Medical Benefit Drug Policy

Fabrazyme (agalsidase beta) Injection

Policy Number: MC/PC 013
Effective Date: December 1, 2025

Instructions for Use

Table of Contents **Page**

Related Policies

- N/A

Coverage Rationale

Fabry disease:

For initial coverage of Fabrazyme (agalsidase beta) for Fabry Disease, the following will be required:

- Diagnosis of Fabry disease **and**
- Patient is 2 years of age or older **and**
- One of the following:
  - Detection of pathogenic mutations in the GLA gene by molecular genetic testing
  - Deficiency in α-galactosidase A (α-Gal A) enzyme activity in plasma, isolated leukocytes, or dried blood spots (DBS)
  - Significant clinical manifestations (e.g., neuropathic pain, cardiomyopathy, renal insufficiency, angiokeratomas, cornea verticillata) **and**
- Will not be used in combination with other drugs indicated for Fabry disease

For reauthorization coverage of Fabrazyme (agalsidase beta) the following will be required:

- Patient demonstrates positive clinical response to therapy

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J0180	Injection, agalsidase beta, 1 mg; 1 billable unit = 1 mg.

ICD-10 Code	Description
E75.21	Fabry (-Anderson) disease

Background

Fabry disease (FD), also referred to as Anderson-Fabry disease, is one of the most common lysosomal storage disorders. The prevalence of FD is estimated to range from 1 in 8454 to 1 in 117,000 males, and FD is present across all ethnic and racial groups. However, this prevalence is most likely underestimated due to misdiagnosis (*Mauer et al 2025*). Fabrazyme (agalsidase beta) is a recombinant human α-galactosidase A enzyme. Fabry disease is caused by a deficiency of α-galactosidase A, a lysosomal enzyme that catalyzes the hydrolysis of globotriaosylceramide (GL-3) and other α-galactyl-terminated neutral glycosphingolipids. Fabrazyme is intended to provide an exogenous source of α-galactosidase A and reduce accumulated Gb3 in Fabry disease patients.

Clinical Evidence

Fabrazyme (agalsidase-beta) was evaluated in a randomized, double-blinded (DB), placebo-controlled (PC), and multicenter (MC) study in 58 patients with FD. Patients were randomized to receive α-galactosidase at a dose of 1 mg/kg of body weight or a placebo every 2 weeks for 20 weeks. The primary efficacy endpoint was the percentage of individuals who cleared renal, endomyocardial and skin microvascular endothelial deposits of GL-3 (*Eng et al 2001*). After 20 weeks, GL-3 inclusions in the renal interstitial capillary endothelial cells were normal or near normal levels in 20 of 29 (69%) of those who received α-Gal A vs 0 of 29 (0%) who received the placebo. Microvascular endothelial deposits of GL-3 in the skin ($p < 0.001$) and heart ($p < 0.001$) were also decreased in those who received α-Gal A.

Agalsidase-beta in patients with advanced FD was evaluated in a randomized, DB, PC, MC, multinational trial (N=82). Patients received agalsidase-beta (n=51) or placebo (n=31) every 2 weeks, for up to 35 months. The primary endpoint was the time to the first occurrence of a clinically significant renal, cardiovascular, or cerebrovascular event and/or death (*Banikazemi et al 2007*). Baseline characteristics between both treatment groups were well matched, except for those with proteinuria, a common clinical indicator of clinical events. The agalsidase-beta treatment group experienced delayed clinical events compared to those in the placebo group, with a total of 14 of 51 (27%) in the agalsidase-beta group and 13 of 31 (42%) in the placebo experiencing clinical events (hazard ratio [HR], 0.47; 95% confidence interval [CI], 0.21 to 1.03; $p = 0.06$). A secondary analysis in protocol-adherent patients, adjusting for baseline proteinuria, demonstrated a treatment effect for agalsidase beta vs placebo (HR, 0.39; 95% CI, 0.16 to 0.93; $p = 0.034$).

A 48-week, open-label (OL), single-arm (SA) study evaluated the use of agalsidase beta 1 mg/kg IV every 2 weeks (up to 48 weeks) in 16 pediatric patients (14 males) 8 to 16 years of age. The trial demonstrated reductions in each of the following: GL-3 deposits in skin biopsies, plasma GL-3 (in males), GI symptoms, urinary protein excretion, and days absent from school (*Wraith et al 2018*).

A study investigated the long-term outcomes of 52 patients (50 males and 2 females) with classic FD from the pivotal phase 3 trial, using data from the PC trial, the extension study, and the Fabry registry over a median period of 10 years. Of the 52 patients, 49 (94%) were alive at the end of the 10-year period, and 42 (81%) had not experienced any severe clinical event. Mean plasma GL-3 normalized within 6 months of treatment initiation and remained normal throughout the last follow-up. Overall, agalsidase beta continued to be effective through this follow-up period. Patients who initiated treatment at a younger age benefited more from therapy (*Germain et al 2015*).

A MC, international, longitudinal observational program initiated in 2001 to monitor the outcomes of agalsidase-beta-treated FD patients enrolled in the Fabry Registry compared these patients with historical data from a MC, international natural history study using matched controls (*Batista et al 2022 [poster]*). The 1:1 matched group contained only 1 occurrence of each untreated patient, along with their treated match. From the pool of matched pairs, the pair containing the untreated patient with the longest follow-up was selected. For the X:X group, untreated patients occurred more than once in the matched dataset. The contribution of untreated patients was down-weighted according

to how many times each occurred in the analysis. Results indicated a 53.9% slc ed glomerular filtration rate (eGFR) (p = 0.007); mean difference 1.74; 95% CI, 0.4 was inversely associated with the composite clinical event rate (first report of major renal, cardiovascular or cerebrovascular event, or death):

- 1:1 matched patients: 59% reduction; HR 0.41; 95% CI, 0.22 to 0.74; p = 0.003
- X:X matched patients: 33% reduction; HR 0.67; 95% CI, 0.49 to 0.90; p = 0.008.
- The association was primarily driven by the all-male subgroup.

Clinical Guidelines:

Fabry Disease Practice Guidelines (recommendations of the National Society of Genetic Counselors (NSGC) state that diagnosis of FD should be confirmed using a combination of biochemical and molecular testing. In males, the diagnosis can be confirmed through identifying a deficiency of α-Gal A and the presence of a disease-causing mutation in the GLA gene. In the past, low α-Gal A activity was considered sufficient for diagnosis in males; however, it is now suggested that a diagnosis of FD should not be finalized until a disease-causing *GLA* mutation is identified. Confirmation in females is through identification of a disease-causing *GLA* mutation. Measurement of α-Gal A enzyme activity is not reliable for diagnosis in females. (*Laney et al 2013*) Newborn screening is now possible, and programs have begun in some states. Most methods are based on enzyme measurement, which will predominantly diagnose males and a subset of affected females. Ongoing research into the natural history of FD further confirms that there is a spectrum of disease severity for males and females in this X-linked condition that ranges from a severe classic FD phenotype with childhood onset to the more variable nonclassical FD. Better outcomes of FD-specific treatments and other related therapies occur if patients are managed with the following in mind: patients should have personalized care, a comprehensive evaluation prior to starting Enzyme Replacement Therapy (ERT), start ERT earlier in life, continue to have thorough routine monitoring for both untreated and treated patients, use of adjuvant therapies, and be managed by a multidisciplinary team (*Henderson et al 2020*).

In 2018, FD management and treatment recommendations for adult patients were revisited (*Ortiz et al 2018*), where it was stated that treatment practices vary widely in terms of the timing of ERT initiation. Initiation of ERT requires a confirmed diagnosis of FD. Recommendations for initiation of ERT in adults include the following:

- Classic Fabry mutation, male patients (asymptomatic or symptomatic): ERT should be considered and is appropriate in all patients at any age of presentation.
- Classic Fabry mutation, symptomatic female patient: Signs/symptoms suggesting major organ involvement warrant initiation of ERT.
- Classic Fabry mutation, asymptomatic female patient: ERT should be considered if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or central nervous system (CNS). It should also be considered if a skewed X chromosome inactivation pattern with predominant expression of the mutant GLA allele with or without low α-Gal A activity has been demonstrated in the presence of signs and symptoms of disease.
- Later-onset Fabry mutation or missense GLA variant of uncertain significance (male and female patients): ERT should be considered and is appropriate if there is laboratory, histological, or imaging evidence of injury to the kidney, heart, or CNS, even in the absence of typical Fabry symptoms. The abnormalities should be attributable to FD, which may require histological assessment or biochemical evidence of GL-3 accumulation. The advice of an expert in genetics and management of FD should be sought for interpretation of the pathogenicity of any variant of uncertain significance. Individuals with well-characterized benign GLA polymorphisms should not be treated with ERT. In the absence of demonstrable FD-related tissue pathology or clinical symptoms, ERT may not be appropriate, particularly in heterozygous female patients. These patients should be monitored regularly.

During ERT treatment, periodic monitoring of the patient's IgG anti-agalsidase antibody status is recommended. IgG antibody formation is relatively common and has been reported with both forms of recombinant agalsidase in male patients with more severe mutations (especially in those with absent α-Gal A production). However, the impact of IgG antibodies on ERT clinical effectiveness requires further study. IgE antibodies have also developed in a small number of

patients; in some cases, ERT has been reinstated in these patients using a rech with ERT should be combined with supportive interventions, if indicated, to clinicall gical, and other complications of FD-induced chronic tissue injury. Examples of adjunctive treatments include ACE inhibitors or ARBs to manage proteinuria; stroke prophylaxis in select patients; and neuropathic pain management. The oral pharmacological chaperone migalastat can have significant effects on some aspects of the course of FD in a subset of patients with suitable mutations. At the time of publication, authors noted that FD experts do not yet have sufficient clinical experience to make recommendations about the use of migalastat (*Ortiz et al 2018*).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Fabrazyme (Agalsidase beta) is indicated for the treatment of adult and pediatric patients 2 years of age and older with confirmed Fabry disease. Agalsidase beta is a recombinant human α-galactosidase A enzyme with the same amino acid sequence as the native enzyme. Purified agalsidase beta is a homodimeric glycoprotein with a molecular weight of approximately 100 kD.

References

1. Banikazemi M, Bultas J, Waldek S, et al. Agalsidase-Beta therapy for advanced fabry disease. *Ann Intern Med.* 2007;146(2):77-86.
2. Batista JL, Maski M, Richards S, Gudivada B, Ponce E, Desnick RJ. Overall slowing of decline in kidney function and reduction in severe clinical events in Fabry disease patients treated with agalsidase beta: A matched analysis. Poster presented at: WORLD Symposium 2022, February 2022, San Diego, CA, USA.
3. Bernardes TP, Foresto RD, Kirsztajn GM. Fabry disease: genetics, pathology, and treatment. *Rev Assoc Med Bras* (1992). 2020;66Suppl 1(Suppl 1):s10-s16. doi:10.1590/1806-9282.66.S1.10.
4. Eng CM, Germain DP, Banikazemi M, et al. Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. Genet Med. 2006;8(9):539-548. doi:10.1097/01.gim.0000237866.70357.c6
5. Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry' disease. *N Engl J Med*. 2001;345(1):9-16.
6. Fabrazyme [prescribing information]. Cambridge, MA: Genzyme Corporation; July 2024.
7. Fuller M, Meikle PJ, Hopwood JJ. Epidemiology of lysosomal storage diseases: an overview. In: Mehta A, Beck M, Sunder-Plassmann G, eds. *Fabry Disease: Perspectives from 5 Years of FOS*. Oxford: Oxford PharmaGenesis; 2006. Accessed December 1, 2022.https://www.ncbi.nlm.nih.gov/books/NBK11603/.
8. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's Disease with the pharmacological chaperone migalastat. *N Engl J Med*. 2016;375:545-555.
9. 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;52(5):353-358.
10. Germain DP. Fabry disease. *Orphanet J Rare Dis*. 2010;5(30).
11. Henderson N, Berry L, Laney DA. Fabry Disease practice resource: Focused revision. J Genet Couns. 2020;29:715-717.
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;22(5):555-564. doi:10.1007/s10897-013-9613-3.
13. Mauer M, Wallace E, Schiffmann R. Fabry disease: clinical features and diagnosis. UpToDate Web site. www.uptodate.com. Updated July 2025. Accessed September 10, 2025.
14. Mauer M, Wallace E, Schiffmann R. Fabry disease: treatment and prognosis. UpToDate Web site. www.uptodate.com. Updated March 2025. Accessed September 10, 2025.

15. Michaud M, Mauhin W, Belmatoug N, et al. When and How to Diagnose Fa Med Sci. 2020;360(6):641-649. doi:10.1016/j.amjms.2020.07.011
16. Ortiz A, Germain DP, Desnick RJ, et al. Fabry disease revisited: management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123(4):416-427. doi:10.1016/j.ymgme.2018.02.014.
17. Wraith JE, Tylkio-Syzmanska A, Guffon N, et al. Safety and efficacy of enzyme replacement therapy with agalsidase beta: an international, open-label study in pediatric patients with Fabry disease. Pediatr. 2008;152(4):563-70, 570.e1.

Policy History/Revision Information

Date	Summary of Changes
11/16/2023	Approved by OptumRx P&T Committee
10/16/2024	Annual review. Updated references and formatting.
10/15/2025	Annual review. Added details of Batista et al clinical study. Updated Clinical Guideline details. Updated references and formatting.

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. The insurance reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

OptumRx may also use tools developed by third parties to assist us in administering health benefits. OptumRx Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Nondiscrimination & Language Access Policy

Discrimination is Against the Law. Aspirus Health Plan, Inc. complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex, (including sex characteristics, including intersex traits; pregnancy or related conditions; sexual orientation, gender identity and sex stereotypes), consistent with the scope of sex discrimination described at 45 CFR § 92.101(a)(2). Aspirus Health Plan, Inc. does not exclude people or treat them less favorably because of race, color, national origin, age, disability, or sex.

Aspirus Health Plan, Inc.:
Provides people with disabilities reasonable modifications and free appropriate auxiliary aids and services to communicate effectively with us, such as:

- Qualified sign language interpreters.
- Written information in other formats (large print, audio, accessible electronic formats, other formats).

Provides free language assistance services to people whose primary language is not English, which may include:

- Qualified interpreters.
- Information written in other languages.

If *you* need reasonable modifications, appropriate auxiliary aids and services, or language assistance services, contact the Nondiscrimination Grievance Coordinator at the address, phone number, fax number, or email address below.

If *you* believe that Aspirus Health Plan, Inc. has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, *you* can file a *grievance* with:

Nondiscrimination Grievance Coordinator
Aspirus Health Plan, Inc.
PO Box 1890
Southampton, PA 18966-9998
Phone: 1-866-631-5404 (TTY: 711)
Fax: 763-847-4010
Email: customerservice@aspirushealthplan.com

You can file a *grievance* in person or by mail, fax, or email. If *you* need help filing a *grievance*, the Nondiscrimination Grievance Coordinator is available to help *you*.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue, SW
Room 509F, HHH Building
Washington, D.C. 20201
1.800.368.1019, 800.537.7697 (TDD)

Complaint forms are available at http://www.hhs.gov/ocr/office/file/index.html. This notice is available at Aspirus Health Plan, Inc.'s website: https://aspirushealthplan.com/webdocs/70021-AHP-NonDiscrim_Lang-Assist-Notice.pdf.

Language Assistance Services

Albanian: KUJDES: Nëse flitni shqip, për ju ka në dispozicion shërbime të asistencës gjuhësore, pa pagesë.Telefononi në 1-800-332-6501 (TTY: 711).

Arabic تنبيه: إذا كنت تتحدث اللغة العربية، فإن خدمات المساعدة اللغوية متاحة لك مجاناً. اتصل بن اعلى رقم الهاتف1-800-332-6501(رقم هاتف الصم والبك : 711)

French: ATTENTION: Si vous parlez français, des services d'aide linguistique vous sont proposés gratuitement. Appelez le 1-800-332-6501 (ATS: 711).

German: ACHTUNG: Wenn Sie Deutsch sprechen, stehen Ihnen kostenlos sprachliche Hilfsdienstleistungen zurVerfügung. Rufnummer: 1-800-332-6501 (TTY: 711).

Hindi: _यान द_: य_द आप ि हंदी बोलते ह_ तो आपके ि लए मु_त म_ भाषा सहायता सेवाएं उपल_ध ह_।1-800-332-6501 (TTY: 711) पर कॉल कर_।

Hmong: LUS CEEV: Yog tias koj hais lus Hmoob, cov kev pab txog lus, muaj kev pab dawb rau koj. Hu rau 1-800-332-6501 (TTY: 711).

Korean: 주의: 한국어를 사용하시는 경우, 언어 지원 서비스를 무료로 이용하실 수 있습니다.1-800-332-6501 (TTY: 711)번으로 전화해 주십시오.

Polish: UWAGA: Jeżeli mówisz po polsku, możesz skorzystać z bezpłatnej pomocy językowej. Zadzwoń pod numer1-800-332-6501 (TTY: 711).

Russian: ВНИМАНИЕ: Если вы говорите на русском языке, то вам доступны бесплатные услуги перевода.Звоните 1-800-332-6501 (телетайп: 711).

Spanish: ATENCIÓN: si habla español, tiene a su disposición servicios gratuitos de asistencia lingüística. Llame al1-800-332-6501 (TTY: 711).

Tagalog: PAUNAWA: Kung nagsasalita ka ng Tagalog, maaari kang gumamit ng mga serbisyo ng tulong sa wika nangwalang bayad. Tumawag sa 1-800-332-6501 (TTY: 711).

Traditional Chinese: 注意：如果您使用繁體中文， 您可以免費獲得語言援助服務。請 致電 1-800-332-6501 (TTY: 711)

Vietnamese: CHÚ Ý: Nếu bạn nói Tiếng Việt, có các dịch vụ hỗ trợ ngôn ngữ miễn phí dành cho bạn. Gọi số 1-800-332-6501 (TTY: 711).

Pennsylvania Dutch: Wann du Deitsch (Pennsylvania German / Dutch) schwetzscht, kannscht du mitaus Koschte ebbergricke, ass dihr helft mit die englisch Schprooch. Ruf selli Nummer uff: Call 1-800-332-6501 (TTY: 711).

Lao: ໂປດຊາບ: ຖ້າວ່າ ທ່ານເວົ້າພາສາ ລາວ, ການບໍລິການຊ່ວຍເຫຼືອດ້ານພາສາ,ໂດຍບໍ່ເສັງຄ່າ, ແມ່ນມີພ້ອມໃຫ້ທ່ານ. ໂທຣ 1-800-332-6501 (TTY: 711).