Medical Policy Bulletin

Title:
Agalsidase beta (Fabrazyme®) and pegunigalsidase alfa-iwxj (Elfabrio)
Policy #:
MA08.033d

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

Agalsidase beta (Fabrazyme) is considered medically necessary and, therefore, covered for individuals 2 years of age and older with Fabry disease (FD) to reduce globotriaosylceramide (GL-3) deposition in the capillary endothelium of the kidney and certain other cell types when all of the following criteria are met, including dosing and frequency:

- Diagnosis is confirmed by one of the following:
  - Deficiency of alpha-galactosidase A (α-Gal A) in plasma or peripheral leukocytes
  - Confirmation of a hemizygous pathogenic variant(s) in the GLA gene
- Dosing and frequency: 1 mg/kg intravenous (IV) infusion every 2 weeks
- No concomitant use of migalastat (Galafold)

Pegunigalsidase alfa-iwxj (Elfabrio) is considered medically necessary and, therefore, covered for adult individuals with confirmed FD when all of the following criteria are met, including dosing and frequency:

- Diagnosis of FD as confirmed by one the following:
  - Absence or deficiency (<5% of mean) of normal α-Gal A enzyme activity in leukocytes, dried blood spots, or serum analysis
- Molecular genetic testing demonstrating deletion or mutations in the galactosidase alpha (GLA) gene
- Medication is prescribed by, or in consultation with, a geneticist, endocrinologist, a metabolic disorder subspecialist, or a physician who specializes in the treatment of lysosomal storage disorders
- Presence of clinical signs and symptoms of the disease (e.g., acroparesthesias, angiokeratomas, whorls, anhidrosis/hypohidrosis, renal disease, exercise/heat/cold intolerance, etc.);

- Dosing and frequency: 1 mg/kg administered intravenously once every 2 weeks
- No concomitant use of migalastat (Galafold)

EXPERIMENTAL/INVESTIGATIONAL

All other uses of agalsidase beta (Fabrazyme®) and pegunigalsidase alfa-iwxj (Elfabrio) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of agalsidase beta (Fabrazyme) and pegunigalsidase alfa-iwxj (Elfabrio). Changes to these guidelines are based on a consensus of information obtained from resources such as, but not limited to: the US Food and Drug Administration (FDA); Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of agalsidase beta (Fabrazyme) or pegunigalsidase alfa-iwxj (Elfabrio) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the utilization management activities. The Company reserves the right to conduct post-payment review and audit procedures for any claims submitted for agalsidase beta (Fabrazyme)and pegunigalsidase alfa-iwxj (Elfabrio).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

When coverage of agalsidase beta (Fabrazyme) or pegunigalsidase alfa-iwxj (Elfabrio) is requested outside of the Dosing and Frequency Requirements listed in this policy, the prescribing professional provider must supply documentation (i.e., published peer-reviewed literature) to the Company that supports this request.

Guidelines

There is no Medicare coverage determination addressing this drug; therefore, the Company policy is applicable.

BLACK BOX WARNINGS

Refer to the specific manufacturer's prescribing information for any applicable Black Box Warnings.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable Evidence of Coverage, agalsidase beta (Fabrazyme®) and pegunigalsidase alfa-iwxj (Elfabrio) may be covered under the medical benefits of the Company’s Medicare Advantage products when medical necessity criteria including dosing and frequency requirements listed in the medical policy are met.

Certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when agalsidase beta (Fabrazyme) and pegunigalsidase alfa-iwxj (Elfabrio) are covered under a member's

medical benefit (Part B benefit). It does not address instances when agalsidase beta (Fabrazyme) and pegunigalsidase alfa-iwxj (Elfabrio) are covered under a member's pharmacy benefit (Part D benefit).

DRUG ADMINISTRATION

Per the FDA labeling, the recommended dosage of agalsidase beta (Fabrazyme) is 1 mg/kg body weight administered every 2 weeks as an intravenous infusion.

Per the US Food and Drug Administration (FDA) labeling, the recommended dosing and frequency of pegunigalsidase alfa-iwxj (Elfabrio) is 1 mg/kg body weight administered every 2 weeks as an intravenous infusion.

US FOOD AND DRUG ADMINISTRATION (FDA) STATUS

The FDA's initial approval of agalsidase beta (Fabrazyme) was issued on April 24, 2003, for the treatment of Fabry disease.

The FDA's initial approval of pegunigalsidase alfa-iwxj (Elfabrio) was issued on May 10, 2023, for the treatment of adult individuals with Fabry disease.

Description

Fabry disease (FD) is a rare gene mutation disorder that is inherited in an X-linked recessive pattern. Because the altered gene is carried on a mother’s X chromosome, sons have a 50% chance of inheriting the disorder, and daughters have a 50% chance of being a carrier. Some female carriers may also exhibit symptoms, especially cloudiness of the cornea.

This mutation causes a deficiency of the lysosomal enzyme known as alpha-galactosidase A. The lack of this enzyme causes an insufficient breakdown of lipids (fats), which then build up to harmful levels in the eyes, kidneys, autonomic nervous system, and cardiovascular system. Symptoms, which usually begin during childhood or adolescence, include the following:

- Generalized fatigue and weakness
- Burning sensation in the hands that worsens with exercise and hot weather
- Small, raised, red-purple blemishes on the skin
- Decreased sweating
- Fever
- Gastrointestinal difficulties, particularly after eating

Although FD usually presents in childhood, a diagnosis may not be confirmed until considerable organ damage has occurred. The average age of diagnosis is about 30. Diagnosis is confirmed by low or absent alpha-galactosidase A activity in plasma or serum, leukocytes, tears, biopsied tissues, or cultured skin fibroblasts. Because of the delay in diagnosis, the increased lipid storage may lead to impaired arterial circulation and an increased risk of heart attack or stroke. The heart may also become enlarged, and the kidneys may become progressively damaged.

Treatment of FD was initially limited to some oral medications (e.g., carbamazepine [Tegretol®], phenytoin [Dilantin®], and metoclopramide [Reglan®]) that were prescribed for an individual's specific symptoms. In the past few years, agalsidase beta (Fabrazyme®) was developed through recombinant DNA technology and was approved by the US Food and Drug Administration on April 24, 2003, as an orphan drug (a drug used to treat, prevent, or diagnose a rare disease) for treatment in individuals with FD. Agalsidase beta (Fabrazyme) is almost identical to alpha-galactosidase A. The replacement of the missing lysosomal enzyme reduces globotriaosylceramide (GL-3), a type of lipid that accumulates in many types of cells, including blood vessels in the kidneys and other organs. With the reduction of fat deposition, it is believed that life-threatening organ damage will be prevented.

CLINICAL STUDIES

The FDA approval of agalsidase beta (Fabrazyme) was based on the results of five clinical studies in individuals with FD.

Study 1 was a randomized, double-blind, placebo-controlled, multinational, multicenter study of 58 individuals, ages between 16 and 61 years, who have a diagnosis of FD and are naive to enzyme-replacement therapy (ERT). For 5 months, individuals received either agalsidase beta (Fabrazyme) or placebo every 2 weeks. The primary efficacy endpoint was assessing GL-3 inclusion in renal interstitial capillary endothelial cells by light microscopy and grading on an inclusion severity scale ranging from 0 (normal or near normal) to 3 (severe inclusions). There was a statistically significant reduction in the inclusion of GL-3 in the Fabrazyme-treated group compared to the placebo-treated group; 69% of the Fabrazyme group achieved a score of 0 compared to the placebo group with none of the individuals reaching a score of 0. These similar reductions were also observed in the capillary endothelium of the heart and the skin.

Study 2 was a randomized, double-blind, placebo-controlled, multinational, multicenter study of 82 individuals, ages 20 to 72 years, who have a diagnosis of FD and are naive to enzyme replacement therapy (ERT). Individuals received either agalsidase beta (Fabrazyme) or placebo every two weeks up to a maximum of 35 months. The reduction in plasma GL-3 levels in the agalsidase beta (Fabrazyme) group compared to the placebo group was statistically significant at 1 year and at 2 years.

Study 3 was an open-label, uncontrolled, multinational, multicenter study evaluating safety, pharmacokinetics, and pharmacodynamics of agalsidase beta (Fabrazyme) in 16 pediatric individuals with FD, ages between 8 and 16 years at first treatment. All individuals received agalsidase beta (Fabrazyme) every 2 weeks for up to 48 weeks. At baseline all the male individuals had elevated plasma GL-3 levels. Twelve of the 12 male individuals had observed GL-3 inclusions in the capillary endothelium on skin biopsies. At week 24 and 48, the 12 male individuals with GL-3 inclusions in capillary endothelium at baseline achieved a GL-3 inclusion score of 0.

Study 4 was an open-label, re-challenge study to evaluate the safety of agalsidase beta (Fabrazyme) in individuals who had a positive skin test to agalsidase beta (Fabrazyme) or who had tested positive for agalsidase beta (Fabrazyme)–specific IgE antibodies. Six adult male individuals, who had experienced multiple or recurrent infusion reactions during previous clinical trials with agalsidase beta (Fabrazyme), were re-challenged with agalsidase beta (Fabrazyme) administered as a graded infusion for up to 52 weeks of treatment. Four of the six individuals treated received at least 26 weeks of agalsidase beta (Fabrazyme). Two individuals discontinued prematurely due to recurrent infusion reactions.

Study 5 was an observational study that analyzed 24 agalsidase beta (Fabrazyme)–treated pediatric individuals with FD aged between 2 to less than 8 years at agalsidase beta (Fabrazyme) initiation and with elevated plasma GL-3 levels (i.e., >7.03 µg/mL) at baseline, plasma GL-3 levels fell within the normal range (i.e., ≤7.03 µg/mL) in 91% (20/22), 95% (18/19), and 92% (12/13) of individuals at 6, 12, and 24 months, respectively. Common adverse reactions reported were upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash.

The long-term safety and efficacy of pegunigalsidase alfa-iwxj (Elfabrio), a novel PEGylated α-Gal-A enzyme replacement therapy (ERT), was evaluated in a phase-1/2 dose-ranging study (NCT02795676). Fifteen ERT-naive adult individuals with FD completed 12 months of pegunigalsidase alfa-iwxj (Elfabrio) and enrolled in this 60-month open-label extension of 1 mg/kg pegunigalsidase alfa-iwxj (Elfabrio) infusions every 2 weeks. Fifteen individuals were enrolled (eight males; seven females); 10 completed 48 months or longer (60 months total treatment), and two completed 60 months (72 months total treatment). Most treatment-emergent adverse events were mild to moderate in severity and all infusion-related reactions were mild to moderate in severity. Four individuals were transiently positive for antipegunigalsidase alfa IgG. Participating individuals showed continuous reduction in plasma lyso-Gb3 concentrations with mean (standard error) reduction of 76.1 ng/mL from baseline to month 24. At 60 months, the estimated glomerular filtration rate slope was comparable to that observed in individuals treated with other ERTs. Cardiac function assessments revealed stability; no cardiac fibrosis was observed. In this first long-term assessment of pegunigalsidase alfa-iwxj (Elfabrio) administration in individuals with FD, pegunigalsidase alfa-iwxj (Elfabrio) had favorable safety/efficacy.

Trial NCT01678898 was a noninferiority randomized, double-blind, and active-controlled trial in ERT-experienced adult individuals diagnosed with FD. Participating individuals were treated with agalsidase beta (Fabrazyme) for at least 1 year prior to trial entry (the mean duration of agalsidase beta [Fabrazyme] treatment prior to enrollment was 5.7 years). Individuals were randomly assigned 2:1 to receive pegunigalsidase alfa-iwxj (Elfabrio) (1 mg/kg intravenous infusion) or agalsidase beta (Fabrazyme) (1 mg/kg intravenous infusion) every 2 weeks for 104 weeks. A total of 77 individuals were randomly assigned and received at least one dose of pegunigalsidase alfa-iwxj (Elfabrio) (N=52; 68%) or agalsidase beta (Fabrazyme) (N=25; 32%). Individuals were between 18 and 60 years of age with a median age of 46 years at baseline; 72 (94%) were White, three (4%) were Black or African-American, and two (3%) were Asian. Two individuals were Hispanic/Latino and 75 individuals were not Hispanic/Latino. Forty-one (53%) individuals had the classic phenotype. The median baseline eGFR and proteinuria was 75 mL/min/1.73

m2 and 0.11 g/g, respectively. The primary efficacy endpoint was the annualized rate of change in eGFR (eGFR slope) assessed over 104 weeks. The estimated mean eGFR slope was −2.4 and −2.3 mL/min/1.73 m2/year on pegunigalsidase alfa-iwxj (Elfabrio) and agalsidase beta (Fabrazyme), respectively. The estimated treatment difference was −0.1 (95% CI, −2.3–2.1) mL/min/1.73 m2/year. Proportions of individuals experiencing treatment-related adverse events and mild or moderate infusion-related reactions were similar in both groups. At the end of the study, neutralizing antibodies were detected in seven of 47 (15%) pegunigalsidase alfa-iwxj (Elfabrio)–treated individuals and six of 23 (26%) agalsidase beta (Fabrazyme)–treated individuals.

The safety and effectiveness of Fabrazyme have been established in pediatric individuals based on adequate and well-controlled studies in adults, a single-arm, open-label study in 16 pediatric individuals with FD aged 8 to 16 years, and additional data in 24 individuals with FD aged between 2 and 7 years.

ERT has been approved by the US Food and Drug Administration for the treatment of FD. This therapy can ease pain, improve organ function, and reduce lipid storage. The National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health (NIH), continues to support research to find ways to treat and prevent lipid storage diseases such as FD.

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
E75.21 Fabry (-Anderson) disease

HCPCS Level II Code Number(s)
J0180 Injection, agalsidase, beta, 1 mg

J2508 Injection, pegunigalsidase alfa-iwxj, 1 mg

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.033d:

12/15/2025	This policy has been reissued in accordance with the Company's annual review process.
12/16/2024	This version of the policy will become effective 12/16/2024. This policy has been updated to communicate coverage for pegunigalsidase alfa-iwxj (Elfabrio). The following HCPCS code was added to the policy: J2508 Injection, pegunigalsidase alfa-iwxj, 1 mg

Revisions From MA08.033c:

05/07/2024	This policy has been reissued in accordance with the Company's annual review process.
12/8/2023	This policy has been reissued in accordance with the Company's annual review process.
04/06/2022	This policy has been reissued in accordance with the Company's annual review process.
08/30/2021	This version of the policy will become effective 08/30/2021. This policy has been updated to communicate coverage for Agalsidase beta (Fabrazyme®) for pediatric individuals two years of age and older

Revisions From MA08.033b:

04/08/2020	This policy has been reissued in accordance with the Company's annual review process.
06/03/2019	This version of the policy will become effective 06/03/2019. The following policy has been updated to communicate dosing and frequency for Agalsidase beta (Fabrazyme®) and laboratory and/or genetic testing.

Revisions From MA08.033a:

06/06/2018	This policy has been reissued in accordance with the Company's annual review process.
06/07/2017	The policy has been reviewed and reissued to communicate the Company’s continuing position on Agalsidase beta (Fabrazyme®).
03/30/2016	The policy has been reviewed and reissued to communicate the Company’s continuing position on Agalsidase beta (Fabrazyme®).
02/11/2015	Updated policy 08.00.69a due to annual review of medical policy. Additional information added to description section about Fabry disease. No changes made to policy criteria.

Revisions From MA08.033:

01/01/2015	This is a new policy.

Version Effective Date:
12/15/2025
Version Issued Date:
12/15/2025
Version Reissued Date:
N/A