Billing Guide Usage

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

Indication and Usage

Fabrazyme® is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL3) deposition in capillary endothelium of the kidney and certain other cell types.

The reduction of GL3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Important Safety Information

Warnings and Precautions

Anaphylaxis and Allergic Reactions: Life-threatening anaphylactic and severe allergic reactions have been observed in patients during Fabrazyme infusions. In clinical trials and postmarketing safety experience, approximately 1% of patients developed anaphylactic or severe allergic reactions during Fabrazyme infusions.

- Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized urticaria, dysphagia, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion.
- Interventions have included cardiopulmonary resuscitation, oxygen supplementation, IV fluids, hospitalization, and treatment with inhaled beta-adrenergic agonists, antihistamines, epinephrine, and IV corticosteroids.
- If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

Infusion-Associated Reactions: In clinical trials with Fabrazyme, 59% of patients experienced infusion-associated reactions, some of which were severe.

- In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment.
- If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administering additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms.

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com
• If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen when clinically indicated. Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

Compromised Cardiac Function: Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions. Patients with compromised cardiac function should be monitored closely if the decision is made to administer Fabrazyme.

Immunogenicity and Rechallenge: In clinical trials, a few patients developed IgE or skin test reactivity specific to Fabrazyme. Physicians should consider testing for IgE in patients who experienced suspected allergic reactions. Re-administration of Fabrazyme to patients who have previously experienced severe or serious allergic reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel and with appropriate medical support measures readily available.

Adverse Reactions
• Common adverse reactions reported (≥20% and >2.5% compared to placebo) were upper respiratory tract infection (44% vs 30%), headache (39% vs 28%), cough (33% vs 25%), paresthesia (31% vs 18%), fatigue (24% vs 17%), dizziness (21% vs 8%), peripheral edema (21% vs 7%), and rash (20% vs 10%).
• Serious and/or frequently occurring (≥ 5% incidence) related adverse reactions based on a pooled analysis of 150 patients treated with Fabrazyme in double-blind and open-label clinical studies consisted of one or more of the following: chills, fever, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paresthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence.
• Other serious adverse events reported in clinical studies included stroke, pain, ataxia, bradycardia, cardiac arrhythmia, cardiac arrest, decreased cardiac output, vertigo, and nephrotic syndrome. These adverse events also occur as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.
• Adverse reactions (regardless of relationship) resulting in death reported in the postmarketing setting with Fabrazyme treatment included cardiorespiratory arrest, respiratory failure, cardiac failure, sepsis, cerebrovascular accident, myocardial infarction, renal failure, and pneumonia. Some of these reactions were reported in Fabry disease patients with significant underlying disease.

The safety and efficacy of Fabrazyme in patients younger than 8 years of age have not been evaluated.

Please see full Prescribing Information on pages 15-18.
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INTRODUCTION

Fabry disease is a rare, inherited lysosomal storage disorder caused by an enzyme deficiency. Deficiency of the lysosomal enzyme alpha-galactosidase A (alpha-GAL) leads to progressive accumulation of glycosphingolipids, predominantly globotriaosylceramide (GL-3), in many body tissues, occurring over a period of years or decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents.

Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces GL-3 deposition in the capillary endothelium of the kidney and certain other cell types. The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established.

Please see the full prescribing information on pages 15-18.

Sanofi Genzyme is committed to working with providers, as well as public and private payers, to help ensure access to treatment for patients who would medically benefit from Fabrazyme. This guide is designed to help you understand coverage, coding and reimbursement for Fabrazyme. Providers retain responsibility for determining reimbursement and insurance issues related to their patients. Sanofi Genzyme cannot be responsible for failure of a provider to obtain reimbursement.

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

Private Payers
Fabrazyme 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 so that problems obtaining reimbursement may be minimized. 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 Fabrazyme
• Periodic reauthorization or recertification for continued treatment
• Letter of Intent to Treat. See the example in Appendix A, page 9
• Statement of Medical Necessity. See the example in Appendix B, page 10

NOTE
If the patient’s private insurer denies coverage, an appeal process may be initiated. CareConnectPSS® Case Managers are available to assist patients through this process.

Medicare Part B
Medicare Part B coverage is determined by the local Medicare Part B carrier. Medicare will not prior authorize, so the patient’s coverage policy should be understood before treatment is initiated. Treatment with Fabrazyme will need to be considered medically necessary in order to be covered under the Medicare program. Fabrazyme 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, Fabrazyme 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 Fabrazyme.

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

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com
Medicare Part D Prescription Drug Coverage
Fabrazyme 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 CareConnectPSS® 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 Fabrazyme will need to be considered medically necessary in order to be covered under the Medicaid program. Depending on the state, initial treatment with Fabrazyme may require prior approval by the state Medicaid program. For information on Medicaid coverage for Fabrazyme in your state, contact your local Medicaid office or a CareConnectPSS® Case Manager.

Medicaid agencies may require the following:
• Prior authorization to establish medical necessity for Fabrazyme.
• Periodic reauthorization or recertification for continued treatment.
• Letter of Intent to Treat. See the example in Appendix A, page 9.
• Statement of Medical Necessity. See the example in Appendix B, page 10.

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

Medicaid Managed Care
Many states require Medicaid patients to be enrolled in Medicaid Managed Care plans. These plans vary considerably from state-to-state, and have different documentation and coverage requirements. For example, referrals for treatment with Fabrazyme 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 Fabrazyme in your state, contact the Medicaid Managed Care plan or a CareConnectPSS® Case Manager.

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com
FABRAZYME® REIMBURSEMENT

Obtaining reimbursement for Fabrazyme 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 Fabrazyme 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 Fabrazyme 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.

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com
FABRAZYME BILLING CODES

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

<table>
<thead>
<tr>
<th>ICD-10-CM</th>
<th>E75.21 Fabry (Anderson) disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDs</td>
<td>58468-0040-1 – 35 mg vial</td>
</tr>
<tr>
<td></td>
<td>58468-0041-1 – 5 mg vial</td>
</tr>
<tr>
<td>HCPCS</td>
<td>J0180 – Fabrazyme – injection agalsidase beta, 1 mg</td>
</tr>
<tr>
<td>CPT</td>
<td>96365 – Intravenous infusion therapy prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
</tr>
<tr>
<td></td>
<td>96366 – Each additional hour. (List separately in addition to primary procedure code, 96365)</td>
</tr>
<tr>
<td>Revenue</td>
<td>260 – General IV therapy service</td>
</tr>
<tr>
<td></td>
<td>261 – Infusion pump</td>
</tr>
<tr>
<td></td>
<td>258 – IV solutions</td>
</tr>
<tr>
<td></td>
<td>636 – Drugs and biologicals requiring a HCPCS code</td>
</tr>
</tbody>
</table>

- Since third party payers evaluate treatment based on medical necessity, expected outcome, and cost, they generally require documentation of diagnosis and clinical symptoms of Fabry 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 CareConnectPSS® Case Manager.
- The treating physician should request written confirmation of coverage from the third party payer prior to initiation of enzyme replacement therapy. A CareConnectPSS® Case Manager can assist in obtaining written authorization for Fabrazyme treatment.

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com
**CODING GLOSSARY OF TERMS**

**ICD-10-CM** *(The International Classification of Diseases, 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. Official use of the ICD-10-CM system in the U.S. started on October 1, 2015.

**NDC** *(National Drug Code)*

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

**HCPCS** *(Healthcare Common Procedure Coding System)*

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

**CPT** *(Current Procedural Terminology)*

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

**Revenue Codes**

Revenue codes are used by hospitals to classify services by category, and typically are required by payers when billing infusions in the hospital setting.
APPENDIX A
SAMPLE LETTER OF INTENT TO TREAT

Date:

Contact Name:

Insurance Company:

Street Address:

City: State: Zip:

Patient Name:

Subscriber ID#:

Group#:

Subject: Intent to Treat with Fabrazyme® (agalsidase beta)

Dear contact name

patient name has been diagnosed with Fabry disease and I plan to treat with

Fabrazyme® (agalsidase beta), an enzyme replacement therapy. Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces GL-3 deposition from the capillary endothelium of the kidney and certain other cell types. The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression of Fabry disease; however, the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established. Fabrazyme is administered intravenously and is typically administered on an outpatient basis. Fabrazyme is the only FDA-approved enzyme replacement therapy for the treatment of this life-threatening, orphan disease.

Fabry disease is an X-linked genetic disorder of glycosphingolipid metabolism. Deficiency of the lysosomal enzyme a-galactosidase A leads to progressive accumulation of glycosphingolipids, predominantly GL-3, in many body tissues, starting early in life and continuing over decades. Clinical manifestations of Fabry disease include renal failure, cardiomyopathy, and cerebrovascular accidents. Accumulation of GL-3 in renal endothelial cells may play a role in renal failure.

Produced by recombinant DNA technology, Fabrazyme has the same amino acid sequence as the native enzyme. Fabrazyme replaces the missing enzyme and works by clearing the fatty substances that accumulate in certain cells and tissues of Fabry patients.

To this end, I feel it is medically necessary to initiate Fabrazyme treatment for patient name as soon as possible.

Documentation Enclosed

The attached Statement of Medical Necessity contains information pertaining to patient name’s clinical history, diagnosis and signs and symptoms - demonstrating that the use of Fabrazyme is medically indicated and necessary for treatment of Fabry disease. Initially, my prescribed dosing regimen will be mg per kilogram, administered every two weeks.

Also enclosed is full Prescribing Information for Fabrazyme.

Action Requested

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

Thank you for your immediate attention to this request.

Sincerely,

physician name

Full Prescribing Information is enclosed.

cc patient name

This is only a model letter. Call a CareConnectPSS® Case Manager to request a sample Letter of Intent to Treat.

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com

Please see Important Safety Information on pages 2-3 and full Prescribing Information on pages 15-18.
APPENDIX B
SAMPLE STATEMENT OF MEDICAL NECESSITY

---

# STATEMENT OF MEDICAL NECESSITY
**FOR THE TREATMENT OF FABRY DISEASE**

<table>
<thead>
<tr>
<th>PATIENT INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient’s Name</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Gender ☐ Male ☐ Female</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INSURANCE INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insurance Co</td>
</tr>
<tr>
<td>Policy Number</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>MEDICAL ASSESSMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Weight (kg/lbs)</td>
</tr>
<tr>
<td>Please list signs and symptoms consistent with Fabry disease:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Fabry Disease (Lipidosis) ICD-9-CM 272.7</td>
</tr>
<tr>
<td>☐ Fabry (Anderson) Disease ICD-10-CM* E75.21</td>
</tr>
<tr>
<td>Method of diagnosis: ☐ Enzyme Assay ☐ Genetic Testing ☐ Tissue Biopsy</td>
</tr>
<tr>
<td>☐ Other [please specify]</td>
</tr>
<tr>
<td>Diagnostic Results (Values):</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Fabrazyme* (agalsidase beta) NDC 58468-0040-1 35mg vial; NDC 58468-0041-1 5mg vial</td>
</tr>
<tr>
<td>Dose ___________________ mg/kg*</td>
</tr>
<tr>
<td>*recommended dosage of Fabrazyme is 1 mg/kg body weight infused every 2 weeks</td>
</tr>
<tr>
<td>Please list any additional treatment information, including follow-up evaluations:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHYSICIAN AUTHORIZATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>I certify that the above-indicated therapy is medically necessary, and the information provided is accurate to the best of my knowledge</td>
</tr>
<tr>
<td>Physician Name (printed)</td>
</tr>
<tr>
<td>Address</td>
</tr>
<tr>
<td>City</td>
</tr>
<tr>
<td>Phone No. (Home)</td>
</tr>
<tr>
<td>Physician’s Signature</td>
</tr>
<tr>
<td>State Issued</td>
</tr>
</tbody>
</table>

---

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

Questions? Contact CareConnectPSS® at 1-800-745-4447, option 3. www.Fabrazyme.com

---

Important Note:
*For dates of service starting on October 1, 2015
**APPENDIX C**

**SAMPLE UB-04 CLAIM FORM**

**Sample CMS-1450 (UB-04) Claim Form**

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

<table>
<thead>
<tr>
<th>0636</th>
<th>Drugs (Fabrazyme)</th>
<th>0180</th>
<th>MMDDYY</th>
<th>XXX</th>
<th>XX</th>
</tr>
</thead>
<tbody>
<tr>
<td>0260</td>
<td>General IV Therapy</td>
<td>96365</td>
<td>MMDDYY</td>
<td>XXX</td>
<td>XX</td>
</tr>
<tr>
<td>0260</td>
<td>General IV Therapy</td>
<td>96366</td>
<td>MMDDYY</td>
<td>XXX</td>
<td>XX</td>
</tr>
</tbody>
</table>


Please see Important Safety Information on pages 2-3 and full Prescribing Information on pages 15-18.
## APPENDIX D
### SAMPLE CMS-1500 (02-12) CLAIM FORM

![Health Insurance Claim Form](image)


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Please see Important Safety Information on pages 2-3 and full Prescribing Information on pages 15-18.
HIGHLIGHTS OF PRESCRIBING INFORMATION

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

1 INDICATIONS AND USAGE
Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. (1)

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage of Fabrazyme is 1 mg/kg body weight infused every two weeks as an intravenous infusion. (2.1)

2.2 Preparation and Administration Instructions
Administer antipyretics prior to infusion. (2.1)

See the full prescribing information for the recommended infusion rate. (2.1)

2.3 Dosage Forms and Strengths
For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion-associated reactions. (5.1)

ADVERSE REACTIONS
Most common adverse reactions (≥20% and ≥2.0% compared to placebo) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, rash. (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.

See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

FULL PRESCRIBING INFORMATION: CONTENTS*
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Preparation and Administration Instructions
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Anaphylaxis and Allergic Reactions
5.2 Infusion-associated Reactions
5.3 Compromised Cardiac Function
5.4 Immunogenicity and Rechallenge
5.5 Monitoring: Laboratory Tests
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
6.3 Postmarketing Experience
7 CLINICAL PHARMACOLOGY
7.1 Mechanism of Action
7.2 Pharmacodynamics
7.3 Pharmacokinetics
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Responses in Women
9 DESCRIPTION
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
15 HOW SUPPLIED/STORAGE AND HANDLING
16 PATIENT COUNSELING INFORMATION
*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Fabrazyme® (agalsidase beta) for injection, for intravenous use

Initial U.S. Approval: 2003

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.1)

2.2 Preparation and Administration Instructions
Administer antipyretics prior to infusion. (2.1)

See the full prescribing information for the recommended infusion rate. (2.1)

2.3 Dosage Forms and Strengths
For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

CONTRAINDICATIONS
None. (4)

WARNINGS AND PRECAUTIONS
Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion-associated reactions. (5.1)

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Most common adverse reactions (≥20% and ≥2.0% compared to placebo) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, rash. (6.1)

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See 17 for PATIENT COUNSELING INFORMATION

Revised: 12/2018

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8.5 Geriatric Use
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
Fabrazyme® (agalsidase beta) for injection, for intravenous use

Initial U.S. Approval: 2003

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. The initial intravenous infusion rate is no more than 0.25 mg/min (15 mg/hour). Slow the infusion rate in the event of infusion-associated reactions (2.1)

After patient tolerance to the infusion is well established, increase the infusion rate in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hour) with each subsequent infusion. (2.1)

The maximum infusion rate for patients weighing less than 30 kg, is 0.025 mg/minute (1.5 mg/hour). Slow the infusion rate in the event of infusion-associated reactions (2.1)

For patients weighing 30 kg or greater, the minimum infusion duration is 1.5 hours (based on patient individual weight). (2.1)

Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully rechallenged with Fabrazyme. The initial rechallenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the therapeutic dose (0.5 mg/kg) at 1/2 the initial standard recommended rate (0.01 mg/min). Once a patient tolerates the infusion, the dose may be increased to reach the approved dose of 1 mg/kg and the infusion rate may be increased by slowly titrating upwards (doubled every 30 minutes up to a maximum rate of 0.25 mg/min), as tolerated. (2.1)

2.2 Preparation and Administration Instructions
Fabrazyme does not contain any preservatives. Vials are for single use only. Discard any unused product. Avoid shaking or agitating this product. Do not use filter needles during the preparation of the infusion. Reconstitution and Dilution Using Aseptic Techniques

1. Allow Fabrazyme vials and diluent to reach room temperature prior to reconstitution (approximately 30 minutes). The number of 35 mg and 5 mg vials needed is based on the patient's body weight (kg) and the recommended dose of 1 mg/kg.

Select a combination of 35 mg and 5 mg vials so that the total number of mg is equal to or greater than the patient's number of kg of body weight.

2. Reconstitute each 35 mg vial of Fabrazyme by slowly injecting 7.2 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 35 mg, 7 mL).

Reconstitute each 5 mg vial of Fabrazyme by slowly injecting 1.1 mL of Sterile Water for Injection, USP down the inside wall of each vial. Roll and tilt each vial gently. Each vial will yield a 5 mg/mL clear, colorless solution (total extractable amount per vial is 5 mg, 1 mL).

3. Visually inspect the reconstituted vials for particulate matter and discoloration. Do not use the reconstituted solution if there is particulate matter or if it is discolored.

4. The reconstituted solution should be further diluted with 0.9% Sodium Chloride Injection, USP to a total volume based on patient weight specified in Table 1 below. Prior to adding the volume of reconstituted Fabrazyme required for the patient dose, remove an equal volume of 0.9% Sodium Chloride Injection, USP from the infusion bag.

Table 1

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Minimum Total Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤35</td>
<td>50</td>
</tr>
<tr>
<td>36.1–70</td>
<td>100</td>
</tr>
<tr>
<td>70.1–100</td>
<td>250</td>
</tr>
<tr>
<td>&gt;100</td>
<td>500</td>
</tr>
</tbody>
</table>

Patient dose (in mg) ÷ 5 mg/mL = Number of mL of reconstituted Fabrazyme required for patient dose

Example: Patient dose = 80 mg

80 mg ÷ 5 mg/mL = 16 mL of Fabrazyme

Please see Important Safety Information on pages 2-3 and full Prescribing Information on pages 15-18.
Slowly withdraw the reconstituted solution from each vial up to the total volume required for the patient, without injecting the reconstituted Fabrazyme solution directly into the Sodium Chloride solution. Do not inject in the airspace within the infusion bag. Discard any vial with unused reconstituted solution.

5. Gently invert the vial to mix the solution, avoiding vigorous shaking and agitation.

6. Do not inject Fabrazyme in the same intravenous line with other products.

7. Administer Fabrazyme using an in-line low protein binding 0.2 µm filter.

Storage
Use reconstituted and diluted solutions of Fabrazyme immediately. If immediate use is not possible, the reconstituted and diluted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).

3 DOSAGE FORMS AND STRENGTHS
For injection: 5 mg or 55 mg of agalsidase beta as a white to off-white, lyophilized cake or powder in the reconstituted and diluted solution may be stored for up to 24 hours at 2°C to 8°C (36°F to 46°F).

Use reconstituted and diluted solutions of Fabrazyme immediately. If immediate use is not possible, the decision is made to readminister the product [see WARNINGS and Precautions (5.2) and Clinical Studies (14)].

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Anaphylaxis and Allergic Reactions
Life-threatening anaphylactic and severe allergic reactions have been observed in patients during Fabrazyme infusions. Reactions have included localized angioedema (including swelling of the face, mouth, and throat), bronchospasm, hypotension, generalized urticaria, dyspnea, rash, dyspnea, flushing, chest discomfort, pruritus, and nasal congestion. Interventions have included cardiopulmonary resuscitation, oxygen supplementation, intravenous fluids, hospitalization, and treatment with intradial beta-adrenergic agonists, epinephrine, and intravenous corticosteroids.

In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylactic or severe allergic reactions during Fabrazyme infusion. If anaphylactic or severe allergic reactions occur, immediately discontinue the administration of Fabrazyme and initiate necessary emergency treatment. Because of the potential for severe allergic reactions, appropriate medical support measures should be readily available when Fabrazyme is administered.

The risks and benefits of readministering Fabrazyme following an anaphylactic or severe allergic reaction must be considered. Extreme care should be exercised, with appropriate medical support measures readily available, if the decision is made to readminister the product [see WARNINGS and Precautions (5.4) and Clinical Studies (14)].

5.2 Infusion-Associated Reactions
In clinical trials with Fabrazyme, 59% of patients experienced infusion-associated reactions during Fabrazyme administration, some of which were severe [see WARNINGS and Precautions (5.4)]. Severe infusion-associated reactions experienced by more than one patient in clinical studies with Fabrazyme included dyspnea, chills, vomiting, hypertension, and pruritus. Other infusion-associated reactions included pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, edema peripheral, myalgia, urticaria, tracheal/pryrexia, and somnolence.

Most patients in clinical trials were pretreated with acetaminophen. In patients experiencing infusion-associated reactions, pretreatment with an antiprretreatment and antihistamine is recommended. Infusion-associated reactions occurred in some patients after receiving pretreatment with antipretreatment, antihistamines, and oral steroids. Infusion-associated reactions tended to decline in frequency with continued use of Fabrazyme. However, infusion-associated reactions may still occur despite extended duration of infusion treatment. If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administering additional antipretreatment, antihistamines, and/or steroids may ameliorate the symptoms. If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered and appropriate medical support treatment should be initiated. Severe reactions are generally managed with administration of antipretreatment, antihistamines, corticosteroids, intravenous fluids, and/or oxygen, when clinically indicated. Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available when Fabrazyme is administered. Patients who have experienced infusion-associated reactions should be treated with caution when readministering Fabrazyme.

5.3 Compromised Cardiac Function
Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions [see WARNINGS and Precautions (5.1, 5.2)]. Patients with compromised cardiac function should be monitored closely if the decision is made to administer Fabrazyme.

5.4 Immunogenicity and Rechallenge
In clinical trials with Fabrazyme, a few patients developed IgE antibodies or skin test reactivity specific to Fabrazyme. Two of six patients in the rechallenge study discontinued treatment with Fabrazyme prematurely due to recurrent infusion-associated reactions. Four serious infusion-associated reactions occurred in three patients during Fabrazyme infusions, including bronchospasm, urticaria, hypotension, and development of Fabrazyme-specific antibodies. Other infusion-associated reactions occurring in more than one patient during the study included rashes, hypertension, nausea, vomiting, and pruritus. Physicians should consider testing for IgE antibodies in patients who experienced suspected allergic reactions and consider the risks and benefits of continued treatment in patients with anti-Fabrazyme IgE antibodies [see WARNINGS and Precautions (5.1)].

Patients who have had a positive skin test to Fabrazyme or who have tested positive for Fabrazyme-specific IgE antibody have been rechallenged with Fabrazyme using a rechallenge protocol [see Clinical Studies (14)]. Rechallenge of these patients should only occur under the direct supervision of qualified personnel, with appropriate medical support measures readily available [see Doseage and Administration (14)].

5.5 Monitoring: Laboratory Tests
There are no marketed tests for antibodies against Fabrazyme. If testing is warranted, contact your local Genzyme representative or Genzyme Corporation at 1-800-745-4447.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are described elsewhere in labeling:

- Anaphylaxis and Allergic Reactions [see WARNINGS and Precautions (5.1)]
- Infusion-Associated Reactions [see WARNINGS and Precautions (5.2)]
- Compromised Cardiac Function [see WARNINGS and Precautions (5.3)]
- Immunogenicity and Rechallenge [see WARNINGS and Precautions (5.4)]

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

6.2 Adverse Reactions
The data described below reflect exposure of 80 patients, ages 16 to 61 years, to 1 mg/kg Fabrazyme every 1 to 3 months in two separate double-blind, placebo-controlled clinical trials, for periods ranging from 1 to 35 months (mean 15.5 months). All 58 patients enrolled in one of the two studies continued into an open-label extension study of Fabrazyme treatment for up to 54 additional months. Patients were treated with antipretreatment and antihistamines prior to the infusions.

Table 2 enumerates adverse reactions that occurred during the double-blind treatment periods of the two placebo-controlled trials (Study 1 and Study 2) [see Clinical Studies (14)]. The most common adverse reactions reported with Fabrazyme were infusion-associated reactions, Fabrazyme 59% vs placebo 27% and some of which were severe. Common adverse reactions which occurred in >20% of patients treated with Fabrazyme and >2.5% compared to placebo are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness and rash.

Common adverse reactions which occurred in >20% of patients treated with Fabrazyme and >2.5% compared to placebo are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness and rash.

Table 2: Summary of Common Adverse Reactions in Clinical Trials of Patients with Fabry Disease

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Fabrazyme (n=80)</th>
<th>Placebo (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>44%</td>
<td>30%</td>
</tr>
<tr>
<td>Chills</td>
<td>43%</td>
<td>12%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>39%</td>
<td>22%</td>
</tr>
<tr>
<td>Headache</td>
<td>39%</td>
<td>28%</td>
</tr>
<tr>
<td>Cough</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>31%</td>
<td>18%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>17%</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>21%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>21%</td>
<td>8%</td>
</tr>
<tr>
<td>Rash</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>19%</td>
<td>8%</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>19%</td>
<td>15%</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>18%</td>
<td>7%</td>
</tr>
<tr>
<td>Pain</td>
<td>16%</td>
<td>13%</td>
</tr>
<tr>
<td>Back pain</td>
<td>16%</td>
<td>10%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14%</td>
<td>5%</td>
</tr>
<tr>
<td>Feeling cold</td>
<td>11%</td>
<td>2%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10%</td>
<td>3%</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Snusitis</td>
<td>9%</td>
<td>3%</td>
</tr>
<tr>
<td>Excoriation</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Increased blood creatinine</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>8%</td>
<td>3%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Respiratory tract congestion</td>
<td>8%</td>
<td>2%</td>
</tr>
<tr>
<td>Toothache</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Fall</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Burning sensation</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6%</td>
<td>3%</td>
</tr>
<tr>
<td>Depression</td>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>Wheezing</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypoacusis</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Viral infection</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Hot flush</td>
<td>5%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Reported at rate of at least 5% in Fabrazyme-treated patients and greater than 2.5% compared to placebo-treated patients.
Serious and/or frequently occurring (>25% incidence) related adverse reactions based on a pooled analysis of 150 patients treated with Fabrazyme consisted of one or more of the following: chills, pyrexia, feeling hot or cold, dyspnea, nausea, flushing, headache, vomiting, paraesthesia, fatigue, pruritus, pain in extremity, hypertension, chest pain, throat tightness, abdominal pain, dizziness, tachycardia, nasal congestion, diarrhea, diarrhea per rectum, myalgia, back pain, pallor, bradycardia, urticaria, hypotension, face edema, rash, and somnolence. The occurrence of somnolence can be attributed to clinical trial specified pretreatment with antihistamines. All infusion-related reactions reported during the study were ameliorated with slowing of the infusion rate, temporarily stopping the infusion, and/or administration of antihistamines, analgesics, or steroids.

Other reported serious adverse events included stroke, pain, ataxia, bradycardia, cardiac arrhythmia, cardiac failure, decreased cardiac output, vertigo, and nephrotic syndrome. These adverse events also occurred as manifestations of Fabry disease; an alteration in frequency or severity cannot be determined from the small numbers of patients studied.

Adverse Reactions in Pediatric Patients

The safety profile of Fabrazyme in pediatric Fabry disease patients, ages 8 to 16 years, was found to be consistent with that seen in adults [see Usage in Specific Populations (8.4) and Clinical Studies (14)]. The safety of Fabrazyme in patients younger than 8 years of age has not been evaluated.

3.5.4 Congenital Anomalies and Supernumerary Limbs

As with all therapeutic proteins, there is potential for immunogenicity. 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 in the studies described below with the incidence of antibodies in other studies or to other agalsidase products may be misleading.

The following data reflect the percentage of patients whose tests results were considered positive for antibodies to Fabrazyme using an ELISA and radioimmunoassay (RIA) assay for antibodies. Ninety-five of 121 (79%) adult patients and 11 of 16 (69%) pediatric patients (106 of 137, 74%) of all patients treated with Fabrazyme in clinical studies have developed IgG antibodies to Fabrazyme. Most patients with antibodies to Fabrazyme do so within the first 12 months of exposure. IgG serum antibody version in pediatric patients was associated with prolonged half-life of Fabrazyme, a phenomenon rarely observed in adult patients [see Clinical Pharmacology (12.3) and Use in Specific Populations (8.4)]. A few patients with antibodies to Fabrazyme have shown a trend toward resolution in the absence of Fabrazyme (see CLINICAL PHARMACOLOGY).

There have been no reports of overdose with Fabrazyme. In clinical trials, patients received doses up to 3 mg/kg body weight. The adverse reactions experienced by patients who received treatment with 3 mg/kg were similar to the adverse reactions experienced by patients who received treatment with 1 mg/kg every 2 weeks.

11 DESCRIPTION

Agalsidase beta is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 kD. The mature protein is comprised of two subunits of 388 amino acids (approximately 51 kD), each of which contains three N-linked glycosylation sites. α-Gal A catalyzes the hydrolysis of globotriaosylceramide (GL-3) and other α-galactiferol-terminated neutral glycosphingolipids, such as galactosylceramide and blood group B substances to ceramide, dihexose and galactose. The specific activity of agalsidase beta is approximately 70 U/mg (one unit is defined as the amount of activity that results in the hydrolysis of 1 µmole of a synthetic substrate, 4-nitrophenyl-α-D-galactopyranoside, per minute under the assay conditions).

Agalsidase beta is produced by recombinant DNA technology in a Chinese hamster ovary mammalian cell expression system. Fabrazyme (agalsidase beta) for injection is intended for intravenous infusion. It is supplied as a sterile, nonpyrogenic, preservative-free, white to off-white, lyophilized cake or powder for reconstitution with Sterile Water for Injection, USP. Each 35 mg vial contains 5 mg of agalsidase beta, as well as 222 mg mannitol, 20.4 mg sodium phosphate monobasic monohydrate, and 56.2 mg sodium chloride for intravenous use. Each 10 mg vial contains 3 mg of agalsidase beta, as well as 33.0 mg mannitol, 3.0 mg sodium phosphate monobasic, and 8.8 mg sodium chloride for intravenous use. Each 3 mg vial contains 1 mg of agalsidase beta, as well as 33.0 mg mannitol, 0.6 mg sodium phosphate dibasic, and 0.8 mg sodium chloride for intravenous use. Each 1 mg vial contains 0.3 mg of agalsidase beta, as well as 33.0 mg mannitol, 0.2 mg sodium phosphate dibasic, and 0.1 mg sodium chloride for intravenous use.

12.2 Pharmacodynamics

In a placebo-controlled study conducted in patients with Fabry disease after intravenous administration of 1 mg/kg of Fabrazyme every two weeks for 20 weeks, a reduction of GL-3 in lymphoid organs was observed in the control arm of the study (Table 1). Plasma agalsidase beta levels were determined by histological and biochemical methods, and plasma concentration was measured by ELISA [see Clinical Studies (14)].

12.3 Pharmacokinetics

Plasma pharmacokinetic profiles of Fabrazyme were characterized at 0.3, 1, and 3 mg/kg in adult patients with Fabry disease. The area under the plasma concentration-time curve (AUC) and the clearance (CL) did not increase proportionately with increasing doses, demonstrating that the enzyme follows non-linear pharmacokinetics (Table 3). Plasma pharmacokinetic profiles were also characterized in patients with Fabry disease (ages ≥12 years) dosed with 1 mg/kg Fabrazyme every 14 days for a total of 11 infusions. Refer to Table 3 below for more details.

In 15 pediatric Fabry patients (ranging in age from 8 to 16 years old and weighing between 27.1 to 64.9 kg) who were dosed with 1 mg/kg every 14 days, Fabrazyme pharmacokinetics were not weight-dependent (Table 3). Fabrazyme concentrations were about five times higher after IgG seroconversion, without any detectable impact on GL-3 clearance. IgG seroconversion in pediatric patients was associated with prolonged half-life and plasma concentrations of agalsidase beta in Fabry, a phenomenon rarely observed in adult patients. A possible cause for this prolongation likely pertains to the inability of antibodies to potentially act as carriers for their antigens [see Adverse Reactions (6.3) and Use in Specific Populations (8.4)].
### Table 3: Fabrazyme Pharmacokinetic Summary

<table>
<thead>
<tr>
<th>Dose</th>
<th>Regimen</th>
<th>Mean Inflation Length (min)</th>
<th>Infusion number (n/total patients)</th>
<th>AUC t∞/Vss mg·h/mL</th>
<th>Cmax/mg/mL</th>
<th>Half-life min</th>
<th>CL mL/min</th>
<th>Vss mL/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg/kg</td>
<td>q14 days x 5</td>
<td>132</td>
<td>1 (n=3)</td>
<td>79 ± 24</td>
<td>0.6 ± 0.2</td>
<td>92 ± 27</td>
<td>4.1 ± 1.2</td>
<td>226 ± 62</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>128</td>
<td>5 (n=3)</td>
<td>74 ± 30</td>
<td>0.6 ± 0.2</td>
<td>78 ± 67</td>
<td>4.6 ± 2.2</td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>q14 days x 5</td>
<td>115</td>
<td>1 (n=3)</td>
<td>498 ± 137</td>
<td>5.0 ± 1.1</td>
<td>67 ± 22</td>
<td>2.1 ± 0.7</td>
<td>112 ± 17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>120</td>
<td>5 (n=2)</td>
<td>499 ± 821</td>
<td>4.7 ± 4.3</td>
<td>45 ± 3</td>
<td>3.2 ± 2.4</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>q14 days x 5</td>
<td>129</td>
<td>1 (n=3)</td>
<td>4188 ± 140</td>
<td>29.7 ± 10</td>
<td>104 ± 4</td>
<td>0.8 ± 0.3</td>
<td>81 ± 45</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>300</td>
<td>5 (n=2)</td>
<td>4327 ± 2074</td>
<td>19.8 ± 5.8</td>
<td>87 ± 21</td>
<td>0.8 ± 0.4</td>
</tr>
</tbody>
</table>

### Table 4: Reduction of GL-3 Inclusions to Normal or Near Normal Levels (0 Score) in the Capillary Endothelium of the Kidney, Heart, and Skin

<table>
<thead>
<tr>
<th>5 Months of the Controlled Study</th>
<th>6 Months of the Open-label Extension Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=29)</td>
<td>Fabrazyme (n=29)</td>
</tr>
<tr>
<td>Kidney</td>
<td>0/29</td>
</tr>
<tr>
<td>Heart</td>
<td>1/29</td>
</tr>
<tr>
<td>Skin</td>
<td>1/29</td>
</tr>
</tbody>
</table>

Results reported where biospies were available.

At 58 patients in Study 1 participated in an open-label extension study of Fabrazyme at 1 mg/kg every two weeks, which continued for an additional 54 months. At the end of 6 months of open-label treatment, most patients achieved a GL-3 inclusion score of 0 in capillary endothelium (Table 4). GL-3 was decreased to normal or near normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells, and non-capillary endothelium. GL-3 deposition was seen in vascular smooth muscle cells, tubular epithelium and podocytes, at variably reduced levels. Forty-four of the 58 patients completed 54 months of the open-label extension study. Thirty-six of these 44 patients underwent follow-up skin biopsy, and 31 of these patients showed sustained GL-3 clearance in the capillary endothelium of the skin. Follow-up heart and kidney biopsies were assessed in only 8 of the 44 patients, which showed sustained GL-3 clearance in the capillary endothelium of the kidney in 8 patients, and sustained GL-3 clearance in the capillary endothelium of the heart in 6 patients. Plasma GL-3 levels were reduced to normal levels (≤7.03 µg/mL, determined by LC/MS/MS) and remained at normal levels after up to 60 months of treatment. The reduction of GL-3 inclusions suggests that Fabrazyme may ameliorate disease expression; however, the relationship of GL-3 inclusions reduction to specific clinical manifestations of Fabry disease has not been established.

Study 2 was a randomized (2:1 Fabrazyme to placebo), double-blind, placebo-controlled, multinational, multicenter study of 62 patients (72 males and 10 females), ages 20 to 72 years, all naive to enzyme replacement therapy. Patients received either 1 mg/kg of Fabrazyme or placebo every two weeks for up to a maximum of 35 months (median 18.5 months). There was significant difference in postbaseline plasma GL-3 levels in the Fabrazyme-treated patients compared to placebo. The reduction in plasma GL-3 levels in the Fabrazyme group compared to the placebo group was significant at one year (p<0.0001) and at two years (p<0.001). Fourteen patients (8 in Fabrazyme-treated and 6 in placebo) had skin biopsies at first infusion and final visit. All Fabrazyme-treated patients had capillary endothelial and deep vessel endothelium scores of zero at the final visit. Four (4) of 10 placebo patients had non-zero capillary endothelium scores (p=0.0150), and 6 of 6 had non-zero deep vessel endothelium scores (p=0.0003).

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There are no animal or human studies to assess the carcinogenic or mutagenic potential of Fabrazyme. A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 13.2 Toxicity Studies

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 13.3 Developmental/Fertility Studies

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 13.4 Carcinogenesis

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 13.5 Mutagenesis

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 13.6 Impairment of Fertility

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

### 14 CLINICAL STUDIES

#### 14.1 Safety and Efficacy of Fabrazyme

A study to assess the safety and efficacy of Fabrazyme in patients with Fabry disease was performed.

#### 14.2 Phase 1/2 Study in Adult Patients with Fabry Disease

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

#### 14.3 Phase 2 Study in Pediatric Patients with Fabry Disease

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

### 15 ADVERSE REACTIONS

#### 15.1 Infusion-Associated Reactions

#### 15.2 Other Adverse Reactions

#### 15.3 Postmarketing Experience

A study to evaluate the effects of agalsidase beta on fertility and general reproduction was performed.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

Fabrazyme (agalsidase beta) for injection is supplied as a sterile, nonpyrogenic, white to off-white lyophilized cake or powder in single-dose vials.

### 17 PATIENT COUNSELING INFORMATION

Inform patients that a Registry has been established in order to better understand the variability and long-term treatment effects of Fabrazyme. The Registry will monitor the effect of Fabrazyme on pregnant women and their offspring. Encourage patients to participate, and to monitor and evaluate long-term treatment effects of Fabrazyme.
AN ONGOING COMMITMENT

For more than 35 years, Sanofi Genzyme has been committed to researching and developing products for people living with lysosomal storage disorders such as Fabry disease. Providing comprehensive and confidential support services that address the unique needs of those living with Fabry disease is part of this ongoing commitment.

To learn more about CareConnectPSS® Support Services, call 1-800-745-4447 (option 3).

www.fabrazyme.com
www.registrynxt.com