommended human dose were observed in orally dosed rats. No fetal harm was observed with oral administration of eliglustat to pregnant rabbits at dose levels 10 times the recommended human dose. CERDELGA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Women with Gaucher disease type 1 have an increased risk of spontaneous abortion, especially if disease symptoms are not treated and controlled pre-conception and during a pregnancy. Pregnancy may exacerbate existing Gaucher disease type 1 symptoms or result in new disease manifestations. Gaucher disease type 1 manifestations may lead to adverse pregnancy outcomes including, hepatosplenomegaly which can interfere with the normal growth of a pregnancy and thrombocytopenia which can lead to increased bleeding and possible hemorrhage.

Animal Data

Reproduction studies have been performed in pregnant rats at oral doses up to 120 mg/kg/day (about 6 times the recommended human dose based on body surface area) and in pregnant rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In rats, at 120 mg/kg/day (about 6 times the recommended human dose based on body surface area), eliglustat increased the number of late resorptions, dead fetuses and post implantation loss, reduced fetal body weight, and caused fetal cerebral variations (dilated cerebral ventricles), fetal skeletal variations (poor bone ossification) and fetal skeletal malformations (abnormal number of ribs or lumbar vertebra). Eliglustat did not cause fetal harm in rabbits at oral doses up to 100 mg/kg/day (about 10 times the recommended human dose based on body surface area). In a pre and postnatal development study in rats, eliglustat did not show any significant adverse effects on pre and postnatal development at doses up to 100 mg/kg/day (about 5 times the recommended human dose based on body surface area).

8.3 Nursing Mothers

It is not known whether CERDELGA is present in human milk. Because many drugs are present in human milk, and because of the potential for serious adverse reactions in nursing infants from CERDELGA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the lactating woman.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of CERDELGA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between the elderly and younger patients.

8.6 Renal Impairment

There is no dosage adjustment required for patients with mild renal impairment. CERDELGA has not been studied in patients with moderate to severe renal impairment or end-stage renal disease (ESRD). Use of CERDELGA in these patients is not recommended.

8.7 Hepatic Impairment

CERDELGA has not been studied in patients with hepatic impairment. Use of CERDELGA is not recommended in all stages of hepatic impairment or cirrhosis.

8.8 Poor Metabolizers

Dosing of CERDELGA 84 mg once daily has not been studied in PMs, however the predicted systemic exposures in these patients are within the range of those observed in clinical studies. Appropriate adverse event monitoring is recommended *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

10 OVERDOSAGE

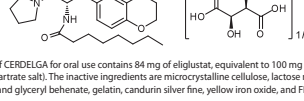
The highest eliglustat plasma concentration experienced to date occurred in a single-dose, dose escalation study in healthy subjects, in a subject taking a dose equivalent to approximately 21 times the recommended dose for GD1 patients. At the time of the highest plasma concentration (59-fold higher than normal therapeutic conditions), the subject experienced dizziness marked by disequilibrium, hypotension, bradycardia, nausea, and vomiting.

In the event of acute overdose, the patient should be carefully observed and given symptomatic and supportive treatment.

Hemodialysis is unlikely to be beneficial given that eliglustat has a large volume of distribution *[see Clinical Pharmacology (12.3)]*.

11 DESCRIPTION

CERDELGA (eliglustat) capsules contain eliglustat tartrate, which is a small molecule inhibitor of glucosylceramide synthase that resembles the ceramide substrate for the enzyme, with the chemical name N-{(1*R*,2*R*)-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-1-hydroxy-3-(pyrrolidin-1-yl)propan-2-yl}octanamide (2*R*,3*R*)-2,3-dihydroxysuccinate. Its molecular weight is 479.59, and the empirical formula is $C_{23}H_{36}N_2O_4 \cdot 1/2(C_4H_6O_6)$ with the following chemical structure:



Each capsule of CERDELGA for oral use contains 84 mg of eliglustat, equivalent to 100 mg of eliglustat tartrate (hemitartrate salt). The inactive ingredients are microcrystalline cellulose, lactose monohydrate, hypromellose and glyceryl behenate, gelatin, candurin silver fine, yellow iron oxide, and FD&C blue 2.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gaucher disease is caused by a deficiency of the lysosomal enzyme acid β-glucosidase. Acid β-glucosidase catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. The enzymatic deficiency causes an accumulation of glucosylceramide (GL-1) primarily in the lysosomal compartment of macrophages, giving rise to foam cells or "Gaucher cells". CERDELGA is a specific inhibitor of glucosylceramide synthase (IC_{50} = 10 ng/mL), and acts as a substrate reduction therapy for GD1. In clinical trials CERDELGA reduced spleen and liver size, and improved anemia and thrombocytopenia.

In this lysosomal storage disorder (LSD), clinical features are reflective of the accumulation of Gaucher cells in the liver, spleen, bone marrow, and other organs. The accumulation of Gaucher cells in the liver, spleen, and bone marrow leads to organomegaly and skeletal disease. Presence of Gaucher cells in the bone marrow and spleen lead to clinically significant anemia and thrombocytopenia.

12.2 Pharmacodynamics

Electrocardiographic Evaluation
QTc interval prolongation was studied in a double-blind, single dose, placebo- and positive-controlled crossover study in 42 healthy subjects. Concentration-related increases were observed for the placebo-corrected change from baseline in the PR, QRS, and QTc intervals. Based on PK/PD modeling, eliglustat plasma concentrations of 500 ng/mL are predicted to cause mean (upper bound of the 95% one-sided confidence interval) increases in the PR, QRS, and QTcF intervals of 22 (26), 7 (10), and 13 (19) msec, respectively. At the highest geometric mean concentrations of 237 ng/mL following a single supratherapeutic dose tested in the thorough QT study, CERDELGA did not prolong the QT/QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

At a given dose, the systemic exposure (C_{max} and AUC) depends on the CYP2D6 phenotype. In CYP2D6 EMs and IMs, the eliglustat pharmacokinetics is time-dependent and the systemic exposure increases in a more than dose proportional manner. After multiple oral doses of 84 mg twice daily in EMs, eliglustat systemic exposure (AUC_{0-12}) increased up to about 2-fold at steady state compared to after the first dose ($AUC_{0-\infty}$). The pharmacokinetics of eliglustat in CYP2D6 PMs is expected to be linear and time-independent. Compared to EMs, the systemic exposure following 84 mg twice daily at steady state is 7- to 9-fold higher in PMs.

Absorption
In CYP2D6 EMs, median time to reach maximum plasma concentrations (t_{max}) occurs at 1.5 to 2 hours following multiple doses of CERDELGA 84 mg twice daily. The corresponding mean C_{max} values range from 12.1 to 25.0 ng/mL in EMs. The mean AUC_{tau} values range from 76.3 to 143 hr*ng/mL in EMs. The C_{max} and AUC_{tau} in one IM subject receiving multiple doses of CERDELGA 84 mg twice daily was 44.6 ng/mL and 306 hr*ng/mL, respectively. The oral bioavailability is low in EMs (<5%) following single dose of CERDELGA 84 mg due to significant first-pass metabolism.

In PMs, median t_{max} occurs at 3 hours following multiple doses of CERDELGA 84 mg twice daily. The corresponding mean C_{max} and AUC_{tau} values range from 113 to 137 ng/mL and 922 to 1057 hr*ng/mL, respectively.

Oral dosing of CERDELGA 84 mg once daily has not been studied in PMs. The predicted C_{max} and AUC_{0-24hr} in PMs using physiologically-based pharmacokinetic (PBPK) model with 84 mg once daily are 75 ng/mL and 956 hr*ng/mL, respectively.

Administration of CERDELGA with a high fat meal resulted in a 15% decrease in C_{max} but no change in AUC. Food does not have a clinically relevant effect on eliglustat pharmacokinetics.

Distribution
Eliglustat is moderately bound to human plasma proteins (76 to 83%). In the blood, it is mainly distributed in plasma and not red blood cells. After intravenous (IV) administration, the volume of distribution of eliglustat was 835 L in CYP2D6 EMs, suggesting wide distribution to tissues (CERDELGA is only for oral use).

Metabolism and Elimination
CERDELGA is extensively metabolized with high clearance, mainly by CYP2D6 and to a lesser extent CYP3A4. Primary metabolic pathways of eliglustat involve sequential oxidation of the octanoyl moiety followed by oxidation of the 2,3-dihydro-1,4-benzodioxane moiety, or a combination of the two pathways, resulting in multiple oxidative metabolites. No active metabolites have been identified.

After oral administration of 84 mg [^{14}C]-eliglustat, the majority of the administered dose is excreted in urine (41.8%) and feces (51.4%), mainly as metabolites. After 42 mg IV administration in healthy volunteers, mean (CV%) of eliglustat total body clearance was 88 L/h (8.8%) in CYP2D6 EMs (CERDELGA is only for oral use). Following multiple oral doses of CERDELGA 84 mg twice daily, eliglustat terminal elimination half-life ($T_{1/2}$) was approximately 6.5 hours in EMs and 8.9 hours in PMs.

Specific Populations
Based on population PK analysis, there was no effect of mild renal impairment on eliglustat PK. Furthermore, gender, body weight, age, and race had no clinically relevant impact on the pharmacokinetics of eliglustat.

Drug Interactions - Effect of Other Drugs on CERDELGA
In vitro, eliglustat is metabolized primarily by CYP2D6 and to a lesser extent by CYP3A4. Eliglustat is also a substrate of P-glycoprotein (P-gp).

Co-administration of CERDELGA with CYP2D6 Inhibitors
Systemic exposure (C_{max} and AUC_{tau}) of eliglustat increased 7.0-fold and 8.4-fold, respectively, following co-administration of CERDELGA 84 mg twice daily with paroxetine (a strong CYP2D6 inhibitor) 30 mg once daily in EMs (N=30), respectively.

Simulations using PBPK models suggested that paroxetine may increase the C_{max} and AUC_{tau} of eliglustat 2.1- and 2.3-fold in IMs, respectively.

Compared to paroxetine, the effects of terbinafine (a moderate inhibitor of CYP2D6) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that terbinafine may increase the C_{max} and AUC_{tau} of eliglustat 3.8- and 4.5-fold in EMs, respectively. Both C_{max} and AUC_{tau} increased 1.6-fold in IMs.

Co-administration of CERDELGA with CYP3A Inhibitors

CYP2D6 EMs and IMs:

Following co-administration of CERDELGA 84 mg twice daily with ketoconazole (a strong CYP3A inhibitor) 400 mg once daily, the systemic exposure (C_{max} and AUC_{tau}) of eliglustat increased 4.0-fold and 4.4-fold in EMs (N=31).

Simulations using PBPK models suggested that ketoconazole may increase the C_{max} and AUC_{tau} of eliglustat 4.4- and 5.4-fold in IMs, respectively.

Compared to ketoconazole, the effects of fluconazole (a moderate inhibitor of CYP3A) on the exposure of eliglustat in EMs or IMs were predicted to be smaller. Simulations using PBPK models suggested that fluconazole may increase the C_{max} and AUC_{tau} of eliglustat 2.8- and 3.2-fold in EMs, respectively, and 2.5- to 2.9-fold in IMs, respectively.

CYP2D6 PMs:
The effect of CYP3A inhibitors on the systemic exposure of eliglustat in PMs has not been evaluated in clinical studies. Simulations using PBPK models suggest that ketoconazole may increase the C_{max} and AUC_{0-24h} of eliglustat 4.3- and 6.2-fold when co-administered with CERDELGA 84 mg once daily in PMs. Simulations using PBPK models suggested that fluconazole may increase the C_{max} and AUC_{0-24h} of eliglustat 2.4- and 3.0-fold, respectively, when co-administered with CERDELGA 84 mg once daily.

Co-administration of CERDELGA with CYP2D6 ***and*** *CYP3A inhibitors*
Simulations using PBPK models suggested that concomitant use of CERDELGA 84 mg twice daily with paroxetine and ketoconazole may increase the C_{max} and AUC_{tau} of eliglustat 16.7- and 24.2-fold in EMs, respectively. The predicted C_{max} and AUC_{tau} of eliglustat increased 7.5- to 9.8-fold in IMs, respectively.

Simulations using PBPK models suggested that concomitant use of CERDELGA 84 mg twice daily with terbinafine and fluconazole may increase the C_{max} and AUC_{tau} of eliglustat 10.2- and 13.6-fold in EMs. The predicted C_{max} and AUC_{tau} of eliglustat increased 4.2- to 5.0-fold in IMs, respectively.

Effect of CYP3A inducers on Eliglustat PK
Systemic exposures (C_{max} and AUC_{tau}) of eliglustat decreased by approximately 90% in EMs and IMs, following co-administration of CERDELGA 127 mg twice daily with rifampin (a strong CYP3A inducer) 600 mg PO once daily. The only approved dose of CERDELGA is 84 mg. Systemic exposures of eliglustat decreased by approximately 95% following co-administration of CERDELGA 84 mg twice daily with rifampin 600 mg PO once daily in PMs.

Effect of OATP (organic anion transporting polypeptide) Inhibitors on Eliglustat PK
Systemic exposures of eliglustat were similar with or without co-administration of single 600 mg IV dose of rifampin (a potent OATP inhibitor) regardless of subjects' CYP2D6 phenotypes.

Effect of P-gp Inhibitors on Eliglustat PK
The effect of P-gp inhibitors on the systemic exposure of eliglustat has not been studied clinically.

Effect of Gastric pH-Modifying Agents on Eliglustat PK
Gastric pH-modifying agents (Maalox®, Tums®, Protonix®) did not have a clinically relevant effect on eliglustat exposure.

Drug Interactions - Effect of CERDELGA on the PK of Other Drugs
Eliglustat is an inhibitor of P-gp and CYP2D6.

Following multiple doses of CERDELGA 127 mg twice daily, systemic exposures (C_{max} and AUC) to metoprolol (a CYP2D6 substrate) increased compared to metoprolol administration alone. Mean C_{max} and AUC increased by 1.7- and 2.3-fold, respectively, in EMs and by 1.2- and 1.6-fold, respectively in IMs. The only approved dose of CERDELGA is 84 mg.

Following multiple doses of CERDELGA 127 mg twice daily in EMs and IMs or 84 mg twice daily in PMs, systemic exposures (C_{max} and AUC) to digoxin (a P-gp substrate, with narrow therapeutic index) increased compared to digoxin administration alone. Mean C_{max} and AUC increased by 1.7- and 1.5-fold, respectively. The only approved dose of CERDELGA is 84 mg.

In vitro, eliglustat is a weak inhibitor of CYP3A. Repeated doses of CERDELGA 84 mg twice daily did not change the exposures to norethindrone (1.0 mg) and ethinyl estradiol (0.035 mg). Therefore, CERDELGA is not expected to impact the efficacy or safety of oral contraceptives containing norethindrone and ethinyl estradiol.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenic potential of CERDELGA was assessed in 2-year carcinogenicity studies in rats and mice. In Sprague-Dawley rats, eliglustat was administered by oral gavage at doses up to 75 mg/kg/day in males (about 3.6 times the recommended human daily dose of 84 mg twice daily, based on body surface area) and 50 mg/kg/day in females (about 2.4 times the recommended human daily dose based on body surface area). In CD-1 mice, eliglustat was administered to males and females at up to 75 mg/kg/day (about 1.8 times the recommended human daily dose based on body surface area) via dietary admixture. Eliglustat did not produce any treatment-related neoplasms in rats or mice.

Mutagenesis
Eliglustat was negative in the Ames test, chromosome aberration test in human peripheral blood lymphocytes, mouse lymphoma gene mutation assay and *in vivo* oral mouse micronucleus test.

Impairment of Fertility
In a fertility and early embryonic development study in rats, eliglustat increased pre-implantation loss at 30 (about 1.5 times the recommended human oral dose based on body surface area) and 100 mg/kg/day (about 5 times the recommended human oral dose based on body surface area).

In mature male rats, eliglustat showed reversible adverse effects on sperm morphology, testes (germ cell necrosis), and sloughed cells in the epididymis at 200 mg/kg/day (about 10 times the recommended human oral dose based on body surface area). Similar effects on sperm were not seen in mature Cynomolgus monkeys at 72 mg/kg/day (about 7 times the recommended human oral dose based on body surface area).

14 CLINICAL STUDIES
The efficacy of CERDELGA was evaluated in three clinical trials in patients with Gaucher disease type 1.

14.1 CERDELGA in Treatment-Naïve GD1 Patients – Trial 1
Trial 1 was a randomized, double-blind, placebo-controlled, multicenter clinical study evaluating the efficacy and safety of CERDELGA in 40 treatment-naive GD1 patients 16 years of age or older (median age 30.4 years) with pre-existing splenomegaly and hematological abnormalities. Patients were required to have received no treatment with substrate reduction therapy within 6 months or ERT within 9 months prior to randomization; all but 5 patients in the study had no prior therapy. Patients were stratified according to baseline spleen volume (≤ 20 or > 20 multiples of normal [MN]) and randomized in a 1:1 ratio to receive CERDELGA or placebo for the duration of the 9-month blinded primary analysis period. The CERDELGA treatment group was comprised of IM (5%), EM (90%) and URM (5%) patients. Patients randomized to CERDELGA treatment received a starting dose of 42 mg twice daily, with a dose increase to 84 mg twice daily possible at Week 4 based on the plasma trough concentration at Week 2. The majority of patients (17 [85%]) received a dose escalation to 84 mg twice daily at Week 4, and 3 (15%) continued to receive 42 mg twice daily for the duration of the 9-month blinded primary analysis period.

The primary endpoint was the percentage change in spleen volume (in MN) from baseline to 9 months as compared to placebo. Secondary endpoints were absolute change in hemoglobin level, percentage change in liver volume (in MN), and percentage change in platelet count from baseline to 9 months compared to placebo.

At baseline, mean spleen volumes were 12.5 and 13.9 MN in the placebo and CERDELGA groups, respectively, and mean liver volumes were 1.4 MN for both groups. Mean hemoglobin levels were 12.8 and 12.1 g/dL, and platelet counts were 78.5 and 75.1 x 10^9/L respectively.

During the 9-month primary analysis period, CERDELGA demonstrated statistically significant improvements in all primary and secondary endpoints compared to placebo, as shown in Table 6.

Table 6: Change from Baseline to Month 9 in Treatment-Naïve Patients with GD1 Receiving Treatment with CERDELGA in Trial 1

	Placebo (n=20)	CERDELGA (n=20)	Difference (CERDELGA – Placebo) [95% CI]	p value*
Percentage Change in Spleen Volume MN (%)	2.3	-27.8	-30.0 [-36.8, -23.2]	<0.0001
Absolute Change in Spleen Volume (MN)	0.3	-3.7	-4.1 [-5.3, -2.9]	NA
Absolute Change in Hemoglobin Level (g/dL)	-0.5	0.7	1.2 [0.6, 1.9]	0.0006
Percentage Change in Liver Volume MN (%)	1.4	-5.2	-6.6 [-11.4, -1.9]	0.0072
Absolute Change in Liver Volume (MN)	0.0	-0.1	-0.1 [-0.2, 0.0]	NA
Percentage Change in Platelet Count (%)	-9.1	32.0	41.1 [24.0, 58.2]	<0.0001
Absolute Change in Platelet Count (x 10^9/L)	-7.2	24.1	31.3 [18.8, 43.8]	NA

MN = Multiples of Normal, CI = confidence interval, NA = Not applicable
*Estimates and p-value are based on ANCOVA model that includes treatment group, baseline spleen severity group (≤20MN, >20MN) and baseline parameter value.

In an uncontrolled study of treatment naïve GD1 patients, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the 4 year treatment period.

14.2 Patients Switching from Enzyme Replacement Therapy to CERDELGA – Trial 2
Trial 2 was a randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluating the efficacy and safety of CERDELGA compared with imiglucerase in 159 treated GD1 patients (median age 37.4 years) previously treated with enzyme replacement therapy (≥3 years of enzyme replacement therapy, dosed at 30-130 U/kg/month in at least 6 of the prior 9 months) who met pre-specified therapeutic goals at baseline. Pre-specified baseline therapeutic goals included: no bone crisis and free of symptomatic bone disease within the last year; mean hemoglobin level of ≥ 11 g/dL in females and ≥ 12 g/dL in males; mean platelet count ≥ 100,000/mm^3; spleen volume < 10 times normal and liver volume < 1.5 times normal.

Patients were randomized 2:1 to receive CERDELGA or imiglucerase for the duration of the 12-month primary analysis period. Seventy-five percent of patients randomized to CERDELGA were previously treated with imiglucerase; 21% with velaglucerase alfa and 4% were unreported. Patients randomized to CERDELGA treatment received a starting dose of 42 mg twice daily, with dose increases to 84 mg twice daily and 127 mg twice daily possible at Weeks 4 and 8 based on plasma trough concentrations of CERDELGA at Weeks 2 and 6, respectively. The percentage of patients receiving the 3 possible CERDELGA doses was: 42 mg twice daily (20%), 84 mg twice daily (32%) and 127 mg twice daily (48%). The CERDELGA treatment group was comprised of PM (4%), IM (10%), EM (80%) and URM (4%) patients.

At baseline, mean spleen volumes were 2.6 and 3.2 MN in the imiglucerase and CERDELGA groups, respectively, and liver volumes were 0.9 MN in both groups. Mean hemoglobin levels were 13.8 and 13.6 g/dL, and platelet counts were 192 and 207 x 10^9/L, respectively.

The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume, and spleen volume) based on changes between baseline and 12 months. Stability was defined by the following pre-specified thresholds of change: hemoglobin level <1.5 g/dL decrease, platelet count < 25% decrease, liver volume <20% increase and spleen volume <25% increase. The percentages of patients meeting the criteria for stability in the individual components of the composite endpoint were assessed as secondary efficacy endpoints.

CERDELGA met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. After 12 months of treatment, the percentage of patients meeting the primary composite endpoint was 84.8% for the CERDELGA group compared to 93.6% for the imiglucerase group. The lower bound of the 95% CI of the 8.8% difference, -17.6%, was within the pre-specified non-inferiority margin of -25%. At Month 12, the percentages of CERDELGA and imiglucerase patients respectively, who met stability criteria for the individual components of the composite endpoint were: hemoglobin level, 94.9% and 100%; platelet count, 92.9% and 100%; spleen volume, 95.8% and 100%; and liver volume, 96.0% and 93.6%. Of the patients who did not meet stability criteria for the individual components, 12 of 15 CERDELGA patients and 3 of 3 imiglucerase patients remained within therapeutic goals for GD1.

Mean changes from baseline in the hematological and visceral parameters through 12 months of treatment are shown in Table 7. There were no clinically meaningful differences between groups for any of the four parameters.

Table 7: Mean Changes from Baseline to Month 12 in Patients with GD1 Switching to CERDELGA in Trial 2

	Imiglucerase (N=47) Mean [95% CI]	CERDELGA (N=99) Mean [95% CI]
Percentage Change in Spleen Volume MN (%)*	-3.0 [-6.4, 0.4]	-6.2 [-9.5, -2.8]
Absolute Change in Spleen Volume (MN)*	-0.1 [-0.2, 0.0]	-0.2 [-0.3, -0.1]
Absolute Change in Hemoglobin Level (g/dL)	0.0 [-0.2, 0.2]	-0.2 [-0.4, -0.1]
Percentage Change in Liver Volume MN (%)	3.6 [0.6, 6.6]	1.8 [-0.2, 3.7]
Absolute Change in Liver Volume (MN)	0.0 [0.0, 0.1]	0.0 [0.0, 0.0]
Percentage Change in Platelet Count (%)	2.9 [-0.6, 6.4]	3.8 [0.0, 7.6]
Absolute Change in Platelet Count (x 10^9/L)	6.0 [-0.9, 13.0]	9.5 [1.4, 17.6]
Patients Stable for 52 Weeks, n (%) (Composite Primary Endpoint)	44 (93.6)	84 (84.8)

MN = Multiples of Normal, CI = confidence interval
* Excludes patients with a total splenectomy.

16 HOW SUPPLIED/STORAGE AND HANDLING

CERDELGA is supplied as 84 mg hard gelatin capsules, with a pearl blue-green opaque cap and pearl white opaque body imprinted with "GZ02" in black.

CERDELGA 84 mg capsules are supplied as:

NDC-58468-0220-1 – Carton containing 4 packs of capsules (56 capsules total). Each pack is composed of 1 blister card of 14 capsules and a cardboard wallet.

NDC-58468-0220-2 – Carton containing 1 pack of capsules (14 capsules total). Each pack is comprised of 1 blister card of 14 capsules and a cardboard wallet.

Store at 68 °F - 77 °F (20 °C - 25 °C) with excursions permitted between 59 °F and 86 °F (15 °C to 30 °C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Drug Interactions
Advise patients to discuss all the medications they are taking, including any herbal supplements or vitamins with their healthcare provider *[see Contraindications (4) and Drug Interactions (7)].*

ECG Changes and Potential for Cardiac Arrhythmias
Advise patients to inform their healthcare provider of the following: history of congestive heart failure; recent acute myocardial infarction; bradycardia; heart block; ventricular arrhythmia; and long QT syndrome *[see Warnings and Precautions (5.2)].*

Advise patients to inform their healthcare provider if they develop new symptoms such as palpitations, fainting, and dizziness.

Administration Instructions
Advise patients:
- Swallow capsules whole, preferably with water, and do not crush, dissolve, or open the capsules.
- CERDELGA can be taken with or without food.
- If a dose of CERDELGA is missed, take the prescribed dose at the next scheduled time; do not double the next dose.
- Avoid consumption of grapefruit or its juice.
- For patients currently treated with imiglucerase, velaglucerase alfa, or taliglucerase alfa, CERDELGA may be administered 24 hours after the last dose of the previous enzyme replacement therapy (ERT).

Manufactured by:
Genzyme Ireland, Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland.

MEDICATION GUIDE
CERDELGA™ (sir-DEL-guh)
(eliglustat) capsules

What is the most important information I should know about CERDELGA?

CERDELGA can affect the way other medicines work and other medicines can affect how CERDELGA works. Using CERDELGA with other medicines or herbal supplements may cause an increased risk of side effects.
Especially tell your doctor if you take:
- St. John's Wort (Hypericum perforatum)
- Medicine for:
  - Fungal infections
  - Tuberculosis
  - Seizures
  - Heart conditions or high blood pressure
  - Depression or other mental health problems

If you take any medicines for the conditions listed above, your doctor may need to prescribe a different medicine, change your dose of other medicines, or change your dose of CERDELGA. Tell your doctor about any new medicines before you start taking them.

What is CERDELGA?

CERDELGA is a prescription medicine used for the long-term treatment of Gaucher disease type 1 (GD1) in adults.
CERDELGA is not used in certain people with Gaucher disease type 1. Your doctor will perform a test to make sure that CERDELGA is right for you.
It is not known if CERDELGA is safe and effective in children.

What should I tell my doctor before taking CERDELGA?

Before taking CERDELGA, tell your doctor about all of your medical conditions, including if you:
- have heart problems, including a condition called long QT syndrome
- have a history of a heart attack
- have kidney or liver problems
- are pregnant or planning to become pregnant. It is not known if CERDELGA will harm your unborn baby.
- are breastfeeding or planning to breastfeed. It is not known if CERDELGA passes into your breast milk. You and your doctor will decide if you should take CERDELGA or breastfeed. You should not do both.

Tell your doctor about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. See **"What is the most important information I should know about CERDELGA?"**

How should I take CERDELGA?

- Take CERDELGA exactly as your doctor tells you to take it.
- Your doctor may change your dose if needed.
- Take CERDELGA capsules whole, preferably with water. Do not open, crush, or dissolve capsules before swallowing.
- CERDELGA can be taken with or without food.
- If you miss a dose of CERDELGA, take the next dose at the usual time. Do not take two doses of CERDELGA at the same time.
- If you take too much CERDELGA, call your doctor or go to the nearest hospital emergency room right away.

What should I avoid while taking CERDELGA?

Avoid eating or drinking grapefruit products while taking CERDELGA. Grapefruit products can increase the amount of CERDELGA in your body.

What are the possible side effects of CERDELGA?

See **"What is the most important information I should know about CERDELGA?"**
- **CERDELGA, used with certain other medicines, may cause changes in the electrical activity of your heart (ECG changes) and irregular heart beat (arrhythmias).** Tell your doctor if you have new symptoms such as palpitations, fainting, or dizziness.

The most common side effects of CERDELGA include:
tiredness, headache, nausea, diarrhea, and pain in the arms, legs, back, or stomach (abdomen).
Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of CERDELGA.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CERDELGA?

- Store CERDELGA at room temperature between 68°F to 77 °F (20°C to 25 °C).
- Keep CERDELGA and all medicines out of reach of children.

General information about the safe and effective use of CERDELGA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CERDELGA for a condition for which it was not prescribed. Do not give CERDELGA to other people, even if they have the same symptoms you have. It may harm them.
If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CERDELGA that is written for health professionals.
For more information, go to www.cerdelga.com or call 1-800-745-4447.

What are the ingredients in CERDELGA?

Active ingredient: eliglustat
Inactive ingredients: microcrystalline cellulose, lactose monohydrate, hypromellose, glyceryl behenate, gelatin, candurin silver fine, yellow iron oxide, and FD&C blue 2

Manufactured by: Genzyme Ireland, Ltd., IDA Industrial Park, Old Kilmeaden Road, Waterford, Ireland

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: August 2014

4LE0118B

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.

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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, pruritus, 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

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

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