Lumizyme®
(alglucosidase alfa)

A Guide to Lumizyme®(alglucosidase alfa)
Billing and Reimbursement

SANOFI GENZYME

Please see full Prescribing Information, including Boxed WARNING (Appendix E)
and Important Safety Information on pages 3 and 4.

Lumizyme®
(alglucosidase alfa)

Billing Guide Usage

The following is provided for informational 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.

INDICATION

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase (GAA) deficiency).

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, and RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur.

Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and institute appropriate medical treatment.

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on page 4.

Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs.

Risk of Acute Cardiorespiratory Failure: Patients with acute underlying respiratory illness and compromised cardiac and/or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion and some patients may require longer observation times.

Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

Risk of Antibody Development: As with all therapeutic proteins, there is potential for immunogenicity. There is some evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy. Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter.

ADVERSE REACTIONS

The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, alglucosidase alfa may cause fetal harm.

To report Suspected Adverse Reactions, contact Sanofi Genzyme Medical Information at 1-800-745-4447, Option 2

Please see the Full Prescribing Information for complete details, including boxed WARNING.

TABLE OF CONTENTS

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

INTRODUCTION

Pompe disease is a rare, inherited neuromuscular disorder that causes progressive muscle weakness in people of all ages. The disease is named after Johannes C. Pompe, a Dutch doctor who first described the disorder in 1932 in an infant patient. However, Pompe disease can affect people of all ages, with symptoms first occurring at any time from infancy to adulthood.

Pompe disease is caused by a defective gene that results in a deficiency of an enzyme, acid alphaglucosidase (pronounced "AL-fa glue-CO-sih-days" and often abbreviated GAA). The absence of this enzyme results in excessive buildup of a substance called glycogen, a form of sugar that is stored in a specialized compartment of muscle cells throughout the body.

Lumizyme® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency).

Sanofi Genzyme is committed to working with providers, as well as public and private payers, to help ensure access to treatment for whom Lumizyme is indicated. This guide is designed to help you understand coverage, coding, and reimbursement for Lumizyme. 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 a Sanofi Genzyme Case Manager at 1-800-745-4447, option 3, Monday—Friday, 8:00 am—6:00 pm, ET. Sanofi Genzyme Case Managers are professionals with expertise in reimbursement, insurance, case management, and the healthcare delivery system, and can help guide physicians and their patients through the reimbursement process.

WARNINGS AND PRECAUTIONS

Anaphylaxis and Hypersensitivity Reactions:

Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and institute appropriate medical treatment. Appropriate medical support and monitoring measures should be available during infusion.

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SANOFI GENZYME SUPPORT SERVICES

Sanofi Genzyme Case Managers

Sanofi Genzyme assigns individual Case Managers who provide free and confidential care coordination, support, and services to both patients living with Pompe disease and their healthcare providers. Our Case Managers have over 25 years of expertise in insurance coverage, reimbursement, and billing issues for enzyme replacement therapies. Sanofi Genzyme Case Managers can work with physicians and their staff to help coordinate patient's access to treatment with Lumizyme.

Reimbursement Support

With experience navigating the billing and reimbursement process for Lumizyme under many types of insurers and plans, Sanofi Genzyme Case Managers can assist healthcare professionals with the reimbursement process by offering:

- Insurance consultations to review, understand, and verify a patient's coverage for treatment
- Information on billing
- Assistance in obtaining prior authorizations and through the entire coverage approval process
- Assistance in preparing correspondence to third-party payers
- Help educating insurance companies
- Assistance with billing and claims issues, including appeal process if coverage is denied

A Sanofi Genzyme Case Manager is only a phone call away from providing personalized assistance

1-800-745-4447, Option 3

Monday—Friday, 8:00 am to 6:00 pm ET

Information you or your patients provide will always be kept confidential.

Support for Your Patients

By working with a Sanofi Genzyme Case Manager, your patients will receive comprehensive case management and one-on-one support personalized to their individual needs.

- Information about treatment with Lumizyme (Alglucosidase alfa) and related insurance coverage
- Educational materials
- Access to other Sanofi Genzyme resources
- Help for insured, underinsured, and uninsured patients with identifying new coverage or alternative funding resources
- Coordination and exchange of information between patients, their healthcare providers, insurers will always be kept confidential.

Sanofi Genzyme Co-Pay Assistance Program

- The Sanofi Genzyme Co-Pay Assistance Program can help eligible patients who are prescribed treatment with Lumizyme with their drug-related out-of-pocket expenses, including co-pays, co-insurance, and deductibles, regardless of financial status
- Please have your patients call, regardless of financial status their Sanofi Genzyme Case Manager or visit **https://www.sanofigenzyme.com/en/patient-support/patient-services/lumizyme-alglucosidase-alfa-support/** for more information about the Sanofi Genzyme Co-Pay Assistance Program, including current eligibility criteria, eligible expenses, program benefit, and application process
- Sanofi Genzyme reserves the right to make eligibility determinations, to set program benefit maximums, to monitor participation, and to modify or discontinue the program at any time

Product Information

To learn more about Lumizyme, please visit www.Lumizyme.com and please see full Prescribing Information, including Boxed Warning, in Appendix E.

Updates to This Guide

This guide is reviewed and updated periodically. As reimbursement information is subject to continuing changes, please contact a Sanofi Genzyme Case Manager for the most up-to-date information.

LUMIZYME® (alglucosidase alfa) COVERAGE

Private Payers

Alglucosidase alfa 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 Lumizyme
- Periodic reauthorization or recertification for continued treatment
- Letter of Intent to Treat. See the example in Appendix A, page 15
- Statement of Medical Necessity. See the example in Appendix B, page 16

Note

- If the patient's private insurer denies coverage, an appeal process may be initiated. Sanofi Genzyme 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 confirm coverage prior to treatment, so the patient's coverage policy should be understood before treatment is initiated. Treatment with Lumizyme will need to be considered medically necessary in order to be covered under the Medicare program. Lumizyme 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, Lumizyme 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 Lumizyme

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 Lumizyme, the Medicare Managed Care Plan must also cover Lumizyme, although prior authorization and other medical management approaches may be required by the managed care plan.

Medicare Part D Prescription Drug Coverage

Lumizyme may be on formulary under the patient's medicare 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 contact a Sanofi Genzyme Case Manager 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 Lumizyme will need to be considered medically necessary in order to be covered under the Medicaid program. Depending on the state, initial treatment with Lumizyme may require prior approval by the state Medicaid program. For information on Medicaid coverage for Lumizyme in your state, contact your local Medicaid office or a Sanofi Genzyme Case Manager.

Medicaid agencies may require the following:

- Prior authorization to establish medical necessity for Lumizyme
- Periodic reauthorization or recertification for continued treatment
- Letter of Intent to Treat. See the example in Appendix A, page 15
- Statement of Medical Necessity. See the example in Appendix B, page 16

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. Sanofi Genzyme Case Managers are available to assist patients and work with their physicians with 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 Lumizyme 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 Lumizyme in your state, contact the Medicaid Managed Care plan or a Sanofi Genzyme Case Manager.

LUMIZYME® (alglucosidase alfa) REIMBURSEMENT

Obtaining reimbursement for Lumizyme® (alglucosidase alfa) varies by payer and setting.

Private Payers, Medicare 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 Lumizyme 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 Lumizyme 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

LUMIZYME BILLING CODES

The following is provided for informational 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.

ICD-10-CM	E74.02 Pompe Disease
NDC	58468-0160-1 carton of 1 single-use vial 58468-0160-2 carton of 10 single-use vials
HCPCS	J0221 Injection, alglucosidase alfa (Lumizyme), 10 mg
CPT	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 Pompe 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 a Sanofi Genzyme Case Manager
- To help avoid potential problems obtaining reimbursement, the treating physician should request written confirmation of coverage from the third-party payer prior to initiation of enzyme replacement therapy. A Sanofi Genzyme Case Manager can assist in obtaining written authorization for Lumizyme treatment

WARNINGS AND PRECAUTIONS

Immune-Mediated Reactions:

Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs.

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

CODING GLOSSARY OF TERMS

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

ICD-10-CM is a revision to the ICD-9-CM system to classify and code all diagnoses. These codes are used by hospitals and physicians, and are recognized by all insurers.

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.

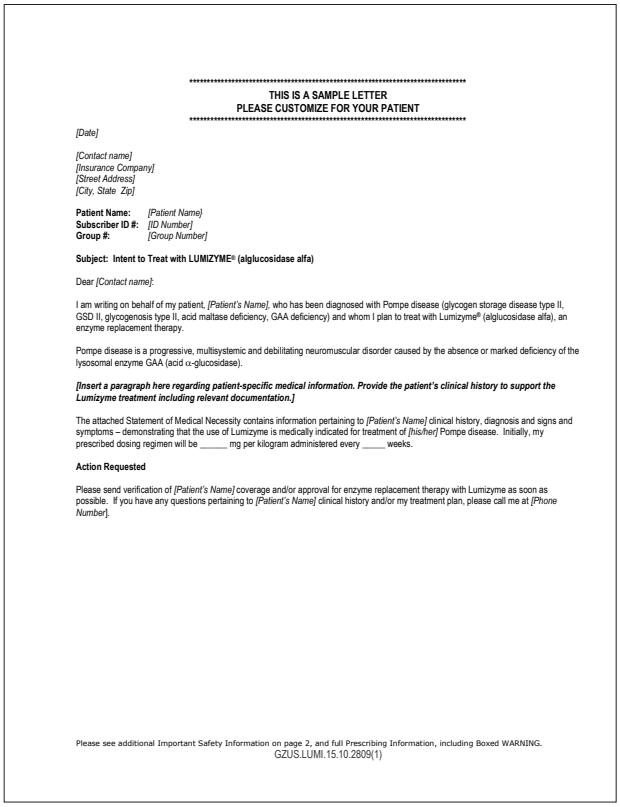
WARNINGS AND PRECAUTIONS

Risk of Acute Cardiorespiratory Failure:

Patients with acute underlying respiratory illness and compromised cardiac and/or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion and some patients may require longer observation times.

Appendix A

Sample Letter of Intent to Treat



****
THIS IS A SAMPLE LETTER
PLEASE CUSTOMIZE FOR YOUR PATIENT
****

[Date]

[Contact name]
[Insurance Company]
[Street Address]
[City, State Zip]

Patient Name: *[Patient Name]*
Subscriber ID #: *[ID Number]*
Group #: *[Group Number]*

Subject: Intent to Treat with LUMIZYME® (alglucosidase alfa)

Dear *[Contact name]*:

I am writing on behalf of my patient, *[Patient's Name]*, who has been diagnosed with Pompe disease (glycogen storage disease type II, GSD II, glycogenosis type II, acid maltase deficiency, GAA deficiency) and whom I plan to treat with Lumizyme® (alglucosidase alfa), an enzyme replacement therapy.

Pompe disease is a progressive, multisystemic and debilitating neuromuscular disorder caused by the absence or marked deficiency of the lysosomal enzyme GAA (acid α-glucosidase).

[Insert a paragraph here regarding patient-specific medical information. Provide the patient's clinical history to support the Lumizyme treatment including relevant documentation.]

The attached Statement of Medical Necessity contains information pertaining to *[Patient's Name]* clinical history, diagnosis and signs and symptoms – demonstrating that the use of Lumizyme is medically indicated for treatment of *[his/her]* Pompe disease. Initially, my prescribed dosing regimen will be _____ mg per kilogram administered every _____ weeks.

Action Requested

Please send verification of *[Patient's Name]* coverage and/or approval for enzyme replacement therapy with Lumizyme as soon as possible. If you have any questions pertaining to *[Patient's Name]* clinical history and/or my treatment plan, please call me at *[Phone Number]*.

Please see additional Important Safety Information on page 2, and full Prescribing Information, including Boxed WARNING.
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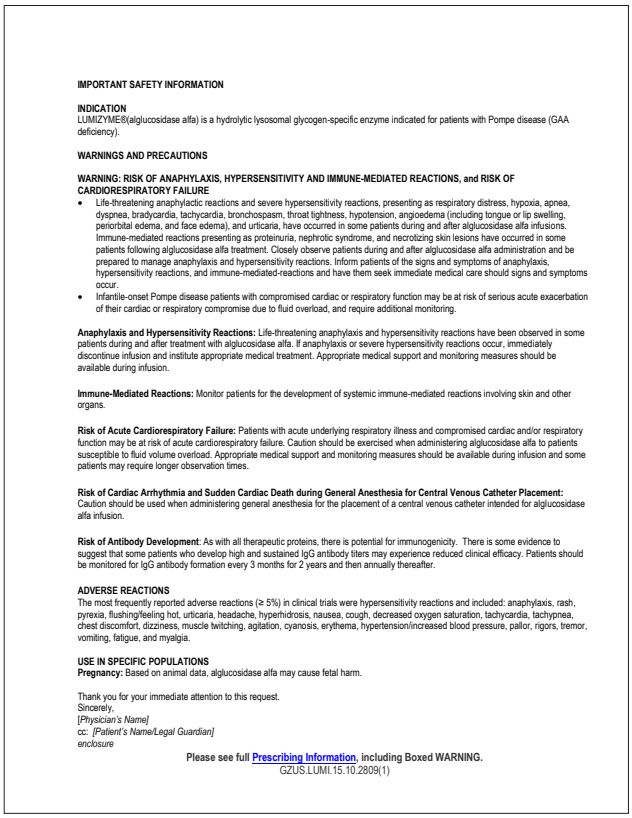

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Risk of Antibody Development: As with all therapeutic proteins, there is potential for immunogenicity. There is some evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy. Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter.

ADVERSE REACTIONS
The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

USE IN SPECIFIC POPULATIONS
Pregnancy: Based on animal data, alglucosidase alfa may cause fetal harm.

Thank you for your immediate attention to this request.
Sincerely,
[Physician's Name]
cc: [Patient's Name/Legal Guardian]
enclosure

Please see full Prescribing Information, including Boxed WARNING.
GZUS.LUMI.15.10.2809(1)

Please see full Prescribing Information, including Boxed Warning available at www.lumizyme.com

GZUS.LUMI.15.10.28091

This is only a model letter and should be customized to address patients' specific issues.
Call a Sanofi Genzyme Case Manager to request a sample Letter of Intent to Treat.

Please see full Prescribing Information, including Boxed WARNING (Appendix E)
and Important Safety Information on pages 3 and 4.

Appendix B

Sample Statement of Medical Necessity

STATEMENT OF MEDICAL NECESSITY

FOR THE TREATMENT OF POMPE DISEASE

Patient Information

Patient Name:	Address:
Date Of Birth:	City: State: Zip:
Gender: □ Male □ Female	Phone No. (Home):
	Phone No. (Work):

Insurance Information

Insurance Co.:	Policy Holder Name:
Subscriber ID No.:	Insurance Phone No.:
Group No.:	

Medical Assessment

Patient Weight:_____ (kg/lb) **Patient Height**:_____ (cm/in)

Respiratory: **Musculoskeletal**

Cardiac: **Other:**

Enclosures <include patient medical history, full prescribing information, additional supporting clinical documents>

Diagnosis

Pompe Disease E74.02: Date of Confirmed Diagnosis:_____ **Was Dried Blood Spot**

Testing used to identify this patient? Yes No ☐ ☐

How was the diagnosis confirmed? Confirmation REQUIRES the presence of #1 OR #2 below

1.	☐ **GAA Enzyme Activity (must be reduced or absent)**: Value:_____ (units) Date:_____ Normal Reference Range:_____ for laboratory & sample	**Sample Type:** ☐Blood [ ] Purified Lymphocytes [ ] Mixed Leukocytes ☐Muscle Tissue ☐Cultured Skin Fibroblasts
2.	☐ **GAA Gene Sequencing** Date:_____ List DNA sequence changes 1._____ 2._____	**Additional information (if needed):**

Treatment Recommendation

Lumizyme® (alglucosidase alfa) **NDC #: 58468-0160-1 (carton of 1 single-use vial)**
NDC #: 58468-0160-2 (carton of 10 single-use vials)

Dose: _____**mg/kg** **Frequency:** _____

Therapy Start Date:_____

Physician Authorization

I certify that the above-indicated therapy is medically necessary, and the information provided is accurate to the best of my knowledge.

Physician Name (printed):_____ Date:_____

Address_____City_____State_____Zip_____
Phone No._____

Physician Signature:_____

Physician's Medical License No._____ **State Issued:**_____

Please see full Prescribing Information, including Boxed Warning attached to this form or available at www.lumizyme.com

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WARNINGS AND PRECAUTIONS

Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement:

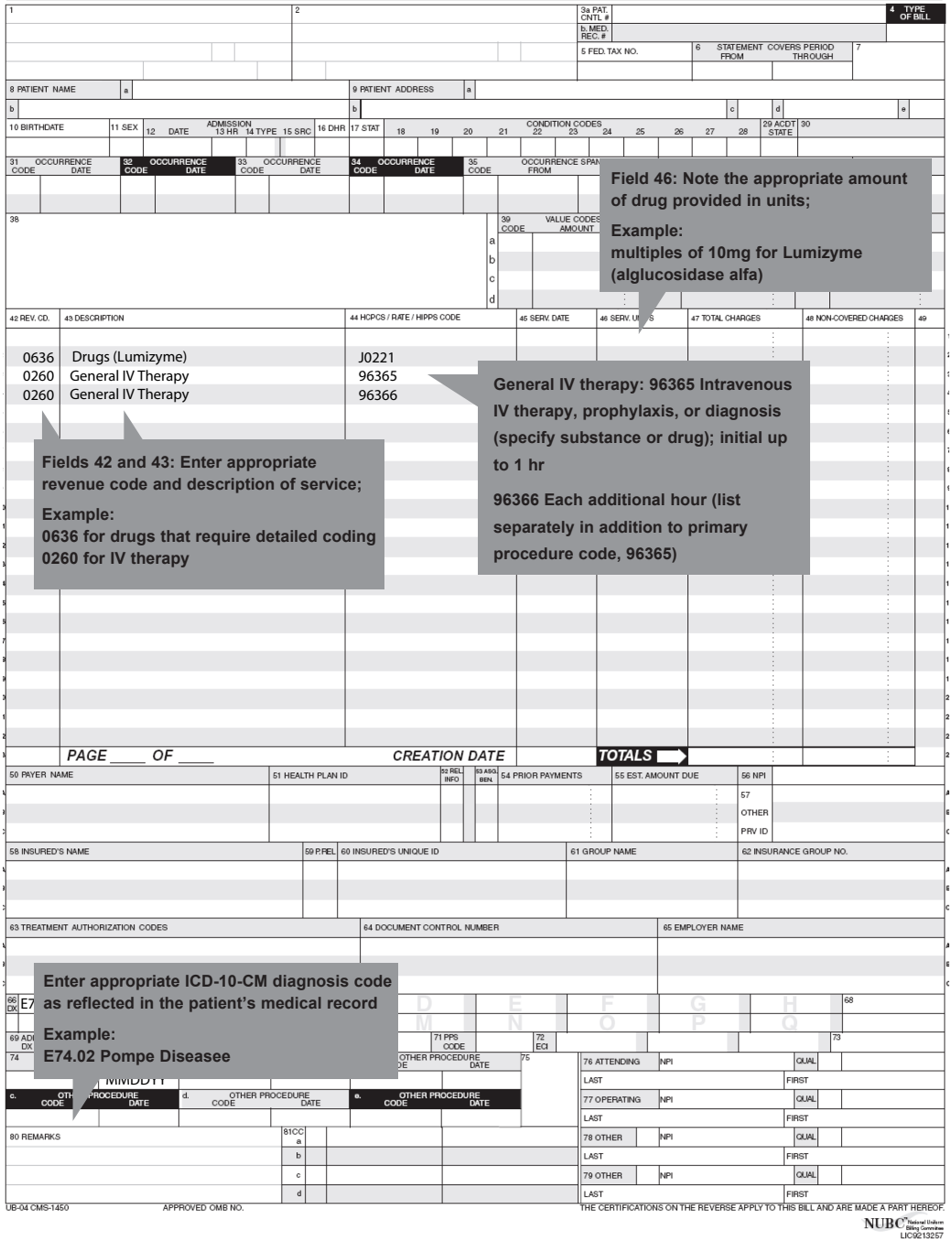
Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion.

Call a Genzyme Case Manager to request a Statement of Medical Necessity form.

Appendix C

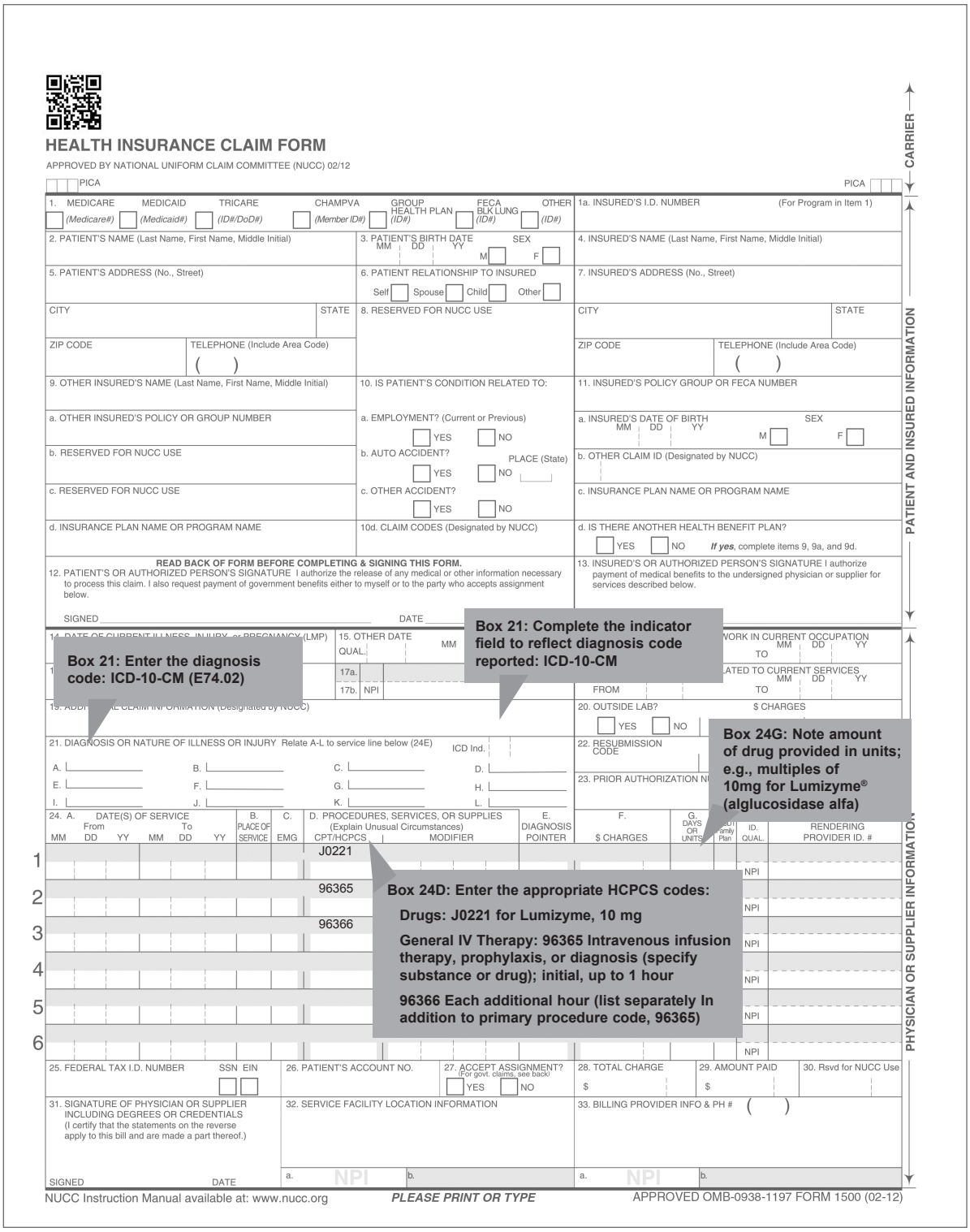
Sample CMS-1450 (UB-04) Claim Form

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.



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.

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

15. OTHER DATE QUAL. MM

WORK IN CURRENT OCCUPATION MM DD YY TO

17a.

17b. NPI

LATED TO CURRENT SERVICES MM DD YY FROM TO

19. ADDITIONAL CLAIM INFORMATION (Designated by NUCC)

20. OUTSIDE LAB? YES NO $ CHARGES

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

A. B. C. D.

E. F. G. H.

I. J. K. L.

22. RESUBMISSION CODE

23. PRIOR AUTHORIZATION N

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	ID. QUAL.	RENDERING PROVIDER ID. #
1				J0221					NPI	
2				96365					NPI	
3				96366					NPI	
4									NPI	
5									NPI	
6									NPI	

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

Box 21: Enter the diagnosis code: ICD-10-CM (E74.02)

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 10mg for Lumizyme® (alglucosidase alfa)

Box 24D: Enter the appropriate HCPCS codes:

Drugs: J0221 for Lumizyme, 10 mg

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)

Questions? Contact a Sanofi Genzyme Case Manager at 1-800-745-4447, option 3 | www.Lumizyme.com

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

Appendix E
Full Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LUMIZYME® (alglucosidase alfa), for injection, for intravenous use

Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, and RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

- **Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur (5.1, 5.2).**
- **Infantile-onset Pompe patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring (5.3).**

RECENT MAJOR CHANGES

• Boxed Warning	08/2014
• Indications and Usage (1)	08/2014
• Warnings and Precautions (5)	08/2014

INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency) (1).

DOSAGE AND ADMINISTRATION

- 20 mg per kg body weight administered every 2 weeks as an intravenous infusion (2).

DOSAGE FORMS AND STRENGTHS

- For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-use vial for reconstitution (3).

CONTRAINDICATIONS

- None (4).

WARNINGS AND PRECAUTIONS

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment (5.1).
- Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs (5.2).
- Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion (5.3).
- Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion (5.4).

ADVERSE REACTIONS

- The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia (6.1).

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

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2014

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

Appendix E

Full Prescribing Information - Continued

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur [*see Warnings and Precautions (5.1, 5.2)*].

Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) *[see Description (11)]* is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase (GAA) deficiency).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage of alglucosidase alfa is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.

2.2 Instructions for Use

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the end of each step. If the patient is stable, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate hypersensitivity reactions. In the event of anaphylaxis or severe hypersensitivity reaction, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. See *Table 1* below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Appendix E
Full Prescribing Information - Continued

Table 1: Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/ kg/hr (mL/hr)	Step 2 3 mg/ kg/hr (mL/hr)	Step 3 5 mg/ kg/hr (mL/hr)	Step 4 7 mg/ kg/hr (mL/hr)
1.25–10	50	3	8	13	18
10.1–20	100	5	15	25	35
20.1–30	150	8	23	38	53
30.1–35	200	10	30	50	70
35.1–50	250	13	38	63	88
50.1–60	300	15	45	75	105
60.1–100	500	25	75	125	175
100.1–120	600	30	90	150	210
120.1–140	700	35	105	175	245
140.1–160	800	40	120	200	280
160.1–180	900	45	135	225	315
180.1–200	1,000	50	150	250	350

2.3 Reconstitution, Dilution, and Administration

Alglucosidase alfa should be reconstituted, diluted and administered by a healthcare professional.

Use aseptic technique during preparation. Do not use filter needles during preparation.

a. Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg.

   Patient weight (kg) x dose (mg/kg) = patient dose (in mg)

   Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

   Example: Patient weight (68 kg) x dose (20 mg/kg) = patient dose (1,360 mg) 1,360 mg divided by 50 mg/vial = 27.2 vials; therefore, 28 vials should be reconstituted.

   Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

b. Reconstitute each alglucosidase alfa vial by slowly injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. Each vial will yield a concentration of 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Tilt and roll each vial gently. Do not invert, swirl, or shake.

c. The reconstituted alglucosidase alfa solution should be protected from light.

d. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.

e. Alglucosidase alfa should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final alglucosidase alfa concentration of 0.5 to 4 mg/mL. See *Table 1* for the recommended total infusion volume based on patient weight.

f. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.

g. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of alglucosidase alfa to air-liquid interfaces.

h. Add the reconstituted alglucosidase alfa solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.

i. Gently invert or massage the infusion bag to mix. Do not shake.

j. Administer alglucosidase alfa using an in-line low protein binding 0.2 µm filter.

k. Do not infuse alglucosidase alfa in the same intravenous line with other products.

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2°C to 8°C (36°F to 46°F). Storage of the reconstituted solution at room temperature is not recommended. The reconstituted and diluted alglucosidase alfa solution should be protected from light. Do not freeze or shake.

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of alglucosidase alfa is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder in a single-use vial for reconstitution. After reconstitution, the resultant solution concentration is 5 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions have been observed in patients during and up to 3 hours after alglucosidase alfa infusion. Some of the reactions were life-threatening and included anaphylactic shock, cardiac arrest, respiratory arrest, respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria. Other accompanying reactions included chest discomfort/pain, wheezing, tachypnea, cyanosis, decreased oxygen saturation, convulsions, pruritus, rash, hyperhidrosis, nausea, dizziness, hypertension/increased blood pressure, flushing/feeling hot, erythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and paresthesia. Some of these reactions were IgE-mediated.

If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. Severe reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis, epinephrine has been administered. Appropriate medical

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

support, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa is administered.

The risks and benefits of re-administering alglucosidase alfa following an anaphylactic or hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product [*see Adverse Reactions (6.2)*].

5.2 Immune-Mediated Reactions

Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrotizing skin lesions [*see Adverse Reactions (6.3)*]. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with pyrexia and elevated erythrocyte sedimentation rate. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in some Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-rhGAA IgG antibody titers. In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. Therefore, patients receiving alglucosidase alfa should undergo periodic urinalysis *[see Adverse Reactions (6.3)*].

Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune-mediated reactions occur, consider discontinuation of the administration of alglucosidase alfa, and initiate appropriate medical treatment. The risks and benefits of re-administering alglucosidase alfa following an immune-mediated reaction should be considered. Some patients have been able to be rechallenged and have continued to receive alglucosidase alfa under close clinical supervision.

5.3 Risk of Acute Cardiorespiratory Failure

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Appropriate medical support and monitoring measures should be readily available during alglucosidase alfa infusion, and some patients may require prolonged observation times that should be individualized based on the needs of the patient. Acute cardiorespiratory failure has been observed in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa *[see Dosage and Administration (2.2)]*.

5.4 Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Venous Catheter Placement

Administration of general anesthesia can be complicated by the presence of severe cardiac and skeletal (including respiratory) muscle weakness. Therefore, caution should be used when administering general anesthesia. Ventricular arrhythmias and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy during general anesthesia for central venous catheter placement.

5.5 Risk of Antibody Development

As with all therapeutic proteins, there is potential for immunogenicity. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy to alglucosidase alfa treatment, such as loss of motor function, ventilator dependence, or death. The effect of antibody development on the long term efficacy of alglucosidase alfa is not fully understood.

Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter. Testing for IgG titers may also be considered if patients develop hypersensitivity reactions, other immune-mediated reactions, or lose clinical response. Patients who experience reduced clinical response may also be tested for inhibitory antibody activity. Patients who experience anaphylactic or hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis *[see Adverse Reactions (6.2)]*.

There are currently no marketed tests for antibodies against alglucosidase alfa; however, a testing service is provided by Genzyme. Contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447 for information on testing and to obtain a sample collection box.

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 clinical practice.

The following serious adverse reactions are described below and elsewhere in the labeling:

- Anaphylaxis and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

In clinical trials, the most common adverse reactions (≥ 5%) following alglucosidase alfa treatment were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease

Two multicenter, open-label clinical trials were conducted in 39 infantile-onset Pompe disease patients, ages 1 month to 3.5 years old. Approximately half of the patients (54%) were male. Patients were treated with alglucosidase alfa 20 or 40 mg/kg every other week for periods ranging from 1 to 106 weeks (mean: 61 weeks).

The most serious adverse reactions reported with alglucosidase alfa treatment included anaphylaxis and acute cardiorespiratory failure.

The most common adverse reactions requiring intervention in clinical trials were hypersensitivity reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa, and included rash, pyrexia, urticaria, flushing, decreased oxygen saturation, cough, tachypnea, tachycardia, hypertension/increased blood pressure, pallor, rigors, vomiting, cyanosis, agitation, and tremor. These reactions were more likely to occur with higher infusion rates. Some patients who were pre-treated with antihistamines, antipyretics and/or corticosteroids still experienced hypersensitivity reactions.

Table 2 summarizes all adverse reactions occurring in ≥ 5% of patients (2 or more patients) treated with alglucosidase alfa in clinical trials described above.

Appendix E

Full Prescribing Information - Continued

Table 2: Adverse Reactions that Occurred in At Least 5% of Infantile-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials

	Number of Patients (N=39) n (%)
Adverse Reaction	**20 (51)**
Rash (including rash erythematous, rash macular and maculo-papular)	7 (18)
Pyrexia	6 (15)
Urticaria	5 (13)
Flushing	5 (13)
Hypertension/Increased Blood Pressure	4 (10)
Decreased Oxygen Saturation	3 (8)
Cough	3 (8)
Tachypnea	3 (8)
Tachycardia	3 (8)
Erythema	2 (5)
Vomiting	2 (5)
Rigors	2 (5)
Pallor	2 (5)
Cyanosis	2 (5)
Agitation	2 (5)
Tremor	2 (5)

An open-label, single-center trial was conducted in 18 treatment-naïve infantile-onset Pompe disease patients who were treated exclusively with alglucosidase alfa. Adverse reactions observed in these patients were similar to infantile-onset Pompe disease patients who received alglucosidase alfa in other clinical trials.

Additional hypersensitivity reactions observed in infantile-onset Pompe disease patients treated in other clinical trials and expanded access programs with alglucosidase alfa included livedo reticularis, irritability, retching, increased lacrimation, ventricular extrasystoles, nodal rhythm, rales, respiratory tract irritation, and cold sweat.

Safety was also evaluated in 99 patients (51 male, 48 females) with Pompe disease in an ongoing, open-label, prospective study in patients 12 months of age and older who were previously treated with the 160 L scale of alglucosidase alfa and switched to the 4000 L scale of alglucosidase alfa. Patients were aged 1 to 18 years with a median duration of treatment of 437 days (range 13 to 466 days). No new safety findings were observed following the switch to 4000 L scale of alglucosidase alfa.

Clinical Trials in Late-Onset Pompe Disease

Assessment of adverse reactions in patients with late-onset Pompe disease is based on the exposure of 90 patients (45 male, 45 female), aged 10 to 70 years, to 20 mg/kg alglucosidase alfa or placebo in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received alglucosidase alfa or placebo every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. Two patients receiving alglucosidase alfa discontinued the trial due to anaphylactic reactions.

Serious adverse reactions reported with alglucosidase alfa included anaphylaxis, which presented as angioedema, throat tightness and chest pain/discomfort. One patient with a history of Wolff-Parkinson-White syndrome experienced a serious adverse reaction of supraventricular tachycardia.

The most common adverse reactions (≥ 3%; 2 or more patients) observed in alglucosidase alfa-treated patients were hypersensitivity reactions and included anaphylaxis, headache, nausea, urticaria, dizziness, chest discomfort, vomiting, hyperhidrosis, flushing/feeling hot, increased blood pressure, paresthesia, pyrexia, local swelling, diarrhea, pruritus, rash, and throat tightness.

Delayed-onset reactions, defined as adverse reactions occurring 2 - 48 hours after completion of alglucosidase alfa infusion, that were observed in ≥ 3% more patients in the alglucosidase alfa-treated group compared to patients in the placebo-treated group in the controlled trial, included hyperhidrosis. Additional delayed-onset reactions occurring in alglucosidase alfa-treated patients included fatigue, myalgia, and nausea. Patients should be counseled about the possibility of delayed-onset hypersensitivity reactions and given proper follow-up instructions.

Table 3 summarizes the most common adverse reactions that occurred in at least 3% of alglucosidase alfa-treated patients and with a higher incidence than the placebo-treated patients during the randomized, double-blind, placebo-controlled study described above.

Table 3: Adverse Reactions Occurring in at Least 3% of Alglucosidase Alfa-Treated Late-Onset Patients and with a Higher Incidence than the Placebo-Treated Patients

Adverse Reaction	Alglucosidase Alfa n=60 N (%)	Placebo n=30 N (%)
Hyperhidrosis	5 (8.3)	0 (0)
Urticaria	5 (8.3)	0 (0)
Anaphylaxis	4 (6.7)	0 (0)
Chest Discomfort	4 (6.7)	1 (3.3)
Muscle Twitching	4 (6.7)	1 (3.3)
Myalgia	3 (5.0)	1 (3.3)
Flushing/Feeling Hot	3 (5.0)	0 (0)
Increased Blood Pressure	3 (5.0)	0 (0)
Vomiting	3 (5.0)	0 (0)
Edema, Peripheral	2 (3.3)	0 (0)
Pruritus	2 (3.3)	0 (0)
Rash Papular	2 (3.3)	0 (0)
Throat Tightness	2 (3.3)	0 (0)

In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion interruption, decreased infusion rate, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions, epinephrine was administered. Patients who have experienced anaphylaxis or hypersensitivity reactions should be treated with caution when they are re-administered alglucosidase alfa.

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The data reflect the percentage of patients whose test results were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and confirmed by a radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies.

In the two clinical trials in infantile-onset patients, the majority of patients (34 of 38; 89%) tested positive for IgG antibodies to alglucosidase alfa. There is evidence to suggest that some patients who develop high sustained titers of anti-alglucosidase alfa antibodies may experience reduced clinical efficacy to alglucosidase alfa treatment *[see Warnings and Precautions (5.5)]*. Some IgG-positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays. Furthermore, CRIM-negative infants have shown reduced clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity. Alglucosidase alfa-treated patients who experience a decrease in motor function should be tested for the presence of inhibitory antibodies that neutralize enzyme uptake or activity.

In the randomized, double-blind, placebo-controlled trial in late-onset patients, all alglucosidase alfa-treated patients with available samples (N=59, 100%) developed IgG antibodies to alglucosidase alfa. Most patients who developed IgG antibodies did so within the first 3 months of exposure (median time to seroconversion was 4 weeks). There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions.

None of the 59 evaluable patients tested positive for inhibition of enzyme activity. Antibody titers for cellular uptake inhibition were present in 18 of 59 (31%) patients by Week 78. All other patients tested negative for inhibition of cellular uptake. Patients who tested positive for uptake inhibition tended to have higher IgG titers than patients who tested negative for uptake inhibition. Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for uptake inhibition. The clinical relevance of this *in vitro* inhibition is not fully understood. The clearance values for 4 of these 5 patients were approximately 1.2- to 1.8-fold greater in the presence of inhibitory antibodies (Week 52) as compared to in the absence of inhibitory antibodies (Week 0) *[see Clinical Pharmacology (12.3)]*.

Some patients in the clinical studies or in the postmarketing setting have undergone testing for alglucosidase alfa-specific IgE antibodies. Testing was performed in patients who experienced moderate to severe or recurrent hypersensitivity reactions, for which mast-cell activation was suspected. Some of the patients who tested positive for alglucosidase alfa-specific IgE antibodies experienced anaphylactic reactions [*see Boxed Warning and Warnings and Precautions (5.1)]*.

Some patients who tested positive for alglucosidase alfa-specific IgE antibodies and experienced hypersensitivity reactions were able to be rechallenged with alglucosidase alfa using a slower infusion rate at lower starting doses and have continued to receive treatment under close clinical supervision *[see Warnings and Precautions (5.1)]*. Since patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for developing anaphylaxis and hypersensitivity reactions, these patients should be monitored more closely during administration of alglucosidase alfa.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alglucosidase alfa with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alglucosidase alfa. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In postmarketing experience with alglucosidase alfa, serious adverse reactions have been reported, including anaphylaxis *[see Boxed Warning and Warnings and Precautions (5.1)]*. Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy *[see Boxed Warning and Warning and Precautions (5.3)]*.

Recurrent reactions consisting of flu-like illness or a combination of events such as pyrexia, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for 1 - 3 days have been observed in some patients treated with alglucosidase alfa. The majority of patients were able to be rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and were able to continue treatment under close clinical supervision.

In addition to the hypersensitivity reactions reported in clinical trials *[see Adverse Reactions (6.1)]*, the following hypersensitivity reactions have been reported in at least 2 patients and included: anaphylactic shock, respiratory failure, respiratory arrest, cardiac arrest, hypoxia, dyspnea, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor, pharyngeal edema, abdominal pain, apnea, muscle spasm, and conjunctivitis. In addition, one case of hyperparathyroidism has been reported.

Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome secondary to membranous glomerulonephritis, and necrotizing skin lesions have been reported in postmarketing safety experience with alglucosidase alfa *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

No drug interaction or *in vitro* metabolism studies were performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There is a registry for Pompe disease patients that monitors the outcomes of women and their offspring exposed to alglucosidase alfa during pregnancy. Patients or their physicians should call 1-800-745-4447 or visit www.pomperegistry.com to enroll [*see Patient Counseling Information (17)]*.

Risk Summary

There are no studies of alglucosidase alfa in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed in mice or rabbits given daily administration of alglucosidase alfa up to 0.4 or 0.5 times the human steady-state AUC (area under the plasma concentration-time curve), respectively, at the recommended human bi-weekly dose during the period of organogenesis. An increase in pup mortality was observed when alglucosidase alfa was administered every other day in mice during the period of organogenesis through lactation at a dose 0.4 times the human steady-state AUC at the recommended human bi-weekly dose. Alglucosidase alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

All reproductive studies included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of alglucosidase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous (IV) administration of alglucosidase alfa up to 40 mg/kg in mice and rabbits (0.4 and 0.5 times the human steady-state AUC, respectively, at the recommended bi-weekly dose) during the period of organogenesis had no effects on embryo-fetal development. Administration of 40 mg/kg IV every other day in mice (0.4 times the human steady-state AUC at the recommended bi-weekly dose) during the period of organogenesis through lactation produced an increase in mortality of offspring during the lactation period.

8.3 Nursing Mothers

Alglucosidase alfa is present in human milk. In one case report, the enzymatic activity of alglucosidase alfa was detected in the breast milk of a lactating woman up to 24 hours after the end of intravenous alglucosidase alfa administration. To minimize infant exposure to alglucosidase alfa, a nursing mother may temporarily pump and discard breast milk produced during the 24 hours after administration of alglucosidase alfa. Exercise caution when administering alglucosidase alfa to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of alglucosidase alfa have been established in pediatric patients with Pompe disease.

The safety and effectiveness of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials *[see Clinical Studies (14.1)]*.

The safety and effectiveness of alglucosidase alfa were assessed in pediatric patients with late (non-infantile) onset Pompe disease in a randomized, double-blind, placebo-controlled study in 90 patients, including 2 patients 16 years of age or less *[see Clinical Studies (14.2)]*.

Anaphylaxis, hypersensitivity reactions, and acute cardiorespiratory failure have occurred in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.1, 5.3)]*. Additionally, cardiac arrhythmia and sudden cardiac death have occurred in pediatric patients during general anesthesia for central venous catheter placement *[see Warnings and Precautions (5.4)]*.

8.5 Geriatric Use

The randomized, double-blind, placebo-controlled study of alglucosidase alfa did not include sufficient numbers (n=4) of patients aged 65 years and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.1)]*.

11 DESCRIPTION

Alglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human acid α-glucosidase (GAA) gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6-glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3.6 to 5.4 units/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 micromole of synthetic substrate per minute under specified assay conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5 mg/mL alglucosidase alfa. Alglucosidase alfa does not contain preservatives; each vial is for single use only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pompe disease (acid maltase deficiency, glycogen storage disease type II, GSD II, glycogenosis type II) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA.

Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted for alglucosidase alfa.

12.3 Pharmacokinetics

The pharmacokinetics of alglucosidase alfa were evaluated in 13 patients with infantile-onset Pompe disease, aged 1 month to 7 months, who received 20 mg/kg (approximately as a 4-hour infusion) or 40 mg/kg (approximately as a 6.5-hour infusion) of alglucosidase alfa every 2 weeks. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and 40 mg/kg doses. Based on the pharmacokinetic blood samples collected for 12 hours after a 4-hour intravenous infusion of 20 mg/kg (n=5), the estimated mean AUC was 811 mcg•hr/mL with 17% coefficient of variation [CV], C_{max} was 162 mcg/mL with 19% CV, clearance was 25 mL/hr/kg with 16% CV, and half-life was 2.3 hours with 17% CV.

The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial of 14 patients with infantile-onset Pompe disease, aged 6 months to 3.5 years, who received 20 mg/kg of alglucosidase alfa as a 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the infantile-onset Pompe disease patients aged 1 month to 7 months who received the 20 mg/kg dose.

Nineteen of 21 patients who received treatment with alglucosidase alfa and had pharmacokinetics and antibody titer data available at Week 12 developed antibodies to alglucosidase alfa. Five patients with antibody titers ≥ 12,800 at Week 12 had an average increase in clearance of 50% (range 5% to 90%) from Week 1 to Week 12. The other 14 patients with antibody titers < 12,800 at Week 12 had similar average clearance values at Week 1 and Week 12.

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

Appendix E
Full Prescribing Information - Continued

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with alglucosidase alfa.

Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg (0.4 times the human AUC at the recommended bi-weekly dose) had no effect on fertility and reproductive performance.

14 CLINICAL STUDIES

14.1 Clinical Trials in Infantile-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials.

Study 1 was an international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe disease patients. This study was conducted between 2003 and 2005. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at study entry. Fourteen patients were Cross Reactive Immunologic Material (CRIM) positive and 4 patients were CRIM-negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age with the mortality experience of a historical cohort of untreated infantile-onset Pompe disease patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilator support, whereas only one of the 61 (2%) historical control patients was alive. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

Other outcome measures in this study included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Study 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 infantile-onset patients aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM-positive and 3 patients were CRIM-negative. All patients received 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52–week interim analysis, 16 of 21 patients were alive. Sixteen patients were free of invasive ventilatory support at the time of first infusion; of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52.

Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

14.2 Clinical Trials in Late-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

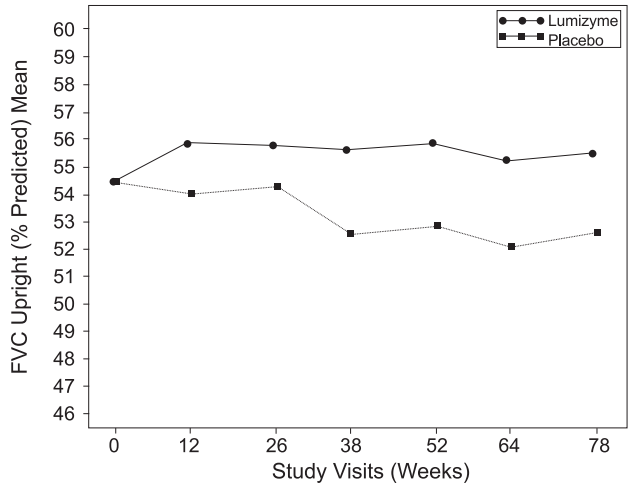
A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event, two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of % predicted FVC in the alglucosidase alfa-treated patients was observed *(see Figure 1)*.

Appendix E

Full Prescribing Information - Continued

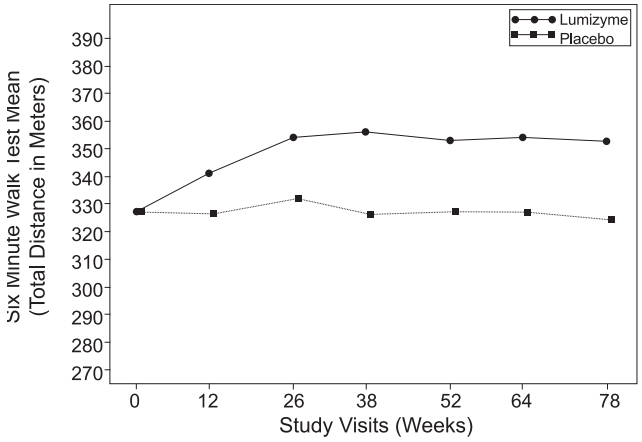
Figure 1: Mean FVC Upright (% Predicted) Over Time



Note: ANCOVA least squares means adjusting for baseline values

At study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval: [-1 to 52 meters]; p=0.06) *(see Figure 2)*.

Figure 2: Mean Six Minute Walk Test Total Distance Walked Over Time



Note: ANCOVA least squares means adjusting for baseline values

16 HOW SUPPLIED/STORAGE AND HANDLING

LUMIZYME 50 mg vials are supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-use vials.

NDC 58468-0160-1 (Carton of one single-use vial)

NDC 58468-0160-2 (Carton of ten single-use vials)

Store LUMIZYME under refrigeration between 2°C to 8°C (36°F to 46°F). Do not use LUMIZYME after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

Anaphylaxis, Hypersensitivity and Immune-Mediated Reactions

Advise the patients and caregivers that reactions related to administration and infusion may occur during and after alglucosidase alfa treatment, including life-threatening anaphylaxis, hypersensitivity reactions, and immune-mediated reactions. Patients who have experienced anaphylaxis or hypersensitivity reactions may require close observation during and after alglucosidase alfa administration. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek medical care should signs and symptoms occur.

Risk of Acute Cardiorespiratory Failure

Advise patients and caregivers that patients with underlying respiratory illness or compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Patients with compromised cardiac or respiratory function may require close observation during and after alglucosidase alfa administration.

Pompe Registry

Inform patients and their caregivers that the Pompe Registry has been established in order to better understand the variability and progression of Pompe disease, and to continue to monitor and evaluate long-term treatment effects of alglucosidase alfa. The Pompe Registry will also monitor the effect of alglucosidase alfa on pregnant women and their offspring *[see Use in Specific Populations (8)]*. Patients and their caregivers should be encouraged to participate in the Pompe Registry and advised that their participation is voluntary and may involve long-term follow-up. For more information regarding the registry program, visit www.pomperegistry.com or call 1-800-745-4447.

LUMIZYME is manufactured and distributed by:

Genzyme Corporation
500 Kendall Street
Cambridge, MA 02142
1-800-745-4447 (phone)

US License Number: 1596

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

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

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

www.Lumizyme.com

www.Pompe.com

www.pomperegistry.com

WARNINGS AND PRECAUTIONS

Risk of Antibody Development: As with all therapeutic proteins, there is potential for immunogenicity. There is some evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy. Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter.

Please see full Prescribing Information, including Boxed WARNING (Appendix E) and Important Safety Information on pages 3 and 4.

SANOFI GENZYME

Genzyme Corporation
50 Binney Street
Cambridge, MA 02142

1-800-745-4447, option 3
Fax 800-737-3642 or 617-591-7178
Monday—Friday, 8:00 am—6:00 pm

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMIZYME safely and effectively. See full prescribing information for LUMIZYME.

LUMIZYME® (alglucosidase alfa), for injection, for intravenous use
Initial U.S. Approval: 2010

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, and RISK OF CARDIORESPIRATORY FAILURE

See full prescribing information for complete boxed warning.

- **Life-threatening anaphylactic reactions and severe hypersensitivity reactions have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur (5.1, 5.2).**
- **Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring (5.3).**

----------RECENT MAJOR CHANGES----------

• Boxed Warning	08/2014
• Indications and Usage (1)	08/2014
• Warnings and Precautions (5)	08/2014

----------INDICATIONS AND USAGE----------

LUMIZYME® (alglucosidase alfa) is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (GAA deficiency) (1).

----------DOSAGE AND ADMINISTRATION----------

- 20 mg per kg body weight administered every 2 weeks as an intravenous infusion (2).

----------DOSAGE FORMS AND STRENGTHS----------

- For injection: 50 mg of alglucosidase alfa as lyophilized powder in a single-use vial for reconstitution (3).

----------CONTRAINDICATIONS----------

- None (4).

----------WARNINGS AND PRECAUTIONS----------

- Anaphylaxis and Hypersensitivity Reactions: Life-threatening anaphylaxis and hypersensitivity reactions have been observed in some patients during and after treatment with alglucosidase alfa. Ensure that appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available. If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue infusion and initiate appropriate medical treatment (5.1).
- Immune-Mediated Reactions: Monitor patients for the development of systemic immune-mediated reactions involving skin and other organs (5.2).
- Risk of Acute Cardiorespiratory Failure: Patients with compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Caution should be exercised when administering alglucosidase alfa to patients susceptible to fluid volume overload. Appropriate medical support and monitoring measures should be available during infusion (5.3).
- Risk of Cardiac Arrhythmia and Sudden Cardiac Death during General Anesthesia for Central Venous Catheter Placement: Caution should be used when administering general anesthesia for the placement of a central venous catheter intended for alglucosidase alfa infusion (5.4).

----------ADVERSE REACTIONS----------

- The most frequently reported adverse reactions (≥ 5%) in clinical trials were hypersensitivity reactions and included: anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia (6.1).

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

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Based on animal data, may cause fetal harm (8.1).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 08/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: RISK OF ANAPHYLAXIS, HYPERSENSITIVITY AND IMMUNE-MEDIATED REACTIONS, AND RISK OF CARDIORESPIRATORY FAILURE

Life-threatening anaphylactic reactions and severe hypersensitivity reactions, presenting as respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria, have occurred in some patients during and after alglucosidase alfa infusions. Immune-mediated reactions presenting as proteinuria, nephrotic syndrome, and necrotizing skin lesions have occurred in some patients following alglucosidase alfa treatment. Closely observe patients during and after alglucosidase alfa administration and be prepared to manage anaphylaxis and hypersensitivity reactions. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek immediate medical care should signs and symptoms occur *[see Warnings and Precautions (5.1, 5.2)]*.

Infantile-onset Pompe disease patients with compromised cardiac or respiratory function may be at risk of serious acute exacerbation of their cardiac or respiratory compromise due to fluid overload, and require additional monitoring *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

LUMIZYME® (alglucosidase alfa) *[see Description (11)]* is a hydrolytic lysosomal glycogen-specific enzyme indicated for patients with Pompe disease (acid α-glucosidase (GAA) deficiency).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dosage of alglucosidase alfa is 20 mg/kg body weight administered every 2 weeks as an intravenous infusion.

2.2 Instructions for Use

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

The total volume of infusion is determined by the patient's body weight and should be administered over approximately 4 hours. Infusions should be administered in a step-wise manner using an infusion pump. The initial infusion rate should be no more than 1 mg/kg/hr. The infusion rate may be increased by 2 mg/kg/hr every 30 minutes, after patient tolerance to the infusion rate is established, until a maximum rate of 7 mg/kg/hr is reached. Vital signs should be obtained at the

end of each step. If the patient is stable, alglucosidase alfa may be administered at the maximum rate of 7 mg/kg/hr until the infusion is completed. The infusion rate may be slowed or temporarily stopped in the event of mild to moderate hypersensitivity reactions. In the event of anaphylaxis or severe hypersensitivity reaction, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. See *Table 1* below for the rate of infusion at each step, expressed as mL/hr based on the recommended infusion volume by patient weight.

Table 1: Recommended Infusion Volumes and Rates

Patient Weight Range (kg)	Total infusion volume (mL)	Step 1 1 mg/kg/hr (mL/hr)	Step 2 3 mg/kg/hr (mL/hr)	Step 3 5 mg/kg/hr (mL/hr)	Step 4 7 mg/kg/hr (mL/hr)
1.25 -10	50	3	8	13	18
10.1 - 20	100	5	15	25	35
20.1 – 30	150	8	23	38	53
30.1 – 35	200	10	30	50	70
35.1 – 50	250	13	38	63	88
50.1 – 60	300	15	45	75	105
60.1 – 100	500	25	75	125	175
100.1 – 120	600	30	90	150	210
120.1 – 140	700	35	105	175	245
140.1 – 160	800	40	120	200	280
160.1 – 180	900	45	135	225	315
180.1 – 200	1,000	50	150	250	350

2.3 Reconstitution, Dilution, and Administration

Alglucosidase alfa should be reconstituted, diluted and administered by a healthcare professional.

Use aseptic technique during preparation. Do not use filter needles during preparation.

a. Determine the number of vials to be reconstituted based on the individual patient's weight and the recommended dose of 20 mg/kg.

   Patient weight (kg) x dose (mg/kg) = patient dose (in mg)

   Patient dose (in mg) divided by 50 mg/vial = number of vials to reconstitute. If the number of vials includes a fraction, round up to the next whole number.

   Example: Patient weight (68 kg) x dose (20 mg/kg) = patient dose (1,360 mg)

   1,360 mg divided by 50 mg/vial = 27.2 vials; therefore, 28 vials should be reconstituted.

   Remove the required number of vials from the refrigerator and allow them to reach room temperature prior to reconstitution (approximately 30 minutes).

b. Reconstitute each alglucosidase alfa vial by slowly injecting 10.3 mL of Sterile Water for Injection, USP to the inside wall of each vial. Each vial will yield a concentration of 5 mg/mL. The total extractable dose per vial is 50 mg per 10 mL. Avoid forceful impact of the water for injection on the powder and avoid foaming. This is done by slow drop-wise addition of the water for injection down the inside of the vial and not directly onto the lyophilized cake. Tilt

and roll each vial gently. Do not invert, swirl, or shake.

c. The reconstituted alglucosidase alfa solution should be protected from light.

d. Perform an immediate visual inspection on the reconstituted vials for particulate matter and discoloration. If upon immediate inspection opaque particles are observed or if the solution is discolored do not use. The reconstituted solution may occasionally contain some alglucosidase alfa particles (typically less than 10 in a vial) in the form of thin white strands or translucent fibers subsequent to the initial inspection. This may also happen following dilution for infusion. These particles have been shown to contain alglucosidase alfa and may appear after the initial reconstitution step and increase over time. Studies have shown that these particles are removed via in-line filtration without having a detectable effect on the purity or strength.

e. Alglucosidase alfa should be diluted in 0.9% Sodium Chloride for Injection, USP, immediately after reconstitution, to a final alglucosidase alfa concentration of 0.5 to 4 mg/mL. See *Table 1* for the recommended total infusion volume based on patient weight.

f. Slowly withdraw the reconstituted solution from each vial. Avoid foaming in the syringe.

g. Remove airspace from the infusion bag to minimize particle formation due to the sensitivity of alglucosidase alfa to air-liquid interfaces.

h. Add the reconstituted alglucosidase alfa solution slowly and directly into the sodium chloride solution. Do not add directly into airspace that may remain within the infusion bag. Avoid foaming in the infusion bag.

i. Gently invert or massage the infusion bag to mix. Do not shake.

j. Administer alglucosidase alfa using an in-line low protein binding 0.2 µm filter.

k. Do not infuse alglucosidase alfa in the same intravenous line with other products.

The reconstituted and diluted solution should be administered without delay. If immediate use is not possible, the reconstituted and diluted solution is stable for up to 24 hours at 2°C to 8°C (36°F to 46°F). Storage of the reconstituted solution at room temperature is not recommended. The reconstituted and diluted alglucosidase alfa solution should be protected from light. Do not freeze or shake.

Alglucosidase alfa does not contain any preservatives. Vials are single-use only. Discard any unused product.

3 DOSAGE FORMS AND STRENGTHS

For injection: 50 mg of alglucosidase alfa is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder in a single-use vial for reconstitution. After reconstitution, the resultant solution concentration is 5 mg/mL.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Anaphylaxis and Hypersensitivity Reactions

Anaphylaxis and hypersensitivity reactions have been observed in patients during and up to 3 hours after alglucosidase alfa infusion. Some of the reactions were life-threatening and included anaphylactic shock, cardiac arrest, respiratory arrest, respiratory distress, hypoxia, apnea, dyspnea, bradycardia, tachycardia, bronchospasm, throat tightness, hypotension, angioedema (including tongue or lip swelling, periorbital edema, and face edema), and urticaria. Other accompanying reactions included chest discomfort/pain, wheezing, tachypnea, cyanosis, decreased oxygen saturation, convulsions, pruritus, rash, hyperhidrosis, nausea, dizziness, hypertension/increased blood pressure, flushing/feeling hot, erythema, pyrexia, pallor, peripheral coldness, restlessness, nervousness, headache, back pain, and paresthesia. Some of these reactions were IgE-mediated.

If anaphylaxis or severe hypersensitivity reactions occur, immediately discontinue administration of alglucosidase alfa, and initiate appropriate medical treatment. Severe reactions are generally managed with infusion interruption, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylaxis, epinephrine has been administered. Appropriate medical support, including cardiopulmonary resuscitation equipment, should be readily available when alglucosidase alfa is administered.

The risks and benefits of re-administering alglucosidase alfa following an anaphylactic or hypersensitivity reaction should be considered. Some patients have been rechallenged and have continued to receive alglucosidase alfa under close clinical supervision. Extreme care should be exercised, with appropriate resuscitation measures available, if the decision is made to re-administer the product *[see Adverse Reactions (6.2)]*.

5.2 Immune-Mediated Reactions

Immune-mediated cutaneous reactions have been reported with alglucosidase alfa including necrotizing skin lesions *[see Adverse Reactions (6.3)]*. Systemic immune-mediated reactions, including possible type III immune-mediated reactions have been observed with alglucosidase alfa. These reactions occurred several weeks to 3 years after initiation of alglucosidase alfa infusions. Skin biopsy in one patient demonstrated deposition of anti-rhGAA antibodies in the lesion. Another patient developed severe inflammatory arthropathy in association with pyrexia and elevated erythrocyte sedimentation rate. Nephrotic syndrome secondary to membranous glomerulonephritis was observed in some Pompe disease patients treated with alglucosidase alfa who had persistently positive anti-rhGAA IgG antibody titers. In these patients, renal biopsy was consistent with immune complex deposition. Patients improved following treatment interruption. Therefore, patients receiving alglucosidase alfa should undergo periodic urinalysis *[see Adverse Reactions (6.3)]*.

Patients should be monitored for the development of systemic immune-mediated reactions involving skin and other organs while receiving alglucosidase alfa. If immune-mediated reactions occur, consider discontinuation of the administration of alglucosidase alfa, and initiate appropriate

medical treatment. The risks and benefits of re-administering alglucosidase alfa following an immune-mediated reaction should be considered. Some patients have been able to be rechallenged and have continued to receive alglucosidase alfa under close clinical supervision.

5.3 Risk of Acute Cardiorespiratory Failure

Patients with acute underlying respiratory illness or compromised cardiac and/or respiratory function may be at risk of serious exacerbation of their cardiac or respiratory compromise during infusions. Appropriate medical support and monitoring measures should be readily available during alglucosidase alfa infusion, and some patients may require prolonged observation times that should be individualized based on the needs of the patient. Acute cardiorespiratory failure has been observed in infantile-onset Pompe disease patients with underlying cardiac hypertrophy, possibly associated with fluid overload with intravenous administration of alglucosidase alfa *[see Dosage and Administration (2.2)]*.

5.4 Risk of Cardiac Arrhythmia and Sudden Cardiac Death During General Anesthesia for Central Venous Catheter Placement

Administration of general anesthesia can be complicated by the presence of severe cardiac and skeletal (including respiratory) muscle weakness. Therefore, caution should be used when administering general anesthesia. Ventricular arrhythmias and bradycardia, resulting in cardiac arrest or death, or requiring cardiac resuscitation or defibrillation have been observed in infantile-onset Pompe disease patients with cardiac hypertrophy during general anesthesia for central venous catheter placement.

5.5 Risk of Antibody Development

As with all therapeutic proteins, there is potential for immunogenicity. In clinical studies, the majority of patients developed IgG antibodies to alglucosidase alfa, typically within 3 months of treatment. There is evidence to suggest that some patients who develop high and sustained IgG antibody titers may experience reduced clinical efficacy to alglucosidase alfa treatment, such as loss of motor function, ventilator dependence, or death. The effect of antibody development on the long term efficacy of alglucosidase alfa is not fully understood.

Patients should be monitored for IgG antibody formation every 3 months for 2 years and then annually thereafter. Testing for IgG titers may also be considered if patients develop hypersensitivity reactions, other immune-mediated reactions, or lose clinical response. Patients who experience reduced clinical response may also be tested for inhibitory antibody activity. Patients who experience anaphylactic or hypersensitivity reactions may also be tested for IgE antibodies to alglucosidase alfa and other mediators of anaphylaxis *[see Adverse Reactions (6.2)]*.

There are currently no marketed tests for antibodies against alglucosidase alfa; however, a testing service is provided by Genzyme. Contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447 for information on testing and to obtain a sample collection box.

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 clinical practice.

The following serious adverse reactions are described below and elsewhere in the labeling:

- Anaphylaxis and hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

In clinical trials, the most common adverse reactions (≥ 5%) following alglucosidase alfa treatment were hypersensitivity reactions, and included anaphylaxis, rash, pyrexia, flushing/feeling hot, urticaria, headache, hyperhidrosis, nausea, cough, decreased oxygen saturation, tachycardia, tachypnea, chest discomfort, dizziness, muscle twitching, agitation, cyanosis, erythema, hypertension/increased blood pressure, pallor, rigors, tremor, vomiting, fatigue, and myalgia.

Clinical Trials in Infantile-Onset and Juvenile-Onset Pompe Disease

Two multicenter, open-label clinical trials were conducted in 39 infantile-onset Pompe disease patients, ages 1 month to 3.5 years old. Approximately half of the patients (54%) were male. Patients were treated with alglucosidase alfa 20 or 40 mg/kg every other week for periods ranging from 1 to 106 weeks (mean: 61 weeks).

The most serious adverse reactions reported with alglucosidase alfa treatment included anaphylaxis and acute cardiorespiratory failure.

The most common adverse reactions requiring intervention in clinical trials were hypersensitivity reactions, occurring in 20 of 39 (51%) patients treated with alglucosidase alfa, and included rash, pyrexia, urticaria, flushing, decreased oxygen saturation, cough, tachypnea, tachycardia, hypertension/increased blood pressure, pallor, rigors, vomiting, cyanosis, agitation, and tremor. These reactions were more likely to occur with higher infusion rates. Some patients who were pre-treated with antihistamines, antipyretics and/or corticosteroids still experienced hypersensitivity reactions.

Table 2 summarizes all adverse reactions occurring in ≥ 5% of patients (2 or more patients) treated with alglucosidase alfa in clinical trials described above.

Table 2: Adverse Reactions that Occurred in At Least 5% of Infantile-Onset Patients Treated with Alglucosidase Alfa in Clinical Trials

	Number of Patients (N=39) n (%)
Adverse Reaction	**20 (51)**
Rash (including rash erythematous, rash macular and maculo-papular)	7 (18)
Pyrexia	6 (15)
Urticaria	5 (13)
Flushing	5 (13)
Hypertension/Increased Blood Pressure	4 (10)
Decreased Oxygen Saturation	3 (8)
Cough	3 (8)
Tachypnea	3 (8)
Tachycardia	3 (8)

Erythema	2 (5)
Vomiting	2 (5)
Rigors	2 (5)
Pallor	2 (5)
Cyanosis	2 (5)
Agitation	2 (5)
Tremor	2 (5)

An open-label, single-center trial was conducted in 18 treatment-naïve infantile-onset Pompe disease patients who were treated exclusively with alglucosidase alfa. Adverse reactions observed in these patients were similar to infantile-onset Pompe disease patients who received alglucosidase alfa in other clinical trials.

Additional hypersensitivity reactions observed in infantile-onset Pompe disease patients treated in other clinical trials and expanded access programs with alglucosidase alfa included livedo reticularis, irritability, retching, increased lacrimation, ventricular extrasystoles, nodal rhythm, rales, respiratory tract irritation, and cold sweat.

Safety was also evaluated in 99 patients (51 male, 48 females) with Pompe disease in an ongoing, open-label, prospective study in patients 12 months of age and older who were previously treated with the 160 L scale of alglucosidase alfa and switched to the 4000 L scale of alglucosidase alfa. Patients were aged 1 to 18 years with a median duration of treatment of 437 days (range 13 to 466 days). No new safety findings were observed following the switch to 4000 L scale of alglucosidase alfa.

Clinical Trials in Late-Onset Pompe Disease

Assessment of adverse reactions in patients with late-onset Pompe disease is based on the exposure of 90 patients (45 male, 45 female), aged 10 to 70 years, to 20 mg/kg alglucosidase alfa or placebo in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were randomized in a 2:1 ratio and received alglucosidase alfa or placebo every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. Two patients receiving alglucosidase alfa discontinued the trial due to anaphylactic reactions.

Serious adverse reactions reported with alglucosidase alfa included anaphylaxis, which presented as angioedema, throat tightness and chest pain/discomfort. One patient with a history of Wolff-Parkinson-White syndrome experienced a serious adverse reaction of supraventricular tachycardia.

The most common adverse reactions (≥ 3%; 2 or more patients) observed in alglucosidase alfa-treated patients were hypersensitivity reactions and included anaphylaxis, headache, nausea, urticaria, dizziness, chest discomfort, vomiting, hyperhidrosis, flushing/feeling hot, increased blood pressure, paresthesia, pyrexia, local swelling, diarrhea, pruritus, rash, and throat tightness.

Delayed-onset reactions, defined as adverse reactions occurring 2 - 48 hours after completion of alglucosidase alfa infusion, that were observed in ≥ 3% more patients in the alglucosidase alfa-treated group compared to patients in the placebo-treated group in the controlled trial, included hyperhidrosis. Additional delayed-onset reactions occurring in alglucosidase alfa-treated patients

included fatigue, myalgia, and nausea. Patients should be counseled about the possibility of delayed-onset hypersensitivity reactions and given proper follow-up instructions.

Table 3 summarizes the most common adverse reactions that occurred in at least 3% of alglucosidase alfa-treated patients and with a higher incidence than the placebo-treated patients during the randomized, double-blind, placebo-controlled study described above.

Table 3: Adverse Reactions Occurring in at Least 3% of Alglucosidase Alfa-Treated Late-Onset Patients and with a Higher Incidence than the Placebo-Treated Patients

Adverse Reaction	Alglucosidase Alfa n=60 N (%)	Placebo n=30 N (%)
Hyperhidrosis	5 (8.3)	0 (0)
Urticaria	5 (8.3)	0 (0)
Anaphylaxis	4 (6.7)	0 (0)
Chest Discomfort	4 (6.7)	1 (3.3)
Muscle Twitching	4 (6.7)	1 (3.3)
Myalgia	3 (5.0)	1 (3.3)
Flushing/Feeling Hot	3 (5.0)	0 (0)
Increased Blood Pressure	3 (5.0)	0 (0)
Vomiting	3 (5.0)	0 (0)
Edema, Peripheral	2 (3.3)	0 (0)
Pruritus	2 (3.3)	0 (0)
Rash Papular	2 (3.3)	0 (0)
Throat Tightness	2 (3.3)	0 (0)

In clinical trials, anaphylaxis and hypersensitivity reactions were managed with infusion interruption, decreased infusion rate, administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. In some cases of anaphylactic reactions, epinephrine was administered. Patients who have experienced anaphylaxis or hypersensitivity reactions should be treated with caution when they are re-administered alglucosidase alfa.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The data reflect the percentage of patients whose test results were considered positive for antibodies to alglucosidase alfa using an enzyme-linked immunosorbent assay (ELISA) and confirmed by a radioimmunoprecipitation (RIP) assay for alglucosidase alfa-specific IgG antibodies.

In the two clinical trials in infantile-onset patients, the majority of patients (34 of 38; 89%) tested positive for IgG antibodies to alglucosidase alfa. There is evidence to suggest that some patients who develop high sustained titers of anti-alglucosidase alfa antibodies may experience reduced clinical efficacy to alglucosidase alfa treatment *[see Warnings and Precautions (5.5)]*. Some IgG-positive patients in clinical trials who were retrospectively evaluated for the presence of inhibitory antibodies tested positive for inhibition of enzyme activity and/or uptake in *in vitro* assays. Furthermore, CRIM-negative infants have shown reduced clinical effect in the presence of high sustained IgG antibody titers with inhibitory activity. Alglucosidase alfa-treated patients who

experience a decrease in motor function should be tested for the presence of inhibitory antibodies that neutralize enzyme uptake or activity.

In the randomized, double-blind, placebo-controlled trial in late-onset patients, all alglucosidase alfa-treated patients with available samples (N=59, 100%) developed IgG antibodies to alglucosidase alfa. Most patients who developed IgG antibodies did so within the first 3 months of exposure (median time to seroconversion was 4 weeks). There was no apparent association between mean or peak IgG antibody titers and the occurrence of adverse reactions.

None of the 59 evaluable patients tested positive for inhibition of enzyme activity. Antibody titers for cellular uptake inhibition were present in 18 of 59 (31%) patients by Week 78. All other patients tested negative for inhibition of cellular uptake. Patients who tested positive for uptake inhibition tended to have higher IgG titers than patients who tested negative for uptake inhibition. Among the 32 patients with evaluable pharmacokinetic (PK) samples, 5 patients tested positive for uptake inhibition. The clinical relevance of this *in vitro* inhibition is not fully understood. The clearance values for 4 of these 5 patients were approximately 1.2- to 1.8-fold greater in the presence of inhibitory antibodies (Week 52) as compared to in the absence of inhibitory antibodies (Week 0) *[see Clinical Pharmacology (12.3)]*.

Some patients in the clinical studies or in the postmarketing setting have undergone testing for alglucosidase alfa-specific IgE antibodies. Testing was performed in patients who experienced moderate to severe or recurrent hypersensitivity reactions, for which mast-cell activation was suspected. Some of the patients who tested positive for alglucosidase alfa-specific IgE antibodies experienced anaphylactic reactions *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Some patients who tested positive for alglucosidase alfa-specific IgE antibodies and experienced hypersensitivity reactions were able to be rechallenged with alglucosidase alfa using a slower infusion rate at lower starting doses and have continued to receive treatment under close clinical supervision *[see Warnings and Precautions (5.1)]*. Since patients who develop IgE antibodies to alglucosidase alfa appear to be at a higher risk for developing anaphylaxis and hypersensitivity reactions, these patients should be monitored more closely during administration of alglucosidase alfa.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to alglucosidase alfa with the incidence of antibodies to other products may be misleading.

6.3 Postmarketing Experience

The following adverse reactions have been identified during post approval use of alglucosidase alfa. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In postmarketing experience with alglucosidase alfa, serious adverse reactions have been reported,

including anaphylaxis *[see Boxed Warning and Warnings and Precautions (5.1)]*. Acute cardiorespiratory failure, possibly associated with fluid overload, has been reported in infantile-onset Pompe disease patients with pre-existing hypertrophic cardiomyopathy *[see Boxed Warning and Warning and Precautions (5.3)]*.

Recurrent reactions consisting of flu-like illness or a combination of events such as pyrexia, chills, myalgia, arthralgia, pain, or fatigue occurring after completion of infusions and lasting usually for 1 - 3 days have been observed in some patients treated with alglucosidase alfa. The majority of patients were able to be rechallenged with alglucosidase alfa using lower doses and/or pretreatment with anti-inflammatory drugs and/or corticosteroids and were able to continue treatment under close clinical supervision.

In addition to the hypersensitivity reactions reported in clinical trials *[see Adverse Reactions (6.1)]*, the following hypersensitivity reactions have been reported in at least 2 patients and included: anaphylactic shock, respiratory failure, respiratory arrest, cardiac arrest, hypoxia, dyspnea, wheezing, convulsions, peripheral coldness, restlessness, nervousness, back pain, stridor, pharyngeal edema, abdominal pain, apnea, muscle spasm, and conjunctivitis. In addition, one case of hyperparathyroidism has been reported.

Systemic and cutaneous immune-mediated reactions, including proteinuria and nephrotic syndrome secondary to membranous glomerulonephritis, and necrotizing skin lesions have been reported in postmarketing safety experience with alglucosidase alfa *[see Warnings and Precautions (5.2)]*.

7 DRUG INTERACTIONS

7.1 Interference with Other Drugs

No drug interaction or *in vitro* metabolism studies were performed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There is a registry for Pompe disease patients that monitors the outcomes of women and their offspring exposed to alglucosidase alfa during pregnancy. Patients or their physicians should call 1-800-745-4447 or visit www.pomperegistry.com to enroll *[see Patient Counseling Information (17)]*.

Risk Summary

There are no studies of alglucosidase alfa in pregnant women. In animal reproduction studies, no effects on embryo-fetal development were observed in mice or rabbits given daily administration of alglucosidase alfa up to 0.4 or 0.5 times the human steady-state AUC (area under the plasma concentration-time curve), respectively, at the recommended human bi-weekly dose during the period of organogenesis. An increase in pup mortality was observed when alglucosidase alfa was administered every other day in mice during the period of organogenesis through lactation at a dose 0.4 times the human steady-state AUC at the recommended human bi-weekly dose. Alglucosidase

alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

All reproductive studies included pre-treatment with diphenhydramine to prevent or minimize hypersensitivity reactions. The effects of alglucosidase alfa were evaluated based on comparison to a control group treated with diphenhydramine alone. Daily intravenous (IV) administration of alglucosidase alfa up to 40 mg/kg in mice and rabbits (0.4 and 0.5 times the human steady-state AUC, respectively, at the recommended bi-weekly dose) during the period of organogenesis had no effects on embryo-fetal development. Administration of 40 mg/kg IV every other day in mice (0.4 times the human steady-state AUC at the recommended bi-weekly dose) during the period of organogenesis through lactation produced an increase in mortality of offspring during the lactation period.

8.3 Nursing Mothers

Alglucosidase alfa is present in human milk. In one case report, the enzymatic activity of alglucosidase alfa was detected in the breast milk of a lactating woman up to 24 hours after the end of intravenous alglucosidase alfa administration. To minimize infant exposure to alglucosidase alfa, a nursing mother may temporarily pump and discard breast milk produced during the 24 hours after administration of alglucosidase alfa. Exercise caution when administering alglucosidase alfa to a nursing mother.

8.4 Pediatric Use

The safety and effectiveness of alglucosidase alfa have been established in pediatric patients with Pompe disease.

The safety and effectiveness of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials *[see Clinical Studies (14.1)]*.

The safety and effectiveness of alglucosidase alfa were assessed in pediatric patients with late (non-infantile) onset Pompe disease in a randomized, double-blind, placebo-controlled study in 90 patients, including 2 patients 16 years of age or less *[see Clinical Studies (14.2)]*.

Anaphylaxis, hypersensitivity reactions, and acute cardiorespiratory failure have occurred in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.1, 5.3)]*. Additionally, cardiac arrhythmia and sudden cardiac death have occurred in pediatric patients during general anesthesia for central venous catheter placement *[see Warnings and Precautions (5.4)]*.

8.5 Geriatric Use

The randomized, double-blind, placebo-controlled study of alglucosidase alfa did not include sufficient numbers (n=4) of patients aged 65 years and over to determine whether they respond differently from younger patients *[see Clinical Studies (14.1)]*.

11 DESCRIPTION

Alglucosidase alfa is a hydrolytic lysosomal glycogen-specific enzyme encoded by the predominant of nine observed haplotypes of the human acid α-glucosidase (GAA) gene. Alglucosidase alfa is produced by recombinant DNA technology in a Chinese hamster ovary cell line. Alglucosidase alfa degrades glycogen by catalyzing the hydrolysis of α-1,4- and α-1,6- glycosidic linkages of lysosomal glycogen.

Alglucosidase alfa is a glycoprotein with a calculated mass of 99,377 daltons for the polypeptide chain, and a total mass of approximately 109,000 daltons, including carbohydrates. Alglucosidase alfa has a specific activity of 3.6 to 5.4 units/mg (one unit is defined as that amount of activity that results in the hydrolysis of 1 micromole of synthetic substrate per minute under specified assay conditions). Alglucosidase alfa is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, white to off-white, lyophilized cake or powder for reconstitution with 10.3 mL Sterile Water for Injection, USP. Each 50 mg vial contains 52.5 mg alglucosidase alfa, 210 mg mannitol, 0.5 mg polysorbate 80, 9.9 mg sodium phosphate dibasic heptahydrate, 31.2 mg sodium phosphate monobasic monohydrate. Following reconstitution as directed, each vial contains 10.5 mL reconstituted solution and a total extractable volume of 10 mL at 5 mg/mL alglucosidase alfa. Alglucosidase alfa does not contain preservatives; each vial is for single use only.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pompe disease (acid maltase deficiency, glycogen storage disease type II, GSD II, glycogenosis type II) is an inherited disorder of glycogen metabolism caused by the absence or marked deficiency of the lysosomal enzyme GAA.

Alglucosidase alfa provides an exogenous source of GAA. Binding to mannose-6-phosphate receptors on the cell surface has been shown to occur via carbohydrate groups on the GAA molecule, after which it is internalized and transported into lysosomes, where it undergoes proteolytic cleavage that results in increased enzymatic activity. It then exerts enzymatic activity in cleaving glycogen.

12.2 Pharmacodynamics

Clinical pharmacodynamic studies have not been conducted for alglucosidase alfa.

12.3 Pharmacokinetics

The pharmacokinetics of alglucosidase alfa were evaluated in 13 patients with infantile-onset Pompe disease, aged 1 month to 7 months, who received 20 mg/kg (approximately as a 4-hour infusion) or 40 mg/kg (approximately as a 6.5-hour infusion) of alglucosidase alfa every 2 weeks. The measurement of alglucosidase alfa plasma concentration was based on an activity assay using an artificial substrate. Systemic exposure was approximately dose proportional between the 20 and 40 mg/kg doses. Based on the pharmacokinetic blood samples collected for 12 hours after a 4-hour intravenous infusion of 20 mg/kg (n=5), the estimated mean AUC was 811 mcg•hr/mL with 17%

coefficient of variation [CV], C_{max} was 162 mcg/mL with 19% CV, clearance was 25 mL/hr/kg with 16% CV, and half-life was 2.3 hours with 17% CV.

The pharmacokinetics of alglucosidase alfa were also evaluated in a separate trial of 14 patients with infantile-onset Pompe disease, aged 6 months to 3.5 years, who received 20 mg/kg of alglucosidase alfa as a 4-hour infusion every 2 weeks. The pharmacokinetic parameters were similar to those observed for the infantile-onset Pompe disease patients aged 1 month to 7 months who received the 20 mg/kg dose.

Nineteen of 21 patients who received treatment with alglucosidase alfa and had pharmacokinetics and antibody titer data available at Week 12 developed antibodies to alglucosidase alfa. Five patients with antibody titers ≥ 12,800 at Week 12 had an average increase in clearance of 50% (range 5% to 90%) from Week 1 to Week 12. The other 14 patients with antibody titers < 12,800 at Week 12 had similar average clearance values at Week 1 and Week 12.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic potential have not been performed with alglucosidase alfa.

Intravenous administration of alglucosidase alfa every other day in mice at doses up to 40 mg/kg (0.4 times the human AUC at the recommended bi-weekly dose) had no effect on fertility and reproductive performance.

14 CLINICAL STUDIES

14.1 Clinical Trials in Infantile-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 57 treatment-naïve infantile-onset Pompe disease patients, aged 0.2 month to 3.5 years at first infusion, in three separate clinical trials.

Study 1 was an international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe disease patients. This study was conducted between 2003 and 2005. Patients were randomized 1:1 to receive either 20 mg/kg or 40 mg/kg alglucosidase alfa every two weeks, with length of treatment ranging from 52 to 106 weeks. Enrollment was restricted to patients 7 months of age or younger at first infusion with clinical signs of Pompe disease and cardiac hypertrophy, and who did not require ventilatory support at study entry. Fourteen patients were Cross Reactive Immunologic Material (CRIM) positive and 4 patients were CRIM-negative.

Efficacy was assessed by comparing the proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age with the mortality experience of a historical cohort of untreated infantile-onset Pompe disease patients with similar age and disease severity. In the historical cohort, 61 untreated patients with infantile-onset Pompe disease diagnosed by age 6 months, born between 1982 and 2002, were identified by a retrospective review of medical charts. By 18 months of age, 15 of 18 (83%) alglucosidase alfa-treated patients were alive without invasive ventilatory support and 3 (17%) required invasive ventilator support,

whereas only one of the 61 (2%) historical control patients was alive. No differences in outcome were observed between patients who received 20 mg/kg versus 40 mg/kg.

Other outcome measures in this study included unblinded assessments of motor function by the Alberta Infant Motor Scale (AIMS), a measure of infant motor performance that assesses motor maturation of the infant through age 18 months. Although gains in motor function were noted in 13 patients, the motor function was substantially delayed compared to normal infants of comparable age in the majority of patients. Two of 9 patients who had initially demonstrated gains in motor function after 12 months of alglucosidase alfa treatment regressed despite continued treatment.

Changes from baseline to Month 12 in left ventricular mass index (LVMI), a measure of pharmacodynamic effect, were evaluated by echocardiography. Fifteen patients who underwent both baseline and Month 12 echocardiograms demonstrated decreases from baseline in LVMI (mean decrease 118 g/m^2, range 45 to 193 g/m^2). However, the magnitude of the decrease in LVMI did not correlate with the clinical outcome measure of ventilator-free survival.

Study 2 was an international, multicenter, non-randomized, open-label clinical trial that enrolled 21 infantile-onset patients aged 3 months to 3.5 years at first infusion. Eighteen patients were CRIM-positive and 3 patients were CRIM-negative. All patients received 20 mg/kg alglucosidase alfa every other week for up to 104 weeks. Five of 21 patients were receiving invasive ventilatory support at the time of first infusion.

The primary outcome measure was the proportion of patients alive at the conclusion of treatment. At the 52–week interim analysis, 16 of 21 patients were alive. Sixteen patients were free of invasive ventilatory support at the time of first infusion; of these, 4 died, 2 required invasive ventilatory support, and 10 were free of invasive ventilatory support after 52 weeks of treatment. For the 5 patients who were receiving invasive ventilatory support at baseline, 1 died, and 4 remained on invasive ventilatory support at Week 52.

Study 3 was an open-label, single-center trial in 18 infantile-onset Pompe disease patients who had a confirmed diagnosis of Pompe disease as identified through a newborn screening program. All patients were CRIM-positive. Patients were treated with alglucosidase alfa prior to 6 months of age (0.2 to 5.8 months at first infusion). Sixteen patients reached 18 months of age at the time of analysis, and all (100%) were alive without invasive ventilator support.

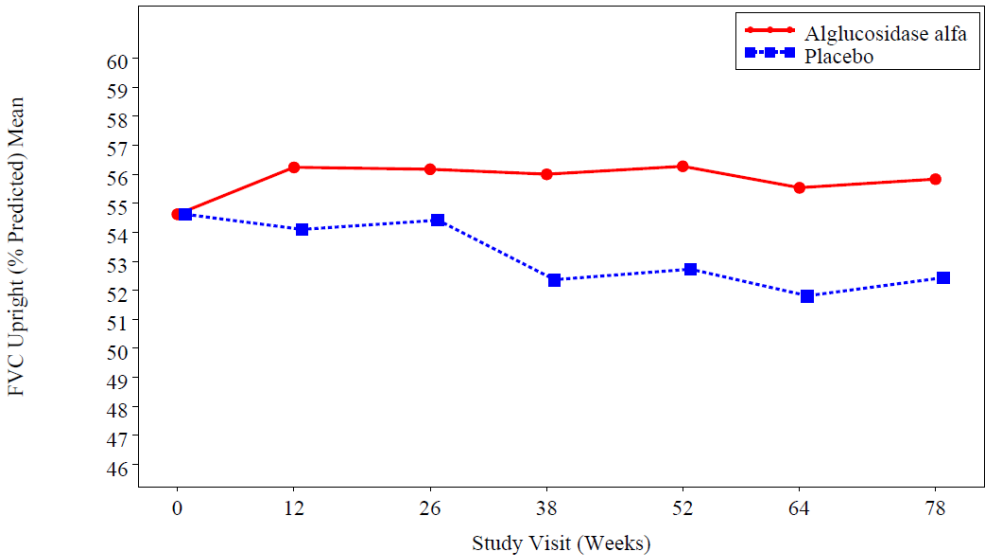
14.2 Clinical Trials in Late-Onset Pompe Disease

The safety and efficacy of alglucosidase alfa were assessed in 90 patients with late-onset Pompe disease, aged 10 to 70 years, in a randomized, double-blind, placebo-controlled trial. The youngest alglucosidase alfa-treated patient was 16 years of age, and the youngest placebo-treated patient was 10 years of age. All patients were naïve to enzyme replacement therapy. Patients were allocated in a 2:1 ratio and received 20 mg/kg alglucosidase alfa (n=60) or placebo (n=30) every other week for 78 weeks (18 months). The study population included 34 males and 26 females (n=60) in the alglucosidase alfa group and 11 males and 19 females (n=30) in the placebo group. At baseline, all patients were ambulatory (some required assistive walking devices), did not require invasive ventilator support or non-invasive ventilation while awake and sitting upright, and had a forced vital capacity (FVC) between 30 and 79% of predicted in the sitting position. Patients who could not walk 40 meters in 6 minutes or were unable to perform appropriate pulmonary and muscle function testing were excluded from the study.

A total of 81 of 90 patients completed the trial. Of the 9 patients who discontinued, 5 were in the alglucosidase alfa group and 4 were in the placebo group. Three patients discontinued the study due to an adverse event, two patients were in the alglucosidase alfa treatment group and one patient was in placebo group.

At study entry, the mean % predicted FVC in the sitting position among all patients was about 55%. After 78 weeks, the mean % predicted FVC increased to 56.2% for alglucosidase alfa-treated patients and decreased to 52.8% for placebo-treated patients indicating an alglucosidase alfa treatment effect of 3.4% (95% confidence interval: [1.3% to 5.5%]; p=0.004). Stabilization of % predicted FVC in the alglucosidase alfa-treated patients was observed (*see Figure 1*).

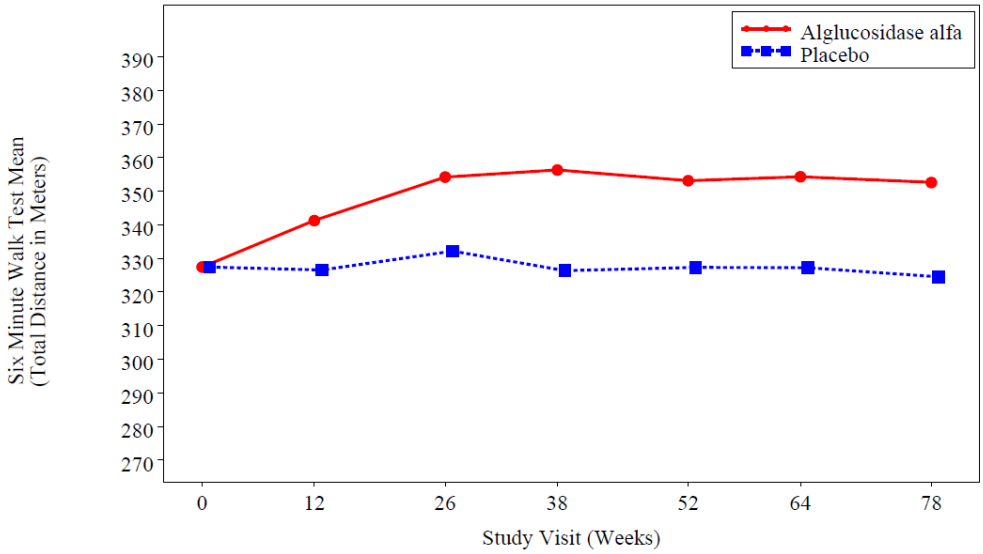
Figure 1: Mean FVC Upright (% Predicted) Over Time



Note: ANCOVA least squares means adjusting for baseline values

At study entry, the mean 6 minute walk test (6MWT) among all patients was about 330 meters. After 78 weeks, the mean 6MWT increased by 25 meters for alglucosidase alfa-treated patients and decreased by 3 meters for placebo-treated patients indicating an alglucosidase alfa treatment effect of 28 meters (95% confidence interval: [-1 to 52 meters]; p=0.06) (*see Figure 2*).

Figure 2: Mean Six Minute Walk Test Total Distance Walked Over Time



Note: ANCOVA least squares means adjusting for baseline values

16 HOW SUPPLIED/STORAGE AND HANDLING

LUMIZYME 50 mg vials are supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-use vials.

NDC 58468-0160-1 (Carton of one single-use vial)

NDC 58468-0160-2 (Carton of ten single-use vials)

Store LUMIZYME under refrigeration between 2°C to 8°C (36°F to 46°F). Do not use LUMIZYME after the expiration date on the vial.

17 PATIENT COUNSELING INFORMATION

Anaphylaxis, Hypersensitivity and Immune-Mediated Reactions

Advise the patients and caregivers that reactions related to administration and infusion may occur during and after alglucosidase alfa treatment, including life-threatening anaphylaxis, hypersensitivity reactions, and immune-mediated reactions. Patients who have experienced anaphylaxis or hypersensitivity reactions may require close observation during and after alglucosidase alfa administration. Inform patients of the signs and symptoms of anaphylaxis, hypersensitivity reactions, and immune-mediated reactions and have them seek medical care should signs and symptoms occur.

Risk of Acute Cardiorespiratory Failure

Advise patients and caregivers that patients with underlying respiratory illness or compromised cardiac or respiratory function may be at risk of acute cardiorespiratory failure. Patients with

compromised cardiac or respiratory function may require close observation during and after alglucosidase alfa administration.

Pompe Registry

Inform patients and their caregivers that the Pompe Registry has been established in order to better understand the variability and progression of Pompe disease, and to continue to monitor and evaluate long-term treatment effects of alglucosidase alfa. The Pompe Registry will also monitor the effect of alglucosidase alfa on pregnant women and their offspring *[see Use in Specific Populations (8)]*. Patients and their caregivers should be encouraged to participate in the Pompe Registry and advised that their participation is voluntary and may involve long-term follow-up. For more information regarding the registry program, visit www.pomperegistry.com or call 1-800-745-4447.

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