migalastat (Galafold™)

Policy # 00653
Original Effective Date: 12/19/2018
Current Effective Date: 01/11/2021

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider migalastat (Galafold™)‡ for the treatment of Fabry disease to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for migalastat (Galafold) will be considered when the following criteria are met:

- Patient has a diagnosis of Fabry disease confirmed by:
  - Males: deficient activity of the enzyme α-galactosidase in plasma and/or leukocytes OR molecular genetic testing of a galactosidase alpha (*GLA*) mutation; OR
  - Females: molecular genetic testing of a *GLA* mutation; AND
- Patient is 18 years of age or older; AND
- Patient has an amenable *GLA* gene variant based on the human embryonic kidney-293 (HEK-293) assay AND the amenable *GLA* gene variant is interpreted by a clinical genetics professional as causing Fabry disease; AND
- Requested drug is NOT used in combination with agalsidase beta (Fabrazyme®)‡.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of migalastat (Galafold) when the patient selection criteria are NOT met to be **investigational.***

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Background/Overview

Galafold is approved 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. A list of amenable *GLA* variants can be found in the product's package insert at: http://www.galafold.com/app/uploads/2018/08/galafold.pdf. The package insert states that: "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)." Galafold is a pharmacological chaperone that reversibly binds to the active site of the alpha-galactosidase A (alpha-Gal A) protein (which is encoded by the *GLA* gene), which is deficient in Fabry disease. This binding stabilizes alpha-Gal A allowing its trafficking from the endoplasmic reticulum into the lysosome where it exerts its action. In the lysosome, at a lower pH and at a higher concentration of relevant substrates, Galafold dissociates from alpha-Gal A allowing it to break down the glycosphingolipids globotriaosylceramide (GL-3) and globotriaosylsphingosine (Gb3). Certain *GLA* variants (mutations) causing Fabry disease result in the production of abnormally folded and less stable forms of the alpha-Gal A protein which, however, retain enzymatic activity. Those *GLA* variants, referred to as amenable variants, produce alpha-Gal A proteins that may be stabilized by Galafold thereby restoring their trafficking to lysosomes and their intralysosomal activity.

Fabry disease is the most prevalent lysosomal storage disorder. The incidence of Fabry disease is estimated to be about 1 in 117,000 live male births. It is an X-linked inborn error of the glycosphingolipid metabolic pathway that results in lysosomal accumulation of Gb3 in a wide variety of cells. This buildup of Gb3 in autonomic ganglia; dorsal root ganglia; renal glomerular,

tubular, and interstitial cells; cardiac muscle cells; vascular smooth muscle cells; vascular and lymphatic endothelial cells in the cornea; valvular fibrocytes; and cardiac conduction fibers leads to the manifestations of the disease. The hydrophilic deacylated derivative of Gb3 is thought to have cytotoxic, pro-inflammatory, and pro-fibrotic effects. Life expectancy in patients with Fabry disease is typically 50 to 55 years in men and 70 years in women. Diagnosis of Fabry disease is suspected based on a patient's clinical presentation but confirmed via enzyme assay and genetic testing of the *GLA* gene. Incidental findings via renal or cardiac biopsies may also lead to the diagnosis. The first

step in the diagnosis in male patients is the measurement of alpha-Gal A activity in leukocytes and/or plasma (leukocyte alpha-Gal A is the standard in most laboratories). Enzymatic testing is often reported as the percent of normal. Different sources define the diagnosis for the percent of normal differently for enzymatic testing. The sensitivity and specificity of the alpha-Gal A assay using leukocytes approaches 100 percent in males, but the assay will identify less than 50 percent of female carriers. Therefore analysis of the *GLA* gene is required in females. Analysis of the *GLA* gene is the gold standard for confirmation in males or females.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Galafold is approved for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable *GLA* variant based on in vitro assay data. A list of amenable *GLA* variants can be found in the product's package insert at http://www.galafold.com/app/uploads/2018/08/galafold.pdf.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, Blue Cross and Blue Shield Association technology assessment program (TEC) and other non-affiliated technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Galafold was studied in 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. Patients received the recommended dosage of Galafold 123 mg every other day. A total of 67 patients with Fabry disease who were naïve to Galafold and enzyme replacement therapy or were previously treated with enzyme replacement therapy and had been off enzyme replacement therapy for at least 6 months were randomized in a 1:1 ratio to receive either Galafold 123 mg every other day or placebo for the first 6 months. In the second 6 months, all patients were treated with Galafold. Of the 67 enrolled patients, 50 patients had amenable *GLA* variants based on the in vitro amenability assay. The major efficacy outcome measure of the average number of globotriaosylceramide (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. Of the 45 evaluable patients, 25 received Galafold and 20 received placebo. Patients with an amenable alpha-gal A had significantly greater mean reduction in GL-3 inclusions per kidney interstitial capillary at 6 months compared with placebo (-0.25 vs. 0.07; P = 0.008) and remained stable through 12 months.

References

1. Galafold [package insert]. Amicus Therapeutics US, Inc. August 2018.
2. Fabry disease: Clinical features, diagnosis, and management of cardiac disease. UpToDate. Updated February 2018.
3. Fabry disease: Treatment. UpToDate. Updated August 2018.
4. Fabry disease – Galafold PA policy. Express Scripts. Updated August 2018.
5. Galafold Drug Evaluation. Express Scripts. Updated August 2018.

Policy History

Original Effective Date: 12/19/2018
Current Effective Date: 01/11/2021

12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. New policy.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/03/2020	Medical Policy Committee review
12/09/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 12/2021

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and

whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.