09-J2000-59

Original Effective Date: 04/15/16

Reviewed: 04/08/26

Revised: 07/01/26

Subject: Agalsidase Beta (Fabrazyme®) IV

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

Dosage/ Administration	Position Statement	Billing/Coding	Reimbursement	Program Exceptions	Definitions
Related Guidelines	Other	References	Updates		

DESCRIPTION:

Agalsidase beta (Fabrazyme) was first FDA-approved in April 2003 for “use in patients with Fabry disease (FD) to decrease globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and other cell types”. Fabrazyme was previously granted orphan drug designation for the treatment of FD in 1988. It was the only FDA-approved treatment available for FD, until the approval of migalastat (Galafold) in August 2018. In March 2021, the approved indication was modified to be “for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease”. The prior label only included data supporting use in children 8 years of age or older. The label update also included new data from a long-term observational study showing Fabrazyme slowed the rate of kidney function decline as compared to a historical control group. Fabrazyme is a recombinant human alpha-galactosidase A enzyme, produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) mammalian cells, with the same amino acid sequence as the native enzyme. Fabrazyme is intended to provide an intravenously infused exogenous source of alpha-galactosidase A (alpha-Gal A) (a.k.a., ceramide trihexosidase) to catalyze the breakdown of glycosphingolipids, including GL-3.

Fabry disease (a.k.a., angiokeratoma corporis diffusum, ceramide trihexosidosis, and Anderson-Fabry disease) is an X-linked genetic disorder of glycosphingolipid metabolism. It is the second most prevalent lysosomal storage disorder after Gaucher disease. Numerous FD-causing mutations have been found in the GLA gene located on the long arm of the X chromosome (Xq22). Mutations associated with the severe, classic manifestation of the disease are present in approximately 1:22,000 to 1:40,000 males, and mutations associated with atypical presentation are present in approximately 1:1,000 to 1:3,000 males and 1:6,000 to 1:40,000 females. Deficient activity of the lysosomal enzyme alpha-Gal A leads to progressive accumulation of glycosphingolipids, predominantly GL-3, in various body tissues, starting early in life and continuing over decades. In males, diagnosis is made by first testing for low alpha-Gal A activity in leukocytes or plasma, and then confirming with mutation analysis of the GLA gene. Alpha-Gal A activity may be normal in up to one-third of females, so mutational analysis is required to screen for disease in women [unless the woman is an obligate heterozygote (i.e., the father is known to have FD)]. In classically affected males (i.e., alpha-Gal A activity is undetectable or <1% of normal), clinical manifestations usually become apparent by 10 years of age. Initial manifestations usually include neuropathy and characteristic skin lesions (i.e., angiokeratomas). Other signs and symptoms may include corneal opacities, hypo- or anhydrosis, heat and cold intolerance, lymphadenopathy, and gastrointestinal symptoms such as abdominal pain and diarrhea. As patients age, cardiovascular, renal, and neurologic

disease become increasingly prominent. Renal disease, particularly proteinuria, occurs in most male patients with a mean age of diagnosis of 35 years. Life-threatening manifestations of FD include renal failure, cardiomyopathy, and cerebrovascular accidents.

There are no studies that definitively guide the timing or duration of Fabrazyme treatment for either symptomatic or asymptomatic patients, and there are no uniform recommendations or guidelines for treatment. The general expert consensus is that classically effected males should receive treatment, regardless of symptoms, as soon as possible after diagnosis. However, the European Renal Best Practice (ERBP) group does not recommend starting treatment in patients with proteinuria (protein-to-creatinine ratio >1 g/g) or eGFR <60 mL/min/1.73 m^2, unless the patient has non-renal indications that warrant treatment. Asymptomatic females and atypically affected males should NOT be routinely treated because not all such patients will develop manifestations of the disease and no rigorous data supports empiric treatment is such patients. The phase II/III trials supporting FDA approval are detailed below.

In a double-blind, placebo-controlled study (the Internation Fabry Disease Study) involving 58 patients with classic FD, infusions of 1 mg/kg every 2 weeks were effective in clearing renal microvascular endothelial deposits of GL-3 (primary study endpoint). After 20 weeks of treatment, clearance was achieved in 69% and 0% of patients receiving agalsidase beta and placebo, respectively ($p<0.001$). Significant reductions in plasma GL-3 and microvascular deposits of GGL-3 in skin and endomyocardium were also demonstrated via biopsy. With continued treatment in an open-label extension (6 months), clearance of microvascular deposits of GL-3 was maintained or further reduced; clearance of renal microvascular endothelial Gb3 deposits after 6 months was evident in 98% of biopsied patients who had previously received agalsidase beta and in 100% of patients who had switched from placebo. The clearance of endomyocardial microvascular endothelial deposits was increased by an additional 15% after a further 6 months of therapy. Pain severity related to FD and associated quality of life were, however, not improved to a significant degree. After an additional 4 years of treatment, renal disease progression occurred in 6 patients (all older than 40 years) and remained stable in the other 52 patients.

In a randomized, double-blind, placebo-controlled study (the Fabry Disease Clinical Trial Study Group) of 82 FD patients with kidney dysfunction (SCr 1.2 to <3 mg/dL or CrCl <80 mL/min), agalsidase beta appeared to delay the time to renal, cardiovascular, and cerebrovascular events. Clinical events occurred in 27% of the agalsidase beta group and 42% of the control group; although suggestive of treatment efficacy, statistical significance with intent-to-treat analysis was not achieved ($p=0.06$). Proteinuria was strongly associated with any clinical event. Sub-analysis of renal events in protocol-adherent patients ($n=74$) revealed a significant treatment effect in the agalsidase beta group versus placebo after adjustment for proteinuria, implying earlier intervention may be more efficacious than intervention during advanced disease.

POSITION STATEMENT:

Site of Care: If agalsidase beta (Fabrazyme) is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-46, Site of Care Policy for Select Non-Oncology Medications.

Initiation of agalsidase beta (Fabrazyme) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "5"):

1. The member has a confirmed diagnosis of Fabry disease (FD) as identified by mutational analysis - laboratory documentation of the gene sequencing results showing a pathogenic or likely pathogenic mutation in the galactosidase alpha gene (GLA) must be submitted*

   **One exception is for female members whose biological father has confirmed FD, in which case either the member's or the father's gene sequencing results can be submitted for validation*

2. The member meets **EITHER** of the following criteria ("a" or "b"):

   a. Alpha-galactosidase A (alpha-Gal A) enzyme activity is undetectable or less than 1% of mean normal enzyme activity (i.e., the "classic" form of FD) – laboratory documentation of serum, blood

spot, or leukocyte alpha-Gal A enzyme activity less than 1% of mean normal enzyme activity must be submitted

b. **BOTH** of the following ("i" and "ii"):

i. Alpha-Gal A enzyme activity is unknown or 1% or greater than mean normal enzyme activity (i.e., "atypical" or "variant" forms of FD)

ii. Member has clinically-relevant manifestations of FD that include **ANY** of the following – a medical record note documenting the FD-related condition(s) must be submitted

- Cardiac disease (e.g., ventricular hypertrophy, fibrosis, heart failure, coronary artery disease, valve disorders, conduction defects)
- Cerebrovascular disease (e.g., history of stroke or TIA, brain lesions found on imaging studies)
- Persistent and severe gastrointestinal symptoms not explained by other conditions
- Persistent hearing problems (e.g., hearing loss, tinnitus, vertigo)
- Severe neuropathy requiring prescription drug treatment
- Renal disease (e.g., proteinuria, renal cysts, GL-3 accumulation on renal biopsy)

3. Treatment with agalsidase beta is prescribed by, or in consultation with, a specialist with experience in treating patients with FD (e.g., nephrologist, neurologist, endocrinologist, clinical geneticist, cardiologist)
4. Agalsidase beta will **NOT** be used in combination with pegunigalsidase (Elfabrio) or migalastat (Galafold)
5. The dosage of agalsidase beta does not exceed 1 mg/kg (rounded to closest 5-mg increment, e.g., 73 kg = 75 mg, 41 kg = 40 mg) every 2 weeks

Approval duration: 6 months

Continuation of agalsidase beta (Fabrazyme) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. An authorization or reauthorization for agalsidase beta has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of Fabry disease (if another health plan, documentation of a health plan-paid claim for agalsidase beta during the 90 days immediately before the request must be submitted), **OR** the member meets **ALL** indication-specific initiation criteria
2. Treatment with agalsidase beta is prescribed by, or in consultation with a specialist with experience in treating patients with FD (e.g., nephrologist, neurologist, endocrinologist, clinical geneticist, cardiologist); **AND** the member is clinically assessed by this specialist at least annually – a chart note confirming the specialist visit within the past year must be submitted
3. Agalsidase beta will **NOT** be used in combination with pegunigalsidase (Elfabrio) or migalastat (Galafold)
4. The dosage of agalsidase beta does not exceed 1 mg/kg (rounded to closest 5-mg increment, e.g., 73 kg = 75 mg, 41 kg = 40 mg) every 2 weeks

Approval duration: 12 months

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND

OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- Indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. The recommended dosage is 1 mg/kg body weight infused every two weeks as an intravenous (IV) infusion. Patients should receive antipyretics prior to infusion. The initial IV infusion rate should be no more than 0.25 mg/min (15 mg/hr). The infusion rate may be slowed in the event of infusion reactions. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min (increments of 3 to 5 mg/hr) with each subsequent infusion. For patients weighing <30 kg, the maximum infusion rate should remain at 0.25 mg/min (15 mg/hr). For patients weighing ≥30 kg, the administration duration should not be less than 1.5 hours (based on individual patient tolerability).

Dose Adjustments

- Hepatic Impairment - Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Renal Impairment - Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed. It is common for patients with advanced Fabry disease to undergo kidney dialysis and transplantation. To date, there are no data regarding these patient populations, but there is no theoretical reason that these patients should have any dosage adjustment.
- Patients who have had a positive skin test to Fabrazyme or who have tested positive for anti-Fabrazyme IgE may be successfully re-challenged with Fabrazyme. The initial re-challenge administration should be a low dose at a lower infusion rate, e.g., 1/2 the therapeutic dose (0.5 mg/kg) at 1/25 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.

Drug Availability

- Intravenous Powder for Solution: 5 mg, 35 mg.
- Refrigerate vials at 2°C to 8°C (36°F to 46°F). Do not use after the expiration date on the vial. This product contains no preservatives. Reconstituted and diluted solutions should be used 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).

PRECAUTIONS:

Boxed Warning

- WARNING: HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS

  Patients treated with enzyme replacement therapies have experienced life-threatening hypersensitivity reactions, including anaphylaxis. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Initiate Fabrazyme in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue Fabrazyme and immediately initiate appropriate medical treatment, including use of epinephrine. Inform patients of the symptoms of life-threatening hypersensitivity reactions, including anaphylaxis and to seek immediate medical care should symptoms occur.

Contraindications

- None

Precautions/Warnings

- **Anaphylaxis and Allergic Reactions** - life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients treated with enzyme replacement therapies, including Fabrazyme. In clinical trials and postmarketing safety experience with Fabrazyme, approximately 1% of patients developed anaphylaxis or severe hypersensitivity reactions. 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. Anaphylaxis has occurred during the early course of enzyme replacement therapy and after extended duration of therapy. Administration should be supervised by a healthcare provider knowledgeable in the management of hypersensitivity reactions including anaphylaxis. Prior to administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Initiate in a healthcare setting with appropriate medical monitoring and support measures, including access to cardiopulmonary resuscitation equipment.
- **Infusion-Associated Reactions** - infusion reactions occurred in 59% of patients during administration in clinical trials. Some reactions were severe. Infusion-associated reactions are defined as adverse reactions occurring on the same day as the infusion. The incidence of infusion-associated reactions was higher in patients who were positive for anti-Fabrazyme antibodies than in patients who were negative for anti-Fabrazyme antibodies. In patients experiencing infusion reactions, pretreatment with an antipyretic and antihistamine is recommended. If an infusion 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 reactions occur, immediate discontinuation of the administration should be considered, and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, IV fluids and/or oxygen as clinically indicated.
- **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 reactions, and these patients should be monitored closely during administration.
- **Immunogenicity and Re-challenge** – re-administration 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.
- **Pregnancy** - available data from postmarketing case reports and case series with Fabrazyme use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Reproduction studies performed in rats at doses up to 68 times the human dose have revealed no evidence of effects on embryo-fetal development. Pregnant women and women of reproductive potential should be encouraged to enroll in the Fabry patient registry. The registry will monitor the effect of Fabrazyme on pregnant women and their offspring. For more information, visitt.com or call 1-800-745-4447, extension 15500.

BILLING/CODING INFORMATION:

HCPCS Coding

J0180	Injection, agalsidase beta, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

E75.21	Fabry (-Anderson) disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date. The Site of Care Policy for Select Specialty Medications does not apply to Medicare Advantage members.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

Genetic Testing, 05-82000-28
Migalastat (Galafold) Capsule, 09-J3000-12
Pegunigalsidase (Elfabrio), 09-J4000-56

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/08/26.

GUIDELINE UPDATE INFORMATION:

04/15/16	New Medical Coverage Guideline.
04/15/17	Review and revision to guideline consisting of updating the references.
05/15/18	Review and revision to guideline consisting of updating the position statement and references.
12/15/18	Revision to guideline consisting of updating the position statement, related guidelines, and references for consistency with the MCG for newly approved migalastat (Galafold).
05/15/19	Review and revision to guideline consisting of updating the position statement, precautions, and references.
11/11/19	Revision to guideline consisting of adding a reference to the Site of Care Policy for Select Specialty Medications and updating the Program Exceptions.
05/15/20	Review and revision to guideline consisting of updating the position statement and references.
05/15/21	Review and revision to guideline consisting of updating the description, position statement, dosage/administration, precautions, and references.
05/15/22	Review and revision to guideline consisting of updating the references.
05/15/23	Review and revision to guideline consisting of updating the references.
05/15/24	Review and revision to guideline consisting of updating the position statement, precautions, related guidelines, and references. Added that agalsidase beta will NOT be used in combination with pegunigalsidase (Elfabrio).
05/15/25	Review and revision of guidelines consisting of updates to the precautions and references.
05/15/26	Review and revision of guidelines consisting of updates to the references.

07/01/26	Revision: Updated Site of Care statement in Position Statement.