A Guide to Cerezyme® (imiglucerase for injection) Billing and Reimbursement

SANOFI GENZYME

Cerezyme®
imiglucerase for injection

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 supersede 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.

Cerezyme®
imiglucerase for injection

Please see accompanying full Prescribing Information.

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

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Cerezyme®
imiglucerase for injection

Please see accompanying full Prescribing Information.

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.

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.

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.

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.

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 supersede the codes listed below. Use of the following codes does not guarantee reimbursement.

ICD-10-CM	E75.22 Gaucher Disease
NDC	58468-1983-1 200 unit vial 58468-4663-1 400 unit vial
HCPCS	J1786 Cerezyme® - injection, imiglucerase, 10 units
CPT-4	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)
Revenue	260 General IV therapy service 261 Infusion pump 258 IV solutions 636 Drugs and biologicals requiring a HCPCS code

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.

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.

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.

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]**

GZUS.CERZ.15.12.3036

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 _____ Weight in kg _____ Height _____

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

Anemia	☐ Yes: Hemoglobin	_____
Thrombocytopenia	☐ Yes: Platelet Count	_____
Bleeding Event	☐ Yes: Hematocrit	_____

BONE DISEASE

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

Other _____

_____

_____

Cerezyme® (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.

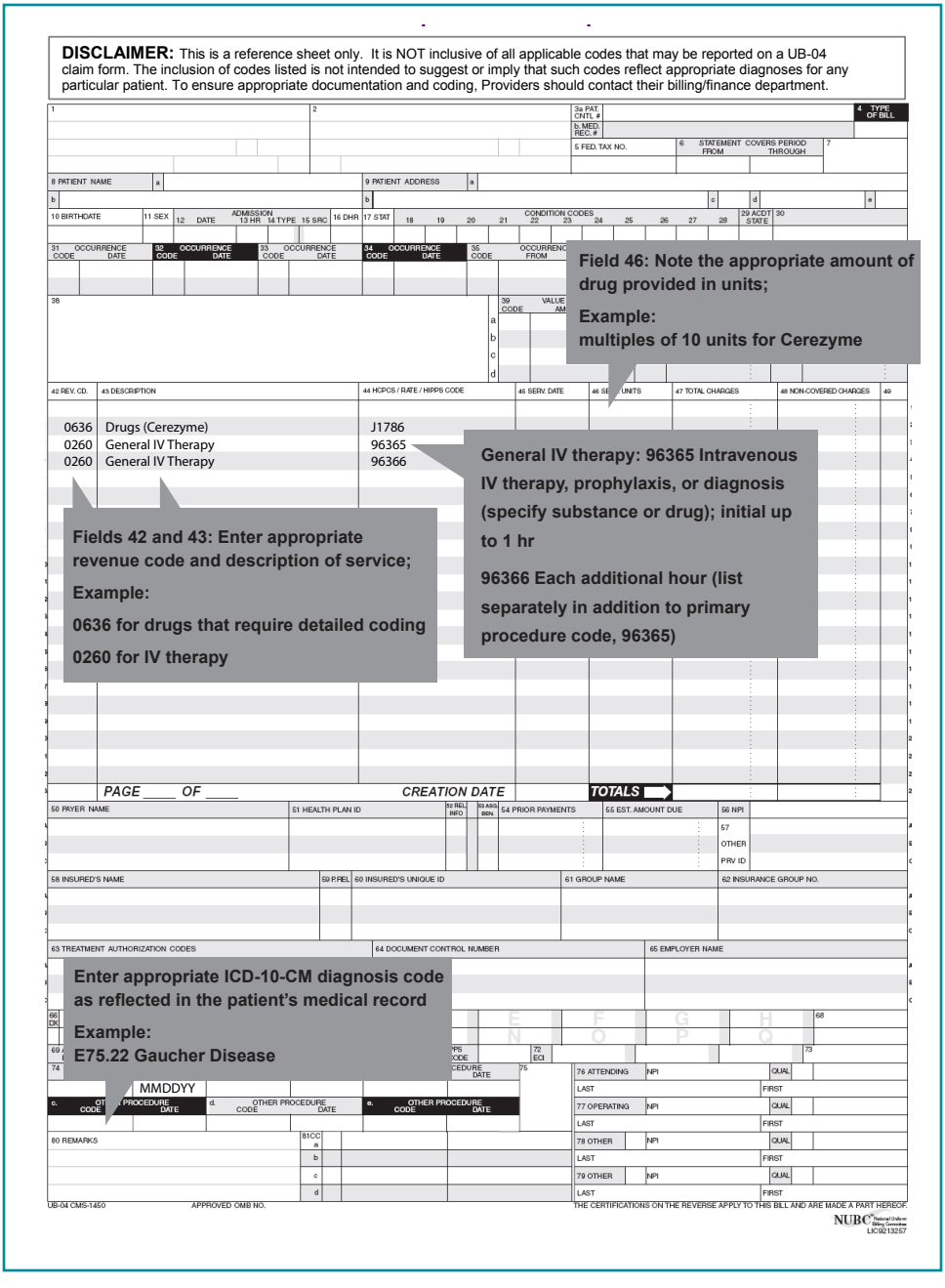
GZUS.CERZ.15.12.3038(2)

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

Please see accompanying full Prescribing Information.

Appendix C

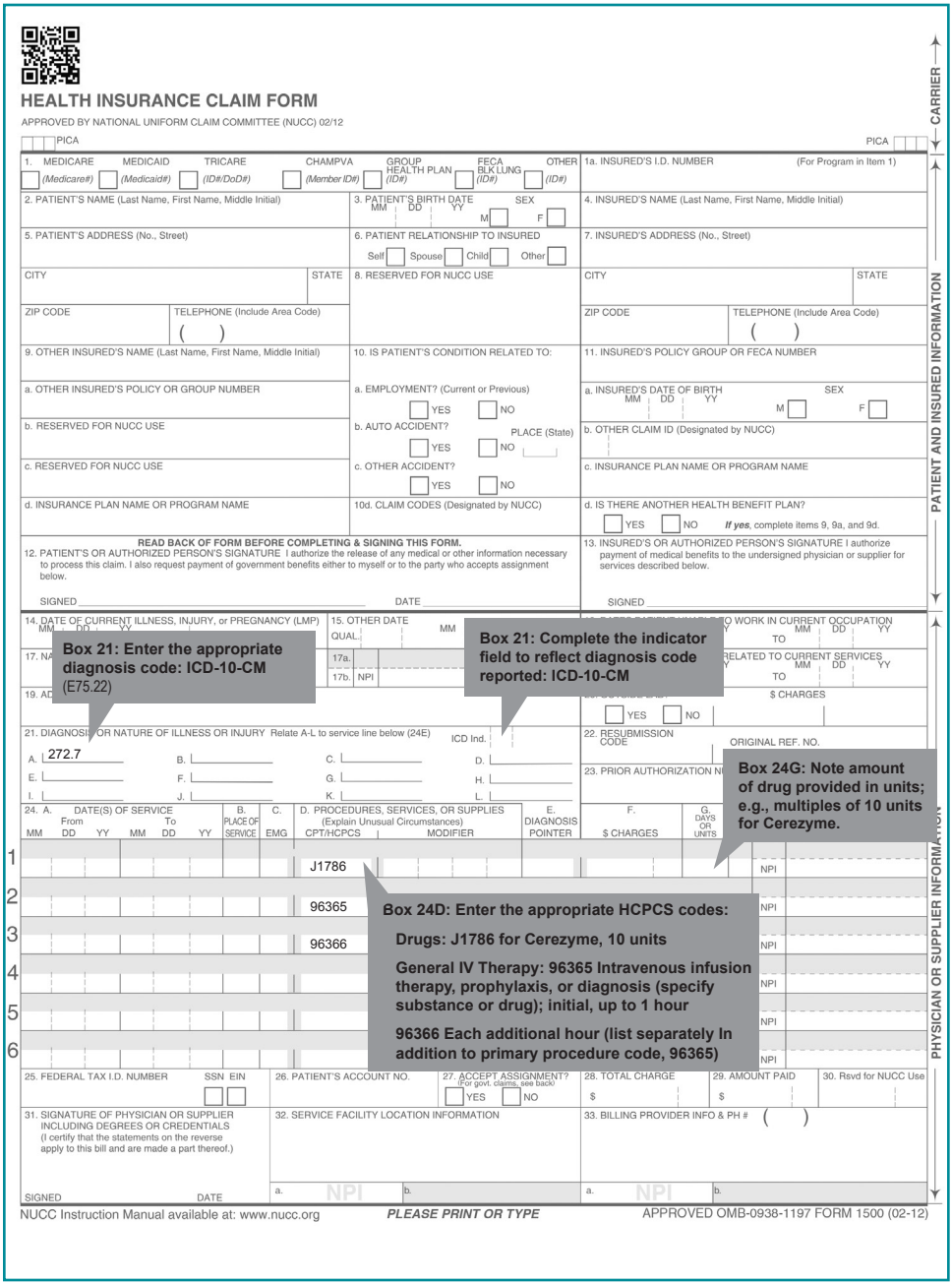
Sample CMS-1450 (UB-04) Claim Form



Please see accompanying full Prescribing Information.

Appendix D

Sample CMS 1500 (02-12) Claim Form



HEALTH INSURANCE CLAIM FORM

APPROVED BY NATIONAL UNIFORM CLAIM COMMITTEE (NUCC) 02/12

PICA

1. MEDICARE (Medicare#) MEDICAID (Medicaid#) TRICARE (ID#/DoD#) CHAMPVA (Member ID#) GROUP HEALTH PLAN (ID#) FECA BLK LUNG (ID#) OTHER (ID#)

1a. INSURED'S I.D. NUMBER (For Program in Item 1)

2. PATIENT'S NAME (Last Name, First Name, Middle Initial)

3. PATIENT'S BIRTH DATE MM DD YY SEX M F

4. INSURED'S NAME (Last Name, First Name, Middle Initial)

5. PATIENT'S ADDRESS (No., Street)

6. PATIENT RELATIONSHIP TO INSURED Self Spouse Child Other

7. INSURED'S ADDRESS (No., Street)

CITY STATE

8. RESERVED FOR NUCC USE

CITY STATE

ZIP CODE TELEPHONE (Include Area Code)

ZIP CODE TELEPHONE (Include Area Code)

9. OTHER INSURED'S NAME (Last Name, First Name, Middle Initial)

10. IS PATIENT'S CONDITION RELATED TO:

11. INSURED'S POLICY GROUP OR FECA NUMBER

a. OTHER INSURED'S POLICY OR GROUP NUMBER

a. EMPLOYMENT? (Current or Previous) YES NO

a. INSURED'S DATE OF BIRTH MM DD YY SEX M F

b. RESERVED FOR NUCC USE

b. AUTO ACCIDENT? PLACE (State) YES NO

b. OTHER CLAIM ID (Designated by NUCC)

c. RESERVED FOR NUCC USE

c. OTHER ACCIDENT? YES NO

c. INSURANCE PLAN NAME OR PROGRAM NAME

d. INSURANCE PLAN NAME OR PROGRAM NAME

10d. CLAIM CODES (Designated by NUCC)

d. IS THERE ANOTHER HEALTH BENEFIT PLAN? YES NO *If yes*, complete items 9, 9a, and 9d.

READ BACK OF FORM BEFORE COMPLETING & SIGNING THIS FORM.

12. PATIENT'S OR AUTHORIZED PERSON'S SIGNATURE I authorize the release of any medical or other information necessary to process this claim. I also request payment of government benefits either to myself or to the party who accepts assignment below.

SIGNED DATE

13. INSURED'S OR AUTHORIZED PERSON'S SIGNATURE I authorize payment of medical benefits to the undersigned physician or supplier for services described below.

SIGNED

14. DATE OF CURRENT ILLNESS, INJURY, or PREGNANCY (LMP) MM DD YY

15. OTHER DATE QUAL. MM

16. DATES PATIENT UNABLE TO WORK IN CURRENT OCCUPATION MM DD YY TO MM DD YY

17. NA

17a.

17b. NPI

RELATED TO CURRENT SERVICES MM DD YY TO

19. AD

$ CHARGES

YES NO

21. DIAGNOSIS OR NATURE OF ILLNESS OR INJURY Relate A-L to service line below (24E) ICD Ind.

A. 272.7 B. C. D.

E. F. G. H.

I. J. K. L.

22. RESUBMISSION CODE ORIGINAL REF. NO.

23. PRIOR AUTHORIZATION N

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

24. A. DATE(S) OF SERVICE From MM DD YY	To MM DD YY	B. PLACE OF SERVICE	C. EMG	D. PROCEDURES, SERVICES, OR SUPPLIES (Explain Unusual Circumstances) CPT/HCPCS	MODIFIER	E. DIAGNOSIS POINTER	F. $ CHARGES	G. DAYS OR UNITS	H.	I.	J.
1				J1786						NPI	
2				96365						NPI	
3				96366						NPI	
4										NPI	
5										NPI	
6										NPI	

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)

25. FEDERAL TAX I.D. NUMBER SSN EIN

26. PATIENT'S ACCOUNT NO.

27. ACCEPT ASSIGNMENT? (For govt. claims, see back) YES NO

28. TOTAL CHARGE $

29. AMOUNT PAID $

30. Rsvd for NUCC Use

31. SIGNATURE OF PHYSICIAN OR SUPPLIER INCLUDING DEGREES OR CREDENTIALS (I certify that the statements on the reverse apply to this bill and are made a part thereof.)

SIGNED DATE

32. SERVICE FACILITY LOCATION INFORMATION

a. NPI b.

33. BILLING PROVIDER INFO & PH # ( )

a. NPI b.

NUCC Instruction Manual available at: www.nucc.org

PLEASE PRINT OR TYPE

APPROVED OMB-0938-1197 FORM 1500 (02-12)

CARRIER

PATIENT AND INSURED INFORMATION

PHYSICIAN OR SUPPLIER INFORMATION

Please see accompanying full Prescribing Information.

Appendix E

Full Prescribing Information

Cerezyme® **Rx Only**
(imiglucerase for injection)
DESCRIPTION

Cerezyme® (imiglucerase for injection) is an analogue of the human enzyme β-glucocerebrosidase, produced by recombinant DNA technology. β-Glucocerebrosidase (β-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 (Trisodium Citrate) (Disodium Hydrogen Citrate)	70 mg (52 mg) (18 mg)	140 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-β-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 β-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** does 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:

- anemia
- thrombocytopenia
- bone disease
- hepatomegaly or splenomegaly

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

PRECAUTIONS
General

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

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Teratogenic Effects

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 postmarketing 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.

Please see accompanying full Prescribing Information.

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

Genzyme Corporation
Cambridge, MA 02142 USA

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

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IMI-FSPL-SL-APR18

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).

Cerezyme®
imiglucerase for injection

Please see enclosed full PRESCRIBING INFORMATION.
Cerezyme.com

SANOFI GENZYME

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