09-J2000-59

Original Effective Date: 04/15/16

Reviewed: 04/10/24

Revised: 05/15/24

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.

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 Specialty 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. Fabrazyme does not contain any preservatives. Vials are for single use only. Discard any unused product.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- **Anaphylaxis and Allergic Reactions** - life-threatening anaphylactic and severe allergic reactions have been observed in some patients during infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration and provide necessary emergency treatment. Prior to administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available when Fabrazyme is administered because of the potential for severe infusion reactions.
- **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.

DEFINITIONS:

None

RELATED GUIDELINES:

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

OTHER:

None

REFERENCES:

1. Banikazemi M, Bultas J, Waldek S, et al.; Fabry Disease Clinical Trial Study Group. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. Ann Intern Med. 2007;146(2):77.
2. Beck M, Ricci R, Widmer U, et al. Fabry disease: overall effects of agalsidase alfa treatment. Eur J Clin Invest. 2004;34(12):838.
3. Biegstraaten M, Arngrímsson R, Barbey F, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. Orphanet J Rare Dis. 2015 Mar 27;10:36.
4. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier; 2024. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 03/20/24.
5. DeSchoenmakere G, Chauveau D, Grunfeld J. Enzyme replacement therapy in Anderson-Fabry's disease: beneficial clinical effect on vital organ function. Nephrol Dial Transplant 2003;18:33-5.
6. Desnick RJ, Brady R, Barranger J, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. Ann Intern Med 2003;138:338-46.
7. El Dib R, Gomaa H, Ortiz A, et al. Enzyme replacement therapy for Anderson-Fabry disease: A complementary overview of a Cochrane publication through a linear regression and a pooled analysis of proportions from cohort studies. pLoS One. 2017;12(3):e0173358. Published 2017 Mar 15.
8. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human agalactosidase a replacement therapy in fabry's disease. N Engl J Med 2001;345:9-16.
9. Eng CM, Banikazemi M, Cordon RE, et al. A phase 1/2 clinical trial of enzyme replacement in Fabry disease: pharmacokinetic, substrate clearance, and safety studies. Am J Hum Genet 2001;68:711-22.
10. Fabrazyme (agalsidase beta) [package insert]. Cambridge, MA: Genzyme, Corp.; February 2024.
11. Frustaci A, Chimenti C, Ricci R, et al. Improvement in cardiac function in the cardiac variant of Fabry's disease with galactose-infusion therapy. Engl J Med. 2001;345(1):25
12. Galafold (migalastat) [package insert]. Cranbury, NJ: Amicus Therapeutics U.S., Inc.; June 2023.
13. Germain DP, Charrow J, Desnick RJ, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. J Med Genet. 2015 May;52(5):353-8.
14. Germain DP, Elliott PM, Falissard B, et al. The effect of enzyme replacement therapy on clinical outcomes in male patients with Fabry disease: A systematic literature review by a European panel of experts. Mol Genet Metab Rep. 2019 Feb 6;19:100454. eCollection 2019 Jun.
15. Germain DP, Fouilhoux A, Decramer S, et al. Consensus recommendations for diagnosis, management and treatment of Fabry disease in paediatric patients. Clin Genet. 2019 Aug;96(2):107-117. Epub 2019 Jun 6.
16. Hopkin RJ, Jefferies JL, Laney DA, et al; Fabry Pediatric Expert Panel. The management and treatment of children with Fabry disease: A United States-based perspective. Mol Genet Metab. 2016 Feb;117(2):104-13.
17. Laney DA, Bennett RL, Clarke V, et al. Fabry disease practice guidelines: recommendations of the National Society of Genetic Counselors. J Genet Couns. 2013 Oct;22(5):555-64. Focused Revision Sept. 2020.

18. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 03/20/24.
19. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Mar 20]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
20. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Mol Genet Metab. 2018 Apr;123(4):416-427. Epub 2018 Feb 28.
21. Schiffmann R, Hughes DA, Linthorst GE, et al. Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney Int. 2017 Feb;91(2):284-293. Epub 2016 Dec 18.
22. Schiffmann R, Kopp JB, Austin HA, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. JAMA. 2001;285(21):2743.
23. Sheng S, Wu L, Nalleballe K, et al. Fabry's disease and stroke: Effectiveness of enzyme replacement therapy (ERT) in stroke prevention, a review with meta-analysis. J Clin Neurosci. 2019 Jul; 65:83-86.
24. Sirrs S, Bichet DG, Iwanochko RM, et al. Canadian Fabry Disease Treatment Guidelines 2017. September 22, 2017. Available at:w.fabrycanada.com/content/uploads/Final-Can-FD-Treatment-Guidelines-2017Oct18.pdf
25. Spada M, Baron R, Elliott PM, et al. The effect of enzyme replacement therapy on clinical outcomes in paediatric patients with Fabry disease - A systematic literature review by a European panel of experts. Mol Genet Metab. 2019;126(3):212-223.
26. Terryn W, Cochat P, Froissart R, et al. Fabry nephropathy: indications for screening and guidance for diagnosis and treatment by the European Renal Best Practice. Nephrol Dial Transplant. 2013 Mar;28(3):505-17. Epub 2012 Dec 12.
27. Thurberg BL, Fallon JT, Mitchell R, et al. Cardiac microvascular pathology in Fabry disease: evaluation of endomyocardial biopsies before and after enzyme replacement therapy. Circulation. 2009 May;119(19):2561-7. Epub 2009 May 4.
28. Waldek S. PR interval and the response to enzyme-replacement therapy for Fabry's disease. N Engl J Med 2003; 348:1186-7.
29. Wanner C, Germain DP, Hilz MJ, et al. Therapeutic goals in Fabry disease: Recommendations of a European expert panel, based on current clinical evidence with enzyme replacement therapy. Mol Genet Metab. 2019 Mar;126(3):210-211. Epub 2018 Apr 11.
30. Weidemann F, Niemann M, Breunig F, et al. Long-term effects of enzyme replacement therapy on fabry cardiomyopathy: evidence for a better outcome with early treatment. Circulation. 2009 Feb;119(4):524-9. Epub 2009 Jan 19.
31. Wilcox WR, Banikazemi M, Guffon N, et al.; International Fabry Disease Study Group. Long-term safety and efficacy of enzyme replacement therapy for Fabry disease. Am J Hum Genet. 2004;75(1):65.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/24.

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).