09-J3000-12

Original Effective Date: 12/15/18

Reviewed: 04/09/25

Revised: 05/15/25

Subject: Migalastat (Galafold®) Capsule

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:

Migalastat (Galafold) (Fabrazyme) is an oral alpha-galactosidase A (alpha-Gal A) pharmacological chaperone approved by the U.S. Food and Drug Administration (FDA) in August 2018 for “the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data”. Migalastat was previously granted orphan drug designation for the treatment of Fabry disease in February 2004. Migalastat reversibly binds to the active site of the alpha-Gal A protein. This stabilizes the protein allowing its trafficking from the endoplasmic reticulum into the lysosome where it exerts its action. In the lysosome, migalastat dissociates from alpha-Gal A allowing it to break down the glycosphingolipids, globotriaosylceramide (GL-3) and globotriaosylsphingosine (lyso-Gb3). Certain GLA variants causing Fabry disease result in the production of abnormally folded and less stable forms of the alpha-Gal A protein which retain enzymatic activity. Those GLA variants produce alpha-Gal A proteins that may be stabilized by migalastat thereby restoring their trafficking to lysosomes and their intralysosomal activity.

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 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 less than 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. At present there is no specific curative treatment for the condition and patient management is limited to symptom control and supportive measures. Prior to the approval of migalastat, the only treatment available in the US for FD was IV agalsidase beta (Fabrazyme). Migalastat offers an oral alternative to IV agalsidase beta for patients unable to adhere to every 2-week IV infusion or are unable to tolerate the infusion.

The safety and efficacy of migalastat leading to FDA approval was established in Study AT1001-011 (i.e., Study 1; NCT00925301). This study included a 6-month randomized, double-blind, placebo-controlled phase followed by a 6-month open-label treatment phase and a 12-month open-label extension phase. A total of 67 patients with FD who were naïve to migalastat and enzyme replacement therapy (ERT) or were previously treated with ERT had been off ERT for at least 6 months were randomized in a 1:1 ratio to receive either migalastat 123 mg every other day or placebo for the first 6 months. In the second 6 months, all patients were treated with migalastat. Of the 67 enrolled patients, 50 patients (32 females, 18 males) had amenable GLA variants based on the *in vitro* amenability assay. The median age of the population was 45 years and 97% were Caucasian. The major efficacy outcome measure of the average number of GL-3 inclusions per kidney interstitial capillary (KIC) in renal biopsy samples was assessed by light microscopy before and after treatment. Efficacy was evaluated after 6 months of treatment in 45 of 50 patients with available histology data both at baseline and month 6. A 50% or greater reduction in the average number of GL-3 inclusions per KIC was achieved by 52% of patients treated with migalastat vs. 45% given placebo. Among women (n=29), the rates were 44% versus 46%, and among men (n=16), the rates were 71% vs. 44%. Higher rates of achievement were reported with migalastat in patients with baseline GL-3 inclusion counts/capillary of 0.3 or greater (78% vs. 25%) compared with patients with baseline GL-3 inclusion counts/capillary of less than 0.3 (38% vs 58%). Patients with non-amenable GLA variants (n=17) had no change from baseline in the average number of GL-3 inclusions per KIC after 6 months of treatment.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of migalastat (Galafold) **meets the definition of medical necessity** when **ALL** of the following criteria are met (“1” to “8”):

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*
2. The member has a GLA mutation that is amenable to migalastat therapy as confirmed by **EITHER** of the following ("a" or "b"):
    a. The GLA variant has been previously determined to be amenable to migalastat therapy and is listed in "Table 2: Amenable GLA Variants Based on the In Vitro Assay" in the Galafold product labeling, or listed in the Galafold (migalastat) Amenability Table search tool (https://www.galafoldamenabilitytable.us/) – the specific amendable GLA variant must be provided
    b. For a non-listed mutation, a Good Laboratory Practice (GLP)-validated Human Embryonic Kidney (GLP HEK) assay result showing an amenable mutation - laboratory documentation of the results categorizing the GLA variant as "amenable" 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 and GLP HEK assay results can be submitted for validation*
3. 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)
4. The member has an estimated glomerular filtration rate (eGFR) of greater than or equal to 30 mL/minute/1.73m^2
5. Treatment with migalastat is prescribed by, or in consultation with, a specialist with experience in treating patients with FD (e.g., nephrologist, neurologist, endocrinologist, clinical geneticist, cardiologist)

6. Migalastat will **NOT** be used in combination with agalsidase beta (Fabrazyme) or pegunigalsidase (Elfabrio)
7. The member is 18 years of age or older, **OR** the member's age is within FDA labeling for the requested indication
8. The dosage of migalastat does not exceed 123 mg once every other day

Approval duration: 6 months

Continuation of migalastat (Galafold) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "6"):

1. An authorization or reauthorization for migalastat 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 migalastat during the 90 days immediately before the request must be submitted), **OR** the member meets **ALL** indication-specific initiation criteria
2. The member is 18 years of age or older, **OR** the member's age is within FDA labeling for the requested indication
3. The member has an estimated glomerular filtration rate (eGFR) of greater than or equal to 30 mL/minute/1.73m^2
4. Treatment with migalastat 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
5. Migalastat will **NOT** be used in combination with agalsidase beta (Fabrazyme) or pegunigalsidase (Elfabrio)
6. The dosage of migalastat does not exceed 123 mg once every other day

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

- Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (GLA) variant based on in vitro assay data. This indication is approved under accelerated approval based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Select adults with confirmed Fabry disease who have an amenable GLA variant for treatment [see Table 2 in Clinical Pharmacology section of the product labeling]. Treatment is indicated for patients with an amenable GLA variant that is interpreted by a clinical genetics professional as causing Fabry

disease (pathogenic, likely pathogenic) in the clinical context of the patient. Consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance (VUS, variant of uncertain significance) or may be benign (not causing Fabry disease).

- The recommended dosage regimen is 123 mg orally once every other day at the same time of day. Take on an empty stomach. Do not consume food or caffeine at least 2 hours before and 2 hours after taking to give a minimum 4 hours fast. Clear liquids can be consumed during this 4-hour period.

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 - no dosage adjustment necessary for patient with an eGFR of 30 mL/minute/1.73m^2 or more. Use is not recommended in patients with more severe renal impairment or end-stage renal disease requiring dialysis. Migalastat is substantially excreted by the kidneys. Systemic exposure was significantly increased in subjects with severe renal impairment.

Drug Availability

- 123 mg capsules packaged as two 7-count capsules blister strips with aluminum foil lidding encased in cardboard blister cards providing 14 capsules per wallet pack that supplies the drug product for 4 weeks.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- None

BILLING/CODING INFORMATION:

HCPCS Coding

J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

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.

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:

Agalsidase Beta (Fabrazyme) IV, 09-J2000-59
Genetic Testing, 05-82000-28
Pegunigalsidase (Elfabrio), 09-J4000-56

OTHER:

None

REFERENCES:

1. 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; 10:36.
2. Burlina A, Brand E, Hughes D, et al. An expert consensus on the recommendations for the use of biomarkers in Fabry disease. Mol Genet Metab. 2023 Jun;139(2):107585. Epub 2023 Apr 17.
3. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 03/25/25.
4. 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.

5. Dolores del Pino M, Andres A, Bernabeu AA, et al. Fabry nephropathy: an evidence-based narrative review. Kidney Blood Press Res 2018; 43:406-421.
6. Galafold (migalastat) [package insert]. Cranbury, NJ: Amicus Therapeutics U.S., Inc.; October 2024.
7. 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.
8. Germain DP, Altarescu G, Barriales-Villa R, et al. An expert consensus on practical clinical recommendations and guidance for patients with classic Fabry disease. Mol Genet Metab. 2022 Jul 26;137(1-2):49-61.
9. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. N Engl J Med. 2016 Aug 11;375(6):545-55.
10. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. J Genet Couns. 2020 Oct;29(5):715-717. doi: 10.1002/jgc4.1318. Epub 2020 Sep 3.
11. Hughes, DA, Nicholls, K, Shankar, SP, et al. Oral pharmacological chaperone Migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. J Med Genet 2017; 54:288-96.
12. 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.
13. Micromedex Healthcare Series [Internet Database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed 03/25/25.
14. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2025 [cited 2025 Mar 25]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
15. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: Management and treatment recommendations for adult patients. Molec Gen and Metab. 2018; 123(4) 416-427.
16. 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.
17. 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.
18. 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.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/09/25.

GUIDELINE UPDATE INFORMATION:

12/15/18	New Medical Coverage Guideline.
05/15/19	Review and revision to guideline consisting of updating the position statement and references.
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 position statement 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 migalastat will NOT be used in combination with pegunigalsidase (Elfabrio).
05/15/25	Review and revision of guidelines consisting of updates to the position statement and references. The Galafold (migalastat) Amenability Table search tool has a new web address.