A Guide to Cerezyme® (imiglucerase for injection) Billing and Reimbursement
The following is provided for information purposes only and is not intended to substitute for the physician’s independent diagnosis or treatment of each patient. Providers are responsible for the accuracy and validity of any claims, invoices, and related documentation submitted to payers. Physicians should contact the payer if they have any specific questions about coverage or payment. Any specific guidance or direction on the submission of claims offered by the payer supersedes the codes listed below. Use of the following codes does not guarantee reimbursement.
Cerezyme® (imiglucerase for injection) Indication and Important Safety Information for Healthcare Providers

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

Approximately 15% of patients have developed IgG antibodies to Cerezyme during the first year of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity, and these patients have a higher risk of hypersensitivity. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Hypersensitivity has also been observed in patients without detectable IgG antibodies. Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of all patients, and anaphylactoid reactions in less than 1%. Treatment with Cerezyme should be approached with caution in patients who have exhibited hypersensitivity symptoms such as pruritus, flushing, urticaria, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. Pre-treatment with antihistamines and/or corticosteroids and a reduced rate of infusion may allow continued treatment in most patients.

In less than 1% of patients, pulmonary hypertension and pneumonia have been observed during treatment with Cerezyme. These are known complications of Gaucher disease regardless of treatment. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

Approximately 13.8% of patients have experienced adverse events related to treatment with Cerezyme. Some of these are injection site reactions such as discomfort, pruritus, burning, swelling or sterile abscess at the site of venipuncture. Additional adverse reactions that have been reported include nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia. Transient peripheral edema has also been reported for this therapeutic class of drug.

Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
# Table of Contents

**Introduction** ................................................................................................................. 1

**Cerezyme® Coverage** ................................................................................................. 2  
Private Payers .................................................................................................................. 2  
Medicare Part B ................................................................................................................. 2  
Medicare Part C ................................................................................................................. 3  
Medicare Part D ................................................................................................................. 3  
Medicaid ............................................................................................................................. 3-4  
Medicaid Managed Care ................................................................................................. 4

**Cerezyme® Reimbursement** ..................................................................................... 5  
Private Payers .................................................................................................................. 5  
Medicare ................................................................................................................................. 5-6  
Medicaid ................................................................................................................................. 6

**Cerezyme® Billing Codes** ........................................................................................... 7

**Glossary of Terms** ........................................................................................................ 8

**Appendices** .................................................................................................................. 9-15  
Appendix A  
Sample Letter of Intent to Treat .......................................................................................... 9  
Appendix B  
Sample Statement of Medical Necessity .............................................................................. 11  
Appendix C  
Sample UB 04 Claim Form ................................................................................................. 12  
Appendix D  
Sample CMS 1500 (02-12) Claim Form .............................................................................. 13  
Appendix E  
Full Prescribing Information ............................................................................................. 14-15

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Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
Introduction

Gaucher disease is an inherited lysosomal storage disorder. In Gaucher disease, a deficiency of the enzyme glucocerebrosidase leads to the accumulation of the lipid glucocerebroside within the lysosomes of the monocyte-macrophage system. When administered to people with type 1 Gaucher disease, Cerezyme® (imiglucerase for injection) acts like the naturally occurring enzyme glucocerebrosidase to break down the fat molecules that have accumulated in Gaucher cells.

Please see the enclosed for full PRESCRIBING INFORMATION in Appendix E.

Sanofi Genzyme is committed to working with providers, as well as public and private payers, to help ensure access to treatment for patients who medically benefit from Cerezyme®.

This guide is designed to help you understand coverage, coding and reimbursement for Cerezyme®. Providers retain responsibility for determining reimbursement and insurance issues related to their patients. Sanofi Genzyme cannot be responsible for failure of a provider to obtain reimbursement.

If you still have questions after reviewing this guide, please contact CareConnectPSS® Services at 1-800-745-4447 or 1-617-768-9000 (option 3). Our CareConnectPSS® Case Managers have expertise in reimbursement, insurance, case management, and the healthcare delivery system, and can help guide physicians and their patients through the reimbursement process.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).

Please see accompanying full Prescribing Information.
Cerezyme® (imiglucerase for injection) Coverage

Private Payers
Cerezyme® treatment is covered by many private payers; however, individual patients’ insurance benefits will vary. A patient’s insurance coverage should be understood before treatment is initiated. Important points related to private payers include:

- Managed care plans may require a referral from the patient’s primary care provider (PCP) to a specialist.

Private payers may require the following:

- Prior authorization to establish medical necessity for Cerezyme®.
- Periodic reauthorization or recertification for continued treatment.
- Letter of Intent to Treat. See the example in Appendix A, page 11
- Statement of Medical Necessity. See the example in Appendix B, page 12

NOTE
- If the patient’s private insurer denies coverage, an appeal process may be initiated. CareConnectPSS® Case Managers are available to assist patients and work with their physicians in this process.

Medicare Part B
Medicare Part B coverage is determined by the local Medicare Part B carrier. Medicare will not prior authorize, so the patient’s coverage policy should be understood before treatment is initiated. Treatment with Cerezyme® will need to be considered medically necessary in order to be covered under the Medicare program. Cerezyme® is generally covered by Medicare Part B when it is administered and billed as incident to a physician’s services. This means that in order for it to be reimbursed, Cerezyme® and all associated supplies and services must be purchased by the physician or hospital.

NOTE
- Confirm the patient’s eligibility under Medicare Part B prior to ordering Cerezyme®.

Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
Medicare Managed Care (Medicare Part C)

In general, Medicare Managed Care plans work like commercial managed care plans and may require prior authorization. While different plans have different guidelines, Medicare Managed Care plans are required by Medicare to provide, at a minimum, the same level of benefits available under the traditional fee for service Medicare program. Therefore, when the local Medicare B carrier covers Cerezyme® (imiglucerase for injection), the Medicare Managed Care Plan must also cover Cerezyme®, although prior authorization and other medical management approaches may be required by the managed care plan.

Medicare Part D Prescription Drug Coverage

Cerezyme® may be on formulary under the patient’s Prescription Drug Plan (PDP) or Medicare Advantage Prescription Drug (MA-PD). The patient’s out of pocket (OOP) costs will vary depending upon plan coverage. Due to the complexity and variability of Medicare Part D prescription drug coverage, contact the PDP, MA-PD or CareConnectPSS® Support Services for further information.

NOTE
• Medicare Part D reimburses the PDP or MA-PD pharmacy for drug.

Medicaid

Medicaid eligibility and benefit plans vary from state-to-state, so the program’s coverage policy should be understood before treatment is initiated. Usually, treatment with Cerezyme® will need to be considered medically necessary in order to be covered under the Medicaid program. Depending on the state, initial treatment with Cerezyme® may require prior approval by the state Medicaid program. For information on Medicaid coverage for Cerezyme® in your state, contact your local Medicaid office or your CareConnectPSS® Case Manager.

Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
Medicaid agencies may require the following:

- Prior authorization to establish medical necessity for Cerezyme® (imiglucerase for injection).
- Periodic reauthorization or recertification for continued treatment.
- Letter of Intent to Treat. See the example in Appendix A, page 11.
- Statement of Medical Necessity. See the example in Appendix B, page 12.

**NOTE**

- Medicaid regularly updates patient eligibility. Therefore, prior to each patient encounter, physicians should verify eligibility and coverage.
- If Medicaid denies coverage, an appeal process may be initiated. CareConnectPSS® Case Managers are available to assist patients and work with their physicians through this process.

**Medicaid Managed Care**

Many states require Medicaid patients to be enrolled in Medicaid Managed Care plans. These plans vary considerably from state-to-state, and have different documentation and coverage requirements. For example, referrals for treatment with Cerezyme® may need to be in place in order for the patient to receive treatment by anyone other than the patient’s primary care provider. For information on Medicaid coverage for Cerezyme® in your state, contact the Medicaid Managed Care plan or your CareConnectPSS® Case Manager.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).

Please see accompanying full Prescribing Information.
Cerezyme® (imiglucerase for injection)

Reimbursement

Obtaining reimbursement for Cerezyme® varies by payer and setting.

Private Payers, Managed Care and Medicaid Managed Care

**Physician Office**

- Reimbursement for office-administered drugs is often based on Average Wholesale Price (AWP) or Average Sales Price (ASP).
- Reimbursement for services varies, depending on the negotiated rate between the provider and insurance company or the insurance company’s fee schedule.

**Hospital Outpatient**

- Reimbursement varies depending on the negotiated rate between the hospital and insurance company or the insurance company’s fee schedule.

Medicare Part B

**Physician Office**

- The Medicare allowable amount for Cerezyme® is Average Sales Price (ASP) plus 6%. Rates are updated quarterly.
- Medicare covers 80% of the allowable amount, and the beneficiary or their supplemental policy is responsible for the remaining 20%.
- Reimbursement for physician services is based upon the Medicare Physician Fee Schedule (MPFS).
**Hospital Outpatient**

- The Medicare allowable amount for Cerezyme® (imiglucerase for injection) is Average Sales Price (ASP) plus 6%. Rates are updated quarterly.
- Medicare covers 80% of the allowable amount, and the beneficiary or their supplemental policy is responsible for the remaining 20% balance; however, in this site of service, the patient’s 20% coinsurance liability is limited to the current year’s Part A deductible dollar amount [Section 1833(t)(8)(C) of the Social Security Act].
- Medicare pays 80% of the allowable amount plus any additional amount remaining on the beneficiary’s 20% coinsurance when the limitation on the coinsurance applies [Section 1833(t)(4)(C)].
- Reimbursement for services is based upon the Ambulatory Payment Classification (APC).

**Medicaid Fee for Service**

*Physician Office and Hospital Outpatient Setting*

- Reimbursement varies from state-to-state.
- For more information, contact your local Medicaid Office.
Cerezyme® (imiglucerase for injection) Billing Codes

The following is provided for information purposes only and is not intended to substitute for the physician's independent diagnosis or treatment of each patient. Providers are responsible for the accuracy and validity of any claims, invoices, and related documentation submitted to payers. Physicians should contact the payer if they have any specific questions about coverage or payment. Any specific guidance or direction on the submission of claims offered by the payer supersedes the codes listed below. Use of the following codes does not guarantee reimbursement.

<table>
<thead>
<tr>
<th>ICD-10-CM</th>
<th>E75.22 Gaucher Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC</td>
<td>58468-1983-1 200 unit vial</td>
</tr>
<tr>
<td></td>
<td>58468-4663-1 400 unit vial</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J1786 Cerezyme® - injection, imiglucerase, 10 units</td>
</tr>
<tr>
<td>CPT-4</td>
<td>96365 Intravenous infusion therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>96366 Each additional hour (List separately in addition to primary procedure code, 96365)</td>
</tr>
<tr>
<td>Revenue</td>
<td>260 General IV therapy service</td>
</tr>
<tr>
<td></td>
<td>261 Infusion pump</td>
</tr>
<tr>
<td></td>
<td>258 IV solutions</td>
</tr>
<tr>
<td></td>
<td>636 Drugs and biologicals requiring a HCPCS code</td>
</tr>
</tbody>
</table>

**NOTE**

Since third party payers evaluate treatment based on medical necessity, expected outcome, and cost, they generally require documentation of diagnosis and clinical symptoms of type I Gaucher disease. Refer to the Statement of Medical Necessity sample in the back of this guide (Appendix B). This information may need to be submitted with the claim; for specific requirements check with the payer or contact your CareConnectPSS® Case Manager.

The treating physician should request written confirmation of coverage from the third party payer prior to initiation of enzyme replacement therapy. CareConnectPSS® Case Managers can assist in obtaining written authorization for Cerezyme® treatment.

Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
Coding Glossary of Terms

ICD-10-CM (International Classification of Diseases, Tenth Revision, Clinical Modification)

ICD-10-CM is a revision to the ICD-9-CM system used by physicians and hospitals to classify and code all diagnoses. These codes used by hospitals and physicians are recognized by all insurers. Official use of the ICD-10-CM system in the U.S. started on October 1, 2015.

NDC (National Drug Code)

NDCs are codes that identify FDA-approved drugs. The NDC identifies the manufacturer, product, and package size. NDCs are used primarily by retail pharmacies.

HCPCS (Healthcare Common Procedure Coding System)

HCPCS codes are assigned by CMS (Center for Medicare and Medicaid Services) and are used by Medicare and most private payers to describe products administered in the physician office or hospital setting.

CPT (Current Procedural Terminology)

CPT Codes are used by physicians and hospitals to designate the procedures performed.

Revenue Codes

Revenue Codes are used by hospitals to classify services by category, and typically are required by payers when billing infusions in the hospital setting.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
Appendix A

Sample Letter of Intent to Treat

******************************************************************************
THIS IS A SAMPLE LETTER—PLEASE CUSTOMIZE FOR YOUR PATIENT AND RETYPE IT ON YOUR OWN LETTERHEAD
******************************************************************************

[Date]
[Contact Name]
(address)

Patient Name:
Subscriber ID#:
Group #:
Subject: Intent to Treat with Cerezyme® (imiglucerase for injection)

Dear:

I am writing to inform you that I plan to treat [patient name] with Cerezyme enzyme replacement product. Cerezyme is indicated for long-term enzyme replacement therapy for pediatric and adult patients with a confirmed diagnosis of Type 1 Gaucher disease that results in one or more of the following conditions: anemia, thrombocytopenia, bone disease, hepatomegaly or splenomegaly. It is given intravenously and is usually administered on an outpatient basis.

Documentation Enclosed

The attached Statement of Medical Necessity contains information pertaining to [patient name]’s clinical history and diagnosis, demonstrating that the use of Cerezyme is medically indicated for treatment of [his/her] Gaucher disease. Initially, my prescribed dosing regimen will be [number] units per kilogram administered [dosing frequency].

Action Requested

Please send me verification of [patient name]’s coverage for enzyme replacement therapy with Cerezyme as soon as possible. If you have any questions pertaining to [patient name]’s clinical history and/or my treatment plan, please call me at [phone number].

Indication 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

Important Safety Information

Approximately 15% of patients have developed IgG antibodies to Cerezyme during the first year of therapy. Approximately 46% of patients with detectable IgG antibodies experienced symptoms of hypersensitivity, and these patients have a higher risk of hypersensitivity. It is suggested that patients be monitored periodically for IgG antibody formation during the first year of treatment.

Hypersensitivity has also been observed in patients without detectable IgG antibodies. Symptoms suggestive of hypersensitivity have been noted in approximately 6.6% of all patients, and anaphylactoid

This is only a model letter and should be customized to address patients’ specific issues. Call your CareConnectPSS® Case Manager to request a copy of this letter.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).

Please see accompanying full Prescribing Information.
reactions in less than 1%. Treatment with Cerezyme should be approached with caution in patients who have exhibited hypersensitivity symptoms such as pruritus, flushing, urticarial, angioedema, chest discomfort, dyspnea, coughing, cyanosis, and hypotension. Pre-treatment with antihistamines and/or corticosteroids and a reduced rate of infusion may allow continued treatment in most patients.

In less than 1% of patients, pulmonary hypertension and pneumonia have been observed during treatment with Cerezyme. These are known complications of Gaucher disease regardless of treatment. Patients with respiratory symptoms in the absence of fever should be evaluated for the presence of pulmonary hypertension.

Approximately 13.8% of patients have experienced adverse events related to treatment with Cerezyme. Some of these are injection site reactions such as discomfort, pruritus, burning, swelling or sterile abscess at the site at the site of venipuncture. Additional adverse reactions that have been reported include nausea, abdominal pain, vomiting, diarrhea, rash, fatigue, headache, fever, dizziness, chills, backache, and tachycardia. Transient peripheral edema has also been reported for this therapeutic class of drug.

To report suspected adverse reactions, contact Genzyme at 800-745-4447, option 2 or FDA at 800-FDA-1088 or http://www.fda.gov/Safety/MedWatch

Please see Full Prescribing Information (PDF).

Thank you for your immediate attention to this request.

Sincerely,
[Physician Name]

Enclosure
cc [patient name]
Appendix B

Sample Statement of Medical Necessity

STATEMENT OF MEDICAL NECESSITY
FOR THE TREATMENT OF GAUCHER DISEASE

Patient Name _______________________________ Insurance ID Number __________________
Address ___________________________________________________________
Phone Number _______________________________ Gender _______ Date of Birth _______________
Symptoms of Gaucher Disease First Diagnosed ___________________________ Date _______________
Method of Diagnosis __________________________________________________ Date _______________

DIAGNOSIS
☐ Gaucher Disease (Lipidosis) ICD-9CM 272.7  ☐ Gaucher Disease ICD-10-CM E75.22*

SPLENECTOMY
☐ No  ☐ Yes: Date _______________________________ Circle One: Total or Partial

ORGANOMEGALY
☐ No  ☐ Yes: Spleen Size _________________________ Liver Size _______________________

HEMATOLOGY
☐ Yes: Hemoglobin _____________________________
Thrombocytopenia ☐ Yes: Platelet Count _____________________________
Bleeding Event ☐ Yes: Hematocrit _____________________________

BONE DISEASE
☐ Yes Lytic lesion(s) ☐ Yes Joint replacement(s) ☐ Yes
☐ Yes Avascular necrosis ☐ Yes Osteopenia ☐ Yes
☐ Yes Bone crises ☐ Yes Pathological fracture(s) ☐ Yes
☐ Yes Bone pain ☐ Yes Marrow infiltration ☐ Yes
☐ Yes Erlenmeyer flask deformity ☐ Yes Infarction(s) ☐ Yes
☐ Yes Bleeding Event ☐ Yes

Other____________________________________________________________________________________

Carezyme® (imiglucerase for injection) Treatment Plan and Dosing Schedule
(NDC 58468-4663-1 400U vial)

Number of units per kg ______________________ Frequency _______________
Physician Signature __________________________ Date __________________
Address __________________________________________ Phone __________________________ Fax __________________________

Important Note: *ICD-10-CM for dates of service starting on 10/01/15
NOTE: This form may not include all information required by your patient’s health plan, as requirements will vary based on health plan guidelines and benefit design. Please note that the requesting provider is responsible for ensuring the accuracy, adequacy and supportability of all information provided on this form.

Call your CareConnectPSS® Case Manager to request a copy of this form.

Please see accompanying full Prescribing Information.

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).
### Sample CMS-1450 (UB-04) Claim Form

**Disclaimer:** This is a reference sheet only. It is **NOT** inclusive of all applicable codes that may be reported on a UB-04 claim form. The inclusion of codes listed is **not** intended to suggest or imply that such codes reflect appropriate diagnoses for any particular patient. To ensure appropriate documentation and coding, Providers should contact their billing/finance department.

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0636</td>
<td>Drugs (Cerezyme)</td>
</tr>
<tr>
<td>0260</td>
<td>General IV Therapy</td>
</tr>
<tr>
<td>96365</td>
<td>Intravenous IV therapy, prophylaxis, or diagnosis (specify substance or drug); initial up to 1 hr</td>
</tr>
<tr>
<td>96366</td>
<td>Each additional hour (list separately in addition to primary procedure code, 96365)</td>
</tr>
</tbody>
</table>

**Fields 42 and 43:** Enter appropriate revenue code and description of service; Example:
- 0636 for drugs that require detailed coding
- 0260 for IV therapy

**Field 46:** Note the appropriate amount of drug provided in units; Example: multiples of 10 units for Cerezyme

**General IV therapy:** 96365 Intravenous IV therapy, prophylaxis, or diagnosis (specify substance or drug); initial up to 1 hr

**Fields 10 and 11:** Enter appropriate ICD-10-CM diagnosis code as reflected in the patient’s medical record; Example:
- E75.22 Gaucher Disease

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).

Please see accompanying full Prescribing Information.
Appendix D

Sample CMS 1500 (02-12) Claim Form

Box 21: Enter the appropriate diagnosis code: ICD-10-CM (E75.22)

Box 21: Complete the indicator field to reflect diagnosis code reported: ICD-10-CM

Box 24D: Enter the appropriate HCPCS codes:
Drugs: J1786 for Cerezyme, 10 units
General IV Therapy: 96365 Intravenous infusion therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366 Each additional hour (list separately in addition to primary procedure code, 96365)

Box 24G: Note amount of drug provided in units; e.g., multiples of 10 units for Cerezyme.
Full Prescribing Information

Appendix E

Cerezyme® (imiglucerase for injection) is an analogue of the human enzyme β-glucocerebrosidase, produced by recombinant DNA technology. β-Glucocerebrosidase (β-D-glucopyranosyl-N-acetylglucosaminyl glycosidase, E.C. 3.2.1.45) is a lysosomal glycoprotein enzyme which catalyzes the hydrolysis of the glucosylceramide to glucose and ceramide.

Cerezyme is produced by recombinant DNA technology using mammalian cell culture (CHO-101 line). The purified enzyme 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 replaced by arginine. The oligosaccharide chains at the glycosylation sites have been modified to terminate in mannose sugars. The modified carbohydrate structures on imiglucerase are specifically recognized by endo H 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:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>200 Unit Vial</th>
<th>400 Unit Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiglucerase (total active)</td>
<td>212 units</td>
<td>424 units</td>
</tr>
<tr>
<td>Mannitol</td>
<td>170 mg</td>
<td>340 mg</td>
</tr>
<tr>
<td>Sodium Citrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trisodium Citrate</td>
<td>70 mg</td>
<td>140 mg</td>
</tr>
<tr>
<td>Disodium Hydrogen Citrate</td>
<td>(52 mg)</td>
<td>(104 mg)</td>
</tr>
<tr>
<td>Citric Acid</td>
<td>(18 mg)</td>
<td>(36 mg)</td>
</tr>
<tr>
<td>Polysorbate 80, NF</td>
<td>0.52 mg</td>
<td>1.06 mg</td>
</tr>
<tr>
<td>Cete Oleic Acid and/or Sodium Hydrosolate May have been added at the time of manufacture to adjust pH.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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-β-D-glucopyranoside (pNP-Glc) per minute at pH 4.0 and 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). 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 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 lymph nodes and lungs. The glucocerebroside accumulation, in turn, results in the characteristic progression of hepatosplenomegaly, skeletal complications, including osteonecrosis and osteopenia with secondary pathological fractures. Cerezyme (imiglucerase for injection) catalyzes the hydrolysis of glucosylceramide 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 Cerazyme® (alglucerase injection).

Pharmacokinetics

During one-hectoliter 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 3.8 to 10.4 minutes. Plasma clearance ranged from 9.8 to 23.3 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 0.14 L/kg. These variables do not appear to be influenced by dose or from placental-derived alglucerase (Cerazyme).

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 for imiglucerase in patients without antibody (see WARNINGS). Indications and Usage

Cerezyme® (imiglucerase for injection) is indicated for long-term enzyme replacement therapy for adult and pediatric patients (infants to adults) with Type I Gaucher disease that results in one or more of the following conditions:

• anemia
• thrombocytopenia
• bone disease
• hepatosplenomegaly 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 48% 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. Anaphylactic reaction has been reported in less than 1% of the patient population.

Further treatment with Cerezyme should be approached with caution in patients who have exhibited symptoms of hypersensitivity to 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 Cerezyme (alglucerase injection) and who have developed antibody to Cerazyme or who have exhibited symptoms of hypersensitivity to Cerazyme.

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 resolving and not resolving 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.

In approximately 6.5% of patients treated with Cerezyme® (imiglucerase for injection), anaphylactoid reaction has been reported in less than 1% of the patient population.

Anaphylactoid reaction has been reported in less than 1% of the patient population, and infusion rate. The pharmacokinetics of Cerezyme® (imiglucerase for injection) during the first year of therapy. Patients who developed IgG antibody to Cerezyme should be carefully re-evaluated if there is significant

ADVERSE REACTIONS

Since the approval of Cerezyme® (imiglucerase for injection) in May 1994, Cerezyme has maintained a worldwide post-marketing database of spontaneously reported adverse events (MedWatch). 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 of patients. In 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 abscesses 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 hypertension. Anaphylactoid reaction has also been reported (see WARNINGS). Each of these events was found to occur in <1.5% of the total patient population.

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, diarrhea, chills, backache, and tachycardia. Each of these events was found to occur in <1.0% 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 common 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 the therapeutic class of drugs.

OVERDOSE

Exposure 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:

<table>
<thead>
<tr>
<th></th>
<th>200 Unit Vial</th>
<th>400 Unit Vial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterile water</td>
<td>5.1 mL</td>
<td>10.2 mL</td>
</tr>
<tr>
<td>for reconstitution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final volume of</td>
<td>5.3 mL</td>
<td>10.6 mL</td>
</tr>
<tr>
<td>reconstituted product</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concentration after reconstitution</td>
<td>40 U/mL</td>
<td>40 U/mL</td>
</tr>
<tr>
<td>Withdrawal volume</td>
<td>5.0 mL</td>
<td>10.0 mL</td>
</tr>
<tr>
<td>Units of enzyme within final volume</td>
<td>200 units</td>
<td>400 units</td>
</tr>
</tbody>
</table>

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 100-300 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 (22°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

Genzyme Corporation
Cambridge, MA 02142 USA

U.S. Patent Numbers: 5,236,838; 5,549,892
Revised: April 2018
IMI-FSPL-SL-APR18

Questions? Contact CareConnectPSS® at 1-800-745-4447 or 1-617-768-9000 (option 3).

Please see accompanying full Prescribing Information.
An Ongoing Commitment

For more than 30 years, Sanofi Genzyme has been committed to researching and developing products for people living with lysosomal storage disorders such as type 1 Gaucher disease.

Providing comprehensive and confidential support services that address the unique needs of those living with Gaucher disease is part of this ongoing commitment.

To learn more about these support services, call a CareConnectPSS® Case Manager at 800-745-4447 (option 3).

Please see enclosed full PRESCRIBING INFORMATION.
Cerezyme.com