UNEXPLAINED CKD?

IT COULD BE FABRY DISEASE

Recognize the signs and symptoms to make an early diagnosis¹⁻⁶

INDICATION AND USAGE

Fabrazyme® (agalsidase beta) 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.

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 Important Safety Information on pages 18–19 and full Prescribing Information.
NEPHROLOGISTS CAN PLAY A CRITICAL ROLE IN THE EARLY DETECTION OF FABRY DISEASE.

Fabry disease: Progressive. Often life threatening.¹⁻⁵

- A multisystemic disease that impacts essential organs, such as the kidney, heart, and brain⁷⁻⁸
- An X-linked disorder that affects men, women, and children¹⁻²

Undiagnosed and unmanaged, Fabry disease can reduce life expectancy⁹,¹⁰

15 YEARS IN FEMALES

20 YEARS IN MALES

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
FABRY DISEASE CAN HAVE A SERIOUS IMPACT ON ESSENTIAL ORGANS, INCLUDING THE KIDNEYS.\textsuperscript{7,8}

Patients with Fabry disease are at high risk of progressing to ESRD at a young age\textsuperscript{2,11}

In the Fabry Registry, female and male patients with ESRD required their first dialysis or transplantation at a median age of 38 years\textsuperscript{12}:

Podocyte damage can be seen as early as the first decade of life, often silent to clinical measures and before overt symptom onset\textsuperscript{2}

Renal failure is one of the main causes of death in patients with Fabry disease\textsuperscript{13}

The prevalence of Fabry disease in the dialysis population is

80x–480x\textsuperscript{14-16} HIGHER IN MEN

10x–108x\textsuperscript{17,18} HIGHER IN WOMEN

than in the general population\textsuperscript{4,19}

ESRD=end-stage renal disease.
**THE HALLMARK OF FABRY DISEASE IS GL-3 ACCUMULATION.**

- Fabry disease is caused by mutations in the *galactosidase alpha (GLA)* gene that cause complete or partial deficiency of α-galactosidase (α-GAL A).
- This results in lifelong, progressive cellular accumulation of globotriaosylceramide (GL-3) throughout the body.
- GL-3 buildup starts in utero and continues throughout life.

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### Renal damage as a result of GL-3 accumulation often precedes laboratory abnormalities and clinical symptom onset

<table>
<thead>
<tr>
<th>Burden of Disease</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular GL-3 Deposits</td>
<td>Stage 1</td>
</tr>
<tr>
<td>Cellular Injury and Damage</td>
<td>Stage 2</td>
</tr>
<tr>
<td>Organ Damage/Initiation of Fibrosis</td>
<td>Stage 3</td>
</tr>
<tr>
<td>Organ Failure/Loss of Function</td>
<td>Stage 4</td>
</tr>
</tbody>
</table>

CKD, including ESRD

Renal manifestations (proteinuria, albuminuria, GFR decline)

GL-3 accumulation in renal cells (podocytes)

GFR=glomerular filtration rate.


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Please see Important Safety Information on pages 18–19 and full Prescribing Information.
NEPHROLOGISTS CAN IDENTIFY FABRY DISEASE BEFORE SERIOUS COMPLICATIONS OCCUR.6

Renal manifestations may include26:

- Proteinuria
- Elevated serum creatinine
- Podocyte injury
- Glomerular sclerosis
- Fibrosis
- Renal failure/ESRD

Nonrenal manifestations may include2:

- Neuropathic pain in the hands and feet
- Impaired sweating
- Heat/cold intolerance
- Angiokeratomas
- Early cardiac disease
- Early TIA/stroke

TIA=transient ischemic attack.
RULE OUT FABRY DISEASE IN YOUR PATIENTS WITH UNEXPLAINED CKD.

Renal Best Practice Guidelines recommend screening patients with unexplained CKD\(^{27}\)

- **Screening MALES** <50 years of age with unexplained CKD
- **Screening FEMALES** at any age with unexplained CKD and other symptoms associated with Fabry disease

**FABRY DISEASE AFFECTS FAMILIES**

For every index patient diagnosed, an average of 5 additional affected family members may be identified\(^{19}\)

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
TESTING FOR FABRY DISEASE IS SIMPLE.

Diagnostic testing can be easily incorporated into standard clinical practice.

- **Affected males** have low $\alpha$-GAL A enzyme activity. Therefore proceed directly to $GLA$ gene sequencing.
  - $\alpha$-GAL A enzyme assay
  - Low $\alpha$-GAL A enzyme activity
  - Fabry disease diagnosis confirmed

- **Affected females** may have normal to low enzyme activity. Therefore proceed directly to $GLA$ gene sequencing.
  - $GLA$ gene sequencing
  - Fabry disease diagnosis confirmed

In affected males, an $\alpha$-GAL A enzyme assay confirms diagnosis.

In affected females, $GLA$ gene sequencing is required to confirm diagnosis.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
CAN YOU SOLVE THIS DIAGNOSTIC CHALLENGE?

CASE STUDY: Ben, a 32-year-old man presenting with unexplained proteinuria

Nonspecific signs and symptoms that overlap with more common diseases often make diagnosis of rare diseases a challenge. Additionally, diagnosis can be delayed when manifestations affect multiple organ systems, if they are considered in isolation rather than holistically.

Ben presented with unexplained proteinuria

**Clinical History**

<table>
<thead>
<tr>
<th>SINCE TEENS</th>
<th>IN 20s</th>
<th>OVER PAST 2 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired sweating and heat/temperature intolerance</td>
<td>Reduced exercise tolerance, recurrent abdominal pain, episodes of diarrhea and constipation</td>
<td>Polyuria and development of pain and numbness in arms/legs following heavy exercise</td>
</tr>
</tbody>
</table>

Do you know a patient like Ben?

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
Pertinent clinical and laboratory findings

<table>
<thead>
<tr>
<th>CLINICAL FINDINGS</th>
<th>LABORATORY FINDINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP 125/85 mmHg</td>
<td>eGFR 80 mL/min/1.73 m²</td>
</tr>
<tr>
<td>BMI and HR in normal ranges</td>
<td>Proteinuria (0.75 g/24 hours)</td>
</tr>
<tr>
<td>Abdominal, pelvic, and genital</td>
<td></td>
</tr>
<tr>
<td>angiokeratomas</td>
<td></td>
</tr>
</tbody>
</table>

Based on clinical and laboratory findings, the nephrologist suspects Fabry disease

Diagnosis of Fabry disease is confirmed by low plasma α-GAL A activity of 0.08 nmol/hr/mL

Family screening was conducted after Ben tested positive for Fabry disease

eGFR=estimated GFR.

Ben exhibited signs and symptoms of Fabry disease since childhood but remained undiagnosed for ~15 years

An earlier diagnosis of Fabry could have helped better manage the disease and identify other affected family members.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
THE PROGRESSION AND MANAGEMENT OF FABRY DISEASE IN CHILDREN AND MEN\textsuperscript{1,2}

**CHILDREN**

In the Fabry Registry:
- 77\% of boys and 51\% of girls reported symptoms (N=352)\textsuperscript{28}
- Median ages of symptom onset were 6 and 9 years in boys and girls, respectively (N=352)\textsuperscript{28}
- 53\% of boys and 87\% of girls with symptoms that warrant treatment remain untreated\textsuperscript{28}

ERT should be considered in symptomatic pediatric patients\textsuperscript{29*}

<table>
<thead>
<tr>
<th>SIGNS AND SYMPTOMS WARRANTING TREATMENT\textsuperscript{29}</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NEUROLOGIC</strong></td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain crises</td>
<td></td>
</tr>
<tr>
<td>Fabry neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>RENAL</strong></td>
<td></td>
</tr>
<tr>
<td>Decline in eGFR</td>
<td></td>
</tr>
<tr>
<td>Pathological albuminuria</td>
<td></td>
</tr>
<tr>
<td>Pathological proteinuria</td>
<td></td>
</tr>
<tr>
<td>Creatinine elevation</td>
<td></td>
</tr>
<tr>
<td>Cellular GL-3 accumulation</td>
<td></td>
</tr>
<tr>
<td>Evidence of tissue damage, such as podocyte effacement</td>
<td></td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia, including sinus bradycardia attributable to Fabry disease</td>
<td></td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td></td>
</tr>
<tr>
<td>Recurrent abdominal pain and diarrhea (excluding alternative causes)</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
</tr>
<tr>
<td>Exercise intolerance and impaired sweating</td>
<td></td>
</tr>
</tbody>
</table>

**MEN**

In the Fabry Registry:
- Male patients experienced a high frequency of symptoms at an early age\textsuperscript{12}
- Median age at time of diagnosis was 24 years\textsuperscript{12}
- Men experienced a mean delay of 14 years from symptom onset to diagnosis\textsuperscript{12}

ERT should be considered for men at time of diagnosis\textsuperscript{6}

**Classic Fabry mutation (symptomatic or asymptomatic):**
- ERT should be considered and is appropriate
- Treatment decisions may be influenced by advanced age of the patient and severe comorbidity

**Nonclassic Fabry mutation or missense GLA VUS:**
- ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or the CNS, even in the absence of typical Fabry symptoms
- The abnormalities should be attributable to Fabry disease; this may require histological assessment or biochemical evidence of GL-3 accumulation
- The advice of an expert in genetics and management of Fabry disease should be sought for interpretation of the pathogenicity of any VUS

VUS=variants of unknown significance.
*Patients younger than 8 years of age were not included in clinical studies of Fabrazyme. The safety and efficacy of Fabrazyme in patients younger than 8 years of age have not been evaluated.

Fabrazyme (agalsidase beta) reduces globotriaosylceramide (GL-3) deposition in 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.\textsuperscript{20}

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
In the Fabry Registry:

- Nearly 70% reported having signs and symptoms (N=1077)\(^\text{12}\)
- 66% of women with symptoms that warrant treatment remain untreated (N=1077)\(^\text{12}\)

ERT should be considered upon early signs of Fabry disease in women\(^\text{6,30}\)

### SIGNS AND SYMPTOMS WARRANTING TREATMENT\(^\text{6,30}\)

<table>
<thead>
<tr>
<th></th>
<th>Classic Symptomatic</th>
<th>Classic Asymptomatic OR Nonclassic(^\text{1})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RENAL</strong></td>
<td>Proteinuria/albuminuria not attributable to other causes, evidence of renal impairment</td>
<td>GFR &lt;90 mL/min/1.73 m(^2) for age &gt;40 years, albuminuria &gt;30 mg/g Podocyte foot process effacement on renal biopsy Moderate or severe GL-3 inclusions in a range of renal cell types</td>
</tr>
<tr>
<td><strong>CARDIAC</strong></td>
<td>Symptomatic cardiac disease not due to other causes (dyspnea, palpitation, syncope, chest pain)</td>
<td>Asymptomatic cardiac disease (cardiomyopathy or arrhythmia, cardiac fibrosis on contrast cardiac MRI)</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>Stroke/TIA</td>
<td>Silent strokes, cerebral white matter lesions (on brain MRI)</td>
</tr>
<tr>
<td><strong>PAIN</strong></td>
<td>Neuropathic pain, pain crises, Fabry disease neuropathy</td>
<td></td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>Recurrent diarrhea; chronic, disabling GI dysfunction (excluding alternative causes)</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td>Exercise intolerance and impaired sweating</td>
<td></td>
</tr>
</tbody>
</table>

VUS=variants of unknown significance.

\(^1\)Nonclassic or missense GLA VUS have the same recommendation for males and females.

Fabrazyme (agalsidase beta) reduces globotriaosylceramide (GL-3) deposition in 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.\(^\text{20}\)
COUNT ON FABRAZYME®.

FABRAZYME cleared GL-3 as quickly as 5 months in the capillary endothelium of the kidney, heart, and skin.

- **Study 1:** At 5 months, a GL-3 inclusion score of 0 was achieved in the capillary endothelium of the kidney by 20 (69%) Fabrazyme patients compared with 0 (0%) placebo patients.

- Similar reductions in GL-3 inclusions were also achieved in the capillary endothelium of the heart and skin, in 21 (72%) Fabrazyme patients compared with 1 (3%) placebo patient, and 29 (100%) Fabrazyme patients compared with 1 (3%) placebo patient, respectively.

- **Study 1 open-label extension:** At 6 months, the majority of patients treated with Fabrazyme had a GL-3 inclusion score of 0 in the capillary endothelium of the kidney, heart, and skin.

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**In the Study 1 open-label extension:**

- GL-3 decreased to normal or near-normal levels in mesangial cells, glomerular capillary endothelium, interstitial cells, and noncapillary endothelium.

- GL-3 was reduced in vascular smooth muscle cells and renal cells, including tubular epithelium and podocytes.

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**SELECTED 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.

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*Study 1: Randomized, 1:1, double-blind, placebo-controlled study. 58 patients with Fabry disease (56 males, 2 females), 16 to 61 years, all naive to ERT. Patients received either 1 mg/kg of Fabrazyme or placebo every 2 weeks for 5 months. Inclusion severity ranged from 0 (normal or near normal) to 3 (severe inclusions). All 58 patients in Study 1 participated in the Study 1 extension, a 54-month, open-label extension trial.

† Placebo patients began Fabrazyme treatment at entry into the open-label extension. This graph represents pooled results from all patients in the study (Fz/Fz and Pz/Fz).

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
COUNT ON FABRAZYME.

FABRAZYME rapidly normalized plasma GL-3 and maintained it for up to 5 years.\(^{20,31}\)

- Similar long-term responses were seen in a majority of patients, with sustained GL-3 clearance in the capillary endothelium of the kidney (8/8), heart (6/8) and skin (31/36) at 4.5 years.\(^{20}\)

- 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.\(^{20}\)

**Fabrazyme Also Cleared GL-3 in Pediatric Populations >8 years:**\(^{20,1}\)

- In 12 male patients, Fabrazyme achieved GL-3 inclusion scores of 0 in the capillary endothelium of the skin at 24 weeks and 48 weeks. Two male patients had no measurable GL-3 inclusions at baseline.

- In 14 male patients, Fabrazyme normalized plasma GL-3 levels at 24 weeks and sustained levels at 48 weeks.

\(^{1}\)Study Design: Open-label, uncontrolled, multinational, multicenter study to evaluate safety, pharmacokinetics, and pharmacodynamics of Fabrazyme treatment in pediatric patients. Study Population: 16 pediatric patients (14 males, 2 females) aged 8 to 16 years at first treatment. Study Dose: Fabrazyme 1 mg/kg every 2 weeks for up to 48 weeks.

Female patients had no measurable GL-3 inclusions and had normal plasma GL-3 levels at baseline, which remained normal through 48 weeks.

**SELECTED IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS** (continued)

- 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.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
SELECTED IMPORTANT SAFETY INFORMATION

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.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
COUNT ON OPTIONS.

FABRAZYME can be administered in multiple treatment settings

• Choice of treatment setting is at the discretion of the physician

• Because of the potential for severe infusion-associated reactions, appropriate medical support measures should be readily available

SELECTED IMPORTANT SAFETY INFORMATION

• 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.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
COUNT ON THE WELL-ESTABLISHED SAFETY PROFILE OF FABRAZYME®.

The safety of FABRAZYME has been assessed in 4 clinical trials involving 162 patients with over 473 patient-years of experience.20,32

- Approximately 1% of patients in clinical trials and postmarketing safety experience developed life-threatening anaphylactic or severe allergic reactions.
- In clinical trials, 59% of patients experienced infusion-associated reactions during Fabrazyme treatment, some of which were severe.
- Over time Fabrazyme, infusion-associated reactions tended to decline during clinical trials; however, they may still occur despite extended duration of treatment.
- A standard pretreatment approach with an antipyretic and antihistamine is recommended for patients experiencing infusion-associated reactions; however, in clinical trials, infusion-associated reactions occurred in some patients after receiving pretreatment.
- 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, and these patients should be monitored closely during Fabrazyme administration.
- 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.

Please see Important Safety Information on pages 18–19 and full Prescribing Information.
SUMMARY OF COMMON ADVERSE REACTIONS IN CLINICAL TRIALS

Occurring in at least 5% of FABRAZYME-treated patients at an incidence >2.5% compared with placebo-treated patients

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Fabrazyme (n=80) %</th>
<th>Placebo (n=60) %</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Fabrazyme (n=80) %</th>
<th>Placebo (n=60) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sinusitis</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>
INDICATION AND USAGE
Fabrazyme® (agalsidase beta) 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.

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.

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 administrating additional antipyretics, 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 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.

REFERENCES

RULE OUT FABRY DISEASE IN YOUR PATIENTS WITH UNEXPLAINED CKD.

- Fabry disease can have a serious impact on essential organs, including the kidney.
- Renal damage as a result of GL-3 accumulation can start as early as the first decade of life, often preceding laboratory abnormalities and clinical symptom onset.
- Renal Best Practice Guidelines recommend screening patients with unexplained CKD for Fabry disease.
- Nephrologists are in a unique position to identify early signs of Fabry disease, which can help lead to timely diagnosis.

COUNT ON FABRAZYME®.

- Can be used in patients regardless of genotype or disease severity.
- Cleared GL-3 as quickly as 5 months in the capillary endothelium of the kidney, heart, and skin in Study 1.
- Normalized plasma GL-3 and sustained clearance for approximately 5 years in the Study 1 open-label extension.
- Has a well-established safety profile.

SELECTED IMPORTANT SAFETY INFORMATION

- If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, 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 treatment should be initiated.
- Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen when clinically indicated.

INDICATION AND USAGE

Fabrazyme® (agalsidase beta) 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.

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.