



## Galafold (migalastat) Prior Authorization with Quantity Limit Program Summary

This program applies to Medicaid.

### FDA APPROVED INDICATIONS AND DOSAGE<sup>1</sup>

Agent(s)	Indication(s)	Dosage
Galafold® (migalastat)  Capsule	Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene ( <i>GLA</i> ) variant based on in vitro assay data	123 mg (one capsule) orally every other day, on an empty stomach

### CLINICAL RATIONALE

Fabry disease, also called Anderson-Fabry disease, is a rare X-linked lysosomal storage disorder caused by pathogenic mutations in the *GLA* (galactosidase alpha) gene, resulting in functional deficiency of the enzyme  $\alpha$ -galactosidase A ( $\alpha$ -Gal A).<sup>4</sup> Markedly reduced, or absent, activity of  $\alpha$ -Gal A results in progressive accumulation of glycolipids, primarily globotriaosylceramide (GL-3, Gb<sub>3</sub>), within lysosomes in multiple cell types throughout the body.<sup>2,4,5</sup> This includes those particularly relevant to disease pathology (e.g., vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells) and other cell types in the kidneys, nervous system, and other organs.<sup>2,5,6</sup> Although some *GLA* variants do not appear to cause disease, more than a thousand disease-causing *GLA* variants have been identified. The severity of symptoms may vary among individuals depending upon the specific *GLA* mutation within their family. In general, mutations that result in little to no  $\alpha$ -Gal A activity cause the classic Fabry phenotype, and those mutations that result in residual  $\alpha$ -Gal A activity cause the atypical later-onset phenotype.<sup>2,4,5</sup>

The "classic" form of Fabry disease is the most severe clinical phenotype and occurs predominantly in males. These patients are characterized by absent or severely reduced  $\alpha$ -Gal A activity, with childhood or adolescent onset of symptoms including severe neuropathic or limb pain, abdominal pain, telangiectasias and angiokeratomas, corneal opacities, renal involvement that may progress to end-stage renal disease (ESRD), and hearing loss, with cardiac and cerebrovascular involvement occurring by adulthood. The spectrum of disease severity in heterozygous female patients ranges from asymptomatic to a severe phenotype resembling the male "classic" phenotype and is, in part, dependent on the mutation and the X chromosome inactivation (Lyonization) profile. The prevalence of signs and symptoms at any given age is lower in females, though increasing age will result in development of cardiac and cerebrovascular involvement.<sup>2,5,6</sup>

Fabry disease should be suspected in patients with a family history of Fabry disease or those who present with the clinical manifestations or laboratory abnormalities associated with the disease. The diagnosis is typically confirmed by biochemical and/or molecular genetic testing, with the latter approach being the final determinant.<sup>5</sup> An initial evaluation includes baseline documentation of renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function),

and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation).<sup>2,5,6</sup>

After a thorough clinical evaluation, mutational analysis of the *GLA* gene is the gold-standard assay to confirm the diagnosis of Fabry disease in males and females. For male patients suspected of having Fabry disease, an initial measurement of  $\alpha$ -Gal A activity (in leukocytes, plasma, fibroblasts, or dried blood spots [DBS]) may be performed. However, the  $\alpha$ -Gal A activity assay is not definitive confirmation of Fabry disease, since the assay will identify less than 50% of female carriers. Additionally, for patients with residual  $\alpha$ -Gal A activity on assay (3-35%), genetic testing for a pathogenic *GLA* gene will confirm the Fabry disease diagnosis, and establish the patient's amenability to treatment with chaperone therapy.<sup>2,5</sup>

There is no cure for Fabry disease. Intravenous enzyme replacement therapy (ERT) with Fabrazyme (agalsidase beta), which focuses on replacing the missing or deficient enzyme ( $\alpha$ -Gal A), had been the only treatment for Fabry disease. However, in August 2018 the FDA approved migalastat, an oral capsule taken every other day, as first-line therapy in patients with amenable *GLA* gene variants.<sup>3,4,6</sup> Migalastat is a pharmacologic chaperone that binds to and stabilizes specific (amenable) mutant forms of  $\alpha$ -Gal A, thereby facilitating proper trafficking of the enzyme to lysosomes. Once in the lysosome, migalastat dissociates from  $\alpha$ -Gal A allowing it to then catabolize accumulated glycolipids.<sup>1,3,4</sup>

Certain *GLA* mutations causing Fabry disease result in the production of abnormally folded and less stable forms of the  $\alpha$ -Gal A protein which retain residual enzymatic activity. These *GLA* variants, referred to as amenable variants, produce  $\alpha$ -Gal A proteins that may be stabilized by migalastat thereby restoring their trafficking to lysosomes and their intralysosomal activity.<sup>1</sup> A complete list of amenable variants is available in the Galafold prescribing information or a specific variant can be verified as amenable at <http://www.galafoldamenabilitytable.us/reference>.

Patients on ERT or migalastat should have a clinical evaluation every 6-12 months. Renal function, cardiac function, ophthalmological signs, peripheral nerve symptoms, and gastrointestinal involvement should all be assessed to monitor disease manifestations, disease severity, and/or side effects of therapy.<sup>3,5</sup>

### **Efficacy**

Study AT1001-011 (NCT00925301) 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 Fabry disease who were naïve to migalastat and enzyme replacement therapy (ERT) or who were previously treated with ERT and had been off ERT for at least 6 months were randomized in a 1:1 ratio to receive migalastat every other day or placebo for the first 6 months. In the second 6 months, all patients were treated with migalastat. At 6 months, patients treated with migalastat had lower plasma globotriaosylceramide (GL-3, Gb<sub>3</sub>) levels compared with placebo. No changes in these parameters occurred in patients with non-amenable *GLA* mutations.<sup>1</sup>

A second trial, 18-month, randomized, active-controlled, with 57 adults, compared migalastat with ERT in patients who were previously treated with ERT. Primary objective was to assess renal function and secondary endpoints of cardiovascular and patient-reported outcomes. At 18 months, migalastat and ERT had comparable effects on kidney function. Left ventricular mass index decreased from baseline in patients on migalastat but did not change significantly in those on ERT.<sup>3</sup>

## Safety<sup>1</sup>

Migalastat has no FDA labeled contraindications.

## REFERENCES

1. Galafold prescribing information. Amicus Therapeutics US, Inc. September 2020.
2. Mauer M, Kopp JB, Schiffmann R, et al. Fabry Disease: Clinical Features and Diagnosis. UpToDate. Last updated June 2020. Literature review current through November 2020. Accessed December 2020.
3. Mauer M, Kopp JB., Schiffmann R, et al. Fabry Disease: Treatment and Prognosis. UpToDate. Last updated September 2019. Literature review current through November 2020. Accessed December 2020.
4. Germain DP, Nicholls K, Giugliani R, et al. Efficacy of the Pharmacologic Chaperone Migalastat in a Subset of Male Patients with the Classic Phenotype of Fabry Disease and Migalastat-Amenable Variants: Data from the Phase 3 Randomized, Multicenter, Double-Blind Clinical Trial and Extension Study. *Genet Med.* 2019 Feb;21(9):1987-1997.
5. 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.
6. Ganesh J, et al. Fabry Disease. National Organization for Rare Disorders (NORD): Rare Disease Database. 2019. Available at: <https://rarediseases.org/rare-diseases/fabry-disease/>. Accessed December 2020.

# Galafold (migalastat) Prior Authorization with Quantity Limit

## TARGET AGENT(S)

Galafold® (migalastat)

Brand (generic)	GPI	Multisource Code	Quantity Limit (per day or as listed)
<b>Galafold (migalastat)</b>			
123 mg oral capsule	30903650100120	M, N, O, or Y	14 capsules/28 days

## PRIOR AUTHORIZATION CRITERIA FOR APPROVAL

### Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of Fabry disease AND BOTH of the following:
  - A. The diagnosis was confirmed by mutation in the galactosidase alpha (GLA) gene  
**AND**
  - B. The patient has a confirmed amenable GLA variant based on in vitro assay data (a complete list of amenable variants is available in the Galafold prescribing information or a specific variant can be verified as amenable at <http://www.galafoldamenabilitytable.us/reference>)  
**AND**
2. ONE of the following:
  - A. The patient's age is within FDA labeling for the requested indication for the requested agent  
**OR**
  - B. The prescriber has provided information in support of using the requested agent for the patient's age  
**AND**
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis  
**AND**
4. The prescriber has assessed current status of ALL of the following: renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function), and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation)  
**AND**
5. The patient will NOT be using the requested agent in combination with enzyme replacement therapy (ERT) (e.g., Fabrazyme) for the requested indication  
**AND**
6. The patient does NOT have any FDA labeled contraindications to the requested agent  
**AND**
7. ONE of the following:
  - A. The requested quantity (dose) does NOT exceed the program quantity limit  
**OR**
  - B. ALL of the following:

- i. The requested quantity (dose) is greater than the program quantity limit  
**AND**
- ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication  
**AND**
- iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

**Length of Approval:** 6 months

### **Renewal Evaluation**

**Target Agent(s)** will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process  
**AND**
2. The patient has had benefit or stabilization with the requested agent as indicated by improvement of at least ONE of the following:
  - A. Renal function (e.g., proteinuria, glomerular filtration rate [GFR])  
**OR**
  - B. Cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities)  
**OR**
  - C. Ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy)  
**OR**
  - D. Peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function)  
**OR**
  - E. Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation)
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis  
**AND**
4. The patient will NOT be using the requested agent in combination with enzyme replacement therapy (ERT) (e.g., Fabrazyme) for the requested indication  
**AND**
5. The patient does NOT have any FDA labeled contraindications to the requested agent  
**AND**
6. ONE of the following:
  - A. The requested quantity (dose) does NOT exceed the program quantity limit  
**OR**
  - B. ALL of the following:
    - i. The requested quantity (dose) is greater than the program quantity limit  
**AND**
    - ii. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication  
**AND**

- iii. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

**Length of Approval:** 12 months