Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-2596

Drug Class Review with New Drug Evaluation: Targeted Therapies for Fabry Disease

Date of Review: September 2019
Generic Name: agalsidase beta, migalastat

End Date of Literature Search: 06/25/2019
Brand Name (Manufacturer): Fabrazyme® (Genzyme)
Galafold™ (Amicus Therapeutics)
Dossiers Received: No

Purpose for Class Review:
To identify appropriate utilization management strategies for drugs used to treat patients with Fabry disease.

Research Questions:
1. What is the comparative efficacy and effectiveness for agalsidase beta and migalastat in treating Fabry disease?
2. What are the comparative harms for agalsidase beta and migalastat in treating Fabry disease?
3. Are there subgroups of patients based on demographics (age, racial or ethnic groups and gender), other medications, or co-morbidities for which one treatment for Fabry disease is more effective or associated with fewer adverse events?

Conclusions:
Agalsidase beta

- The first published trial evaluating the efficacy of agalsidase beta was a randomized, double blind, placebo-controlled trial in 58 patients with Fabry disease.[1] The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of Gb3 were cleared (reduced to normal or near-normal levels) over 20 weeks.[1] The FDA reviewers noted that accumulation of Gb3 within capillary endothelial cells is not a disease feature that is routinely assessed by physicians and validated for a relationship to clinically discernable consequences.[2] Thus, Gb3 accumulation does not constitute a clinically meaningful endpoint, and effects on intracellular Gb3 accumulation should not be regarded as substantial evidence of clinical efficacy.[2] It is also unknown which phase of the disease may be most amenable to demonstrating a clinical impact of treatment; so it is unknown if the most sensitive portion of the disease population was being studied in this first trial to evaluate the efficacy of agalsidase beta.[2] Low quality evidence showed treatment with agalsidase beta resulted in clearance of Gb3 renal deposits in 20 of 29 (69%) treated patients compared with no changes in the placebo group (OR=0, p<0.001).[1] However, no improvements in symptoms or renal function were observed by the end of the 20 week trial.[1]
- The objective of a subsequent randomized, placebo-controlled clinical trial was to evaluate the effect of agalsidase beta on disease progression in a composite analysis of renal, cerebrovascular, and cardiac events in patients with advanced Fabry disease over 18 months.[3] Moderate quality evidence showed 42% (n=13) of the 31 patients in the placebo group and 27% (n=14) of the 51 patients in the agalsidase beta group experienced composite clinical events including reduced renal function, cardiac events, stroke, or death (hazard ratio [HR] 0.47; 95% CI, 0.21 to 1.03; P=0.06), but the results

Author: Deanna Moretz, PharmD, BCPS

were not statistically signficant.[3] Individual assessments of each outcome (decreased renal function and incidence of cardiac and cerebrovascular events) were not significantly different between patients in agalsidase beta and placebo groups.[3]

- Criteria for starting and stopping agalsidase alpha or agalsidase beta for Fabry disease are described in the United Kingdom (U.K.) Adult Fabry disease 2013 Standard Operating Procedures.[4] The U.K. procedures recommend that people with classical Fabry disease start enzyme replacement therapy (ERT) at diagnosis, and people with non-classical Fabry disease start ERT when disease symptoms have an impact on quality of life or there is evidence of renal disease, cardiac disease, neurovascular disease or gastrointestinal symptoms.[4]
- There is insufficient evidence for the effectiveness of agalsidase in delaying the onset or reducing the incidence and severity of Fabry disease-related complications, and its impact on long-term survival remains unclear.

<u>Migalastat</u>

- The National Institute of Health and Care Excellence (NICE) committee concluded that Fabry disease is a serious condition with a major effect on quality of life.[5] NICE guidelines recommend migalastat as an option for treating Fabry disease in people over 16 years of age with an amenable mutation and whose disease meets the existing starting criteria for ERT treatment.[5] NICE has not evaluated agalsidase beta for treating Fabry disease.[5] The authors of the NICE evidence review for migalastat concluded the studies providing clinical effectiveness evidence for this drug are limited and there are concerns about the design of the randomized controlled trials and the related open-label extension studies.[5] These concerns included: small populations and short trial durations, imbalances in patient baseline characteristics between the trial arms, and uncertainty as to how long individual patients had received migalastat because it was not reported how many patients were recruited to the open-label extension study from each arm of the initial study.[5]
- The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends the use of migalastat in treating Fabry disease if the following criteria are met:
    - Patients have an amenable mutation and are otherwise eligible for ERT for the treatment of Fabry disease.[6]
    - Migalastat is not to be used concomitantly with ERT.[6]
    - Patients must be under the care of a clinician experienced in the diagnosis and management of Fabry disease.[6]
- The FDA approval of migalastat was based on data from a phase 3 study in 67 treatment-naïve patients with Fabry disease.[7] The primary efficacy outcome was a surrogate endpoint to evaluate the proportion of patients with 50% or greater reduction in the average number of GL-3 inclusions per kidney interstitial capillary (KIC) in biopsy samples from baseline to month 6.[7] Moderate quality evidence from the intention-to-treat (ITT) population analysis did not show a significant treatment effect. A response was achieved in 13 of 34 (38%) migalastat-treated patients compared to 9 of 33 (27%) placebo-treated patients ($p = 0.3$).[7] In the ITT-amenable population with available histology data 13 of 25 (52%) patients on migalastat achieved the primary efficacy outcome compared to 9 of 20 (45%) patients on placebo (statistical data not reported).[7]
- Published data are not yet available on the effects of migalastat in patients with more advanced disease and with duration of therapy beyond 2 years.[8] There is insufficient data regarding the clinical outcomes of migalastat therapy.

Recommendations:

- Designate agalsidase beta and migalastat as non-preferred agents on the Preferred Drug List (PDL) of the Oregon Practitioner-Managed Prescription Drug Plan (PMPDP).
- Implement PA criteria for the Fabry disease treatments to ensure use according to FDA-approved indications (**Appendix 3**).

Background:

Fabry disease is an inherited, X-linked, lysosomal storage disorder caused by mutations in the galactosidase alpha (GLA) gene, which leads to a deficiency in the enzyme alpha-galactosidase A (AGAL-A).[9] In the glycosphingolipid catabolic pathway, AGAL-A breaks down Gb3, a molecule containing 3 sugars attached to a fatty substance.[10] The deficiency of AGAL-A enzyme causes a progressive accumulation of glycosphingolipids in the lysosomes of multiple organs, which results in cellular dysfunction, tissue remodeling, and progressive organ damage.[11] More than 350 Fabry disease mutations have been identified. Males are more frequently and more severely affected than females, and symptoms are observed at a younger age in boys.[11] As many as 70% of carrier women experience symptoms of the disease, although the clinical manifestations of the disease are generally later in onset and milder in female carriers than in affected males.[12] Fabry disease is a panethnic condition with no racial or ethnic predilection.[13] Given the location of the GLA gene on the X chromosome, an affected male inherits the disease from his mother and can pass it to his daughters only.[11] Female carriers have a 50 percent chance of passing the gene on to daughters or sons.[11] The estimated incidence of Fabry disease is approximately 1 in 40,000 male births.[14] However, recognition of later-onset variants suggest the disease occurs more frequently than previously reported, perhaps up to 1 in 3,100 births.[14] Studies have also found an increased incidence of Fabry disease in dialysis patients, patients with cryptogenic strokes, and patients with hypertrophic cardiomyopathy with frequencies ranging from 1:20 to 1:1000 patients.[13] Fabry disease is a funded condition on line 60 (metabolic disorders) of the Health Evidence Review Commission (HERC) prioritized list of health services.[15]

Fabry disease has a spectrum of disease severity ranging from severe, early-onset disease (classic Fabry disease) to later-onset, milder disease (late-onset Fabry disease) to asymptomatic individuals (some heterozygous females).[8] Clinical presentation of Fabry disease is quite varied, and even within one family considerable variation is seen in the age of onset, rate of progression, and organ manifestations.[9] Fabry disease usually presents in childhood (5-9 years of age) with symptoms such as peripheral neuropathy, angiokeratomas (reddish-purple skin lesions) in the trunk area, abdominal pain, nausea, postprandial diarrhea and poor growth.[9] Decreased sweating (hypohidrosis) is another common problem, which has been attributed to effects on the sweat glands and autonomic nervous system.[9] More than 50% of men and 25% of women with Fabry disease have reported decreased sweating, heat intolerance, or both, in childhood.[9] Ocular involvement is most prominent in the cornea, lens, conjunctiva, and retina.[16] A characteristic corneal opacity, observed only by slit-lamp microscopy, is found in affected males and in most heterozygous females.[16] Neuropathic pain is a major cause of morbidity during the first two decades of life.[9] The clinical manifestations of Fabry disease affect patients' wellbeing, physical and social functioning, and ability to conduct activities of daily living, resulting in a decreased quality of life as compared with the general population.[9] Fabry disease may also present in adulthood with late-onset symptoms including hearing loss, proteinuria, left ventricular hypertrophy, arrhythmia, dyspnea, palpitations, and angina.[9] Chronic renal disease, cardiomyopathy, and cerebrovascular disease leading to renal failure, heart failure, or stroke are major complications of Fabry's disease.[9] Most males affected by Fabry disease die by the end of the sixth decade of life.[12]

Diagnosis of Fabry disease is frequently delayed by several years because of the non-specific nature of the presenting signs and symptoms.[9] Family history plays an important role in the evaluation of patients with possible Fabry disease.[11] Because Fabry disease is an X-linked genetic disorder and most cases result from inherited mutations rather than new mutations, most patients have blood relatives who are either affected males or carrier females.[12] Fabry disease can be reliably diagnosed in men by screening for greatly deficient or absent AGAL-A activity in plasma or peripheral leucocytes, or by genetic testing.[9] In women, screening for AGAL-A activity is unreliable because many heterozygous females have normal levels of AGAL-A.[12] Genetic testing is the only reliable means of confirming Fabry disease in women.[9] Deposition of incompletely metabolized glycosphingolipids, mainly Gb3, in multiple cell types is characteristic of Fabry disease.[17] Globotrysilceramide has been used as a biomarker in Fabry disease as measured in plasma and urine by tandem mass spectrometry.[17] The reference ranges for plasma and urinary Gb3 levels are 5.6 (3.6-7.5) µg/ml and 0.016 (0.01 - 0.03) mg/mmol of creatinine, respectively.[17] Globotrysilceramide levels are consistently elevated in most patients with classic Fabry disease. A summary of diagnostic criteria for Fabry disease is outlined in **Table 1.** Diagnosis of Fabry disease is likely in patients with 3 more points from the findings outlined in **Table 1**.

Table 1. Summary of diagnostic criteria for Fabry disease [18]

Criterion	Relevant Finding	Points toward diagnosis	Comment
Clinical features	Cornea verticillata or biopsy proven angiokeratomas	Presence of either or both of these will contribute 1 point	Need to exclude other causes
Alpha-galactosidase activity in plasma or leukocytes	Below 5%	1 point	Activity may not be reduced in females but low activity in a male member of the family cohort would contribute towards the diagnosis
Elevated plasma and/or urine biomarkers	Above reference range for lab; lyso-Gb3 is preferred	1 point	Conditions other than Fabry disease can elevate biomarkers
Molecular change	Mutation defined in literature as disease causing	1 point	High rate of error in annotation of mutations in available databases; the presence of a variant of uncertain significance should not be used to contribute towards the diagnosis
Pathologic findings	Presence of typical features of Fabry disease on biopsy of involved tissue	2 points in target organs (kidney, heart) 1 point in other organs (skin)	Should be interpreted by a pathologist with expertise in Fabry disease

Abbreviations: Gb3 = Globotrysilceramide

Prenatal diagnosis of Fabry disease can be accomplished by the assay of AGAL-A activity in chorionic villi obtained at 9 to 10 weeks of pregnancy or in cultured amniotic cells obtained by amniocentesis at approximately 15 weeks of pregnancy.[16] However, Fabry disease is not currently included in the United States Advisory Committee on Heritable Disorders in Newborns and Children Recommended Uniform Screening Panel.[19] Fabry disease newborn screening programs have been initiated in Missouri, Washington State, New York State, Pennsylvania, Illinois, New Jersey and New Mexico.[13] Newborn screening raises challenges in defining the most appropriate way to counsel families of infants diagnosed with Fabry disease, and how to effectively monitor and manage those infants in order to optimize clinical outcomes.

In the United States, 2 different Fabry disease treatments are available. The first medication, agalsidase beta (Fabrazyme®), was FDA-approved in 2003 and is administered via intravenous infusion every 2 weeks. Agalsidase beta supplies the deficient AGAL-A enzyme which catabolizes Gb3 in capillary endothelium of the kidney and other cell types.[20] A second therapy, oral migalastat (Galafold™), received FDA approval in 2018. Migalastat stabilizes specific mutant forms of AGAL-A. This increases enzyme trafficking to lysosomes and increases the probability that they mature to functional lysosomal enzymes that can catabolize glycosphingolipids.[21] Adjunctive treatment, including angiotensin converting enzyme inhibitors or angiotensin receptor blockers, antiplatelet drugs, and analgesics may also be initiated to manage other complications of Fabry disease. Studies have shown that therapies targeted towards replacing or enhancing the AGAL-A enzyme can delay but not always prevent some of the clinical complications of the disease.[1,3,7] Agalsidase and migalastat are not cures for Fabry disease and do not remove the need for concomitant medications or monitoring. It has been proposed that Gb3 levels may be considered as a biomarker of response to therapy with agalsidase or migalastat.[17] However, the reliability of Gb3 levels as a surrogate marker of treatment response for all patients has been questioned by investigators as some Fabry disease mutations do not respond to replacement therapy and many female heterozygotes with Fabry disease do not have elevated serum Gb3 levels.[22] More details about both therapies are presented in **Table 2** and discussed in more depth later in this report.

Table 2. FDA-Approved Therapies for Fabry disease[20,21]

Generic Drug Name (Brand)	Description	Indication	Availability/Route	Dose and Frequency	Approved Age for Administration
Agalsidase beta (Fabrazyme®)	Recombinant human a-galactosidase A enzyme with the same amino acid sequence as the native enzyme	Treatment of Fabry disease	5 mg and 35 mg vials for intravenous infusion after appropriate reconstitution and dilution	1 mg/kg intravenously every 2 weeks	≥8 years
Migalastat (Galafold™)	Pharmacological chaperone that reversibly binds to the active site of the alpha-galactosidase A protein which stabilizes the enzyme so it can catabolize lysosomal glycosphingolipids	Treatment of Fabry disease, with an amenable mutation	123 mg oral capsule	123 mg orally once every other day on an empty stomach	Adults (no specific age is referenced)

Abbreviations: gm = gram; kg = kilogram; mg=milligram

In the Oregon Health Plan, 36 patients had claims associated with Fabry disease within the past year. Of these 36 patients, 2 are enrolled in Fee-For-Service (FFS), 30 are enrolled in a Coordinated Care Organization (CCO), and 4 patients are no longer eligible. There have been no pharmacy claims for migalastat in the past 12 months in FFS or CCO populations. However, there were 7 physician administered drug (PAD) claims for agalsidase beta in the CCO population and 0 requests in the FFS population in the past year.

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Boxed Warnings and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

After review, 5 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[17,23-27]

Guidelines:

United Kingdom Adult Fabry Disease Standard Operating Procedures

The U.K. standard operating procedures were prepared in 2012 by a group of prescribing physicians working in designated treatment centers at the invitation of the National Specialist Commissioning team.[4] The document is designed to regulate practice in England and is not a clinical guideline for use elsewhere.[4] At the time of publication, the only available treatments in the U.K. for Fabry disease were the 2 enzymes, agalsidase alpha (Replagal™) and agalsidase beta (Fabrazyme™). The advent of enzyme replacement therapy made it necessary to have explicit guidelines for the diagnosis, assessment, treatment and follow up of patients with Fabry disease and their families.[4]

Inclusion Criteria

1. In males with classic mutations (leukocyte enzyme activity <1%) enzyme replacement therapy should commence at diagnosis.
2. In females and those males with later onset mutations with higher levels of leukocyte enzyme activity enzyme replacement therapy should commence when one of the following criteria are fulfilled:

- Uncontrolled pain leading to a need to alter lifestyle or pain that interferes with quality of life.[4]
- Gastrointestinal symptoms such as pain, vomiting or altered bowel habit which are significantly reducing quality of life and not attributable to other pathology.[4]
- Clinically significant reduction in Glomerular Filtration Rate:
    A. < 80 ml/min adjusted according to age
    B. In males: proteinuria >300 mg/24 hours
    C. In males: microalbuminuria where a renal biopsy showed endothelial deposits, vascular or interstitial changes
    D. In children: persistent microalbuminuria (three consecutive early morning urine samples or 3 early morning urine samples over a period of one month).[4]
- Evidence of cardiac disease:
    A. EKG results:
        - Presence of left ventricular hypertrophy
        - Isolated repolarization abnormalities (in absence of other causes such as hypertension, aortic stenosis)
        - Conduction abnormalities: (Short PR interval, 1, 2 or 3 degree heart block, bundle branch block)
    B. Echocardiogram results:
        - Increased left ventricular mass (in patients with concentric remodeling or hypertrophy)
        - Increased left ventricular wall thickness (13 mm in any segment)
        - Left atrial enlargement
        - Valvular thickening/insufficiency
        - Systolic impairment (regional wall motion abnormality or reduction in left ventricular ejection fraction (< 50%)
        - Diastolic dysfunction (using age corrected Doppler assessment)
    C. Arrhythmia:
        - 24 hour EKG (or other documented EKG evidence) showing bradyarrhythmia, atrial arrhythmia, ventricular tachycardia.[4]
    D. Ischemic heart disease:
        - Positive exercise test, PET scan in the ABSENCE of angiographic ally significant epicardial coronary artery disease.[4]

- Cerebrovascular Disease:
    - Previous stroke or TIA in the absence of other risk factors
    - Progression of abnormal cerebral MRI scans[4]

Exclusion Criteria:
1. The presence of another life-threatening illness or disease where the prognosis is unlikely to be improved by enzyme replacement therapy.[4]
2. Patients with Fabry disease who are deemed too severely affected to benefit from enzyme replacement therapy (e.g. severely incapacitated following stroke/ dementia).[4]
3. End stage renal failure requiring dialysis in the absence of other starting criteria.[4]
4. Severe cardiac fibrosis in the absence of other starting criteria.[4]

Efficacy Endpoints:
An improvement in or a prevention of deterioration in:
1. Renal function (defined by GFR or 24 hour urine creatine clearance or proteinuria)
2. Pain scores
3. Age appropriate Quality of Life measurement
4. Cardiac structure and function
5. Neurological status
6. Growth and development in children[4]

National Institute of Health and Care Excellence

National Institute of Health and Care Excellence (NICE) guidance for the use of migalastat in treating Fabry disease was published in 2017.[5] The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alpha and agalsidase beta) for treating Fabry disease.[5] The manufacturer submitted evidence from 2 randomized clinical trials (ATTRACT and FACETS) and 2 open-label extension studies.[5] ATTRACT was an 18-month open-label randomized controlled trial designed to show comparable effectiveness between migalastat and ERT.[5] The small sample size (n=60) in ATTRACT made a standard non-inferiority analysis impossible and the company presented its own pre-specified criteria for comparability.[5] FACETS was a 6-month double-blind randomized controlled trial, in which patients who had not had treatment before had either migalastat or placebo.[5] The trials reported biochemical outcomes of Gb3 and plasma lyso-Gb3 distributions and activity of the enzyme AGAL-A. These are primarily indicators of migalastat efficacy, but may not directly reflect patients' symptoms and do not themselves have a clear role in clinical decision making.[5] Intention-to-treat analyses were done based on all randomized patients in each trial. However, the ITT population included some patients who had mutations that were later found not to be amenable to migalastat.[5] This was because the assay used to determine the amenability of mutations was changed to conform to GLP laboratory standards; the updated assay is the one referred to in the marketing authorization for migalastat.[5] Therefore the company used modified ITT analyses which excluded these patients.[5]

The authors of the evidence review for NICE concluded the studies providing clinical effectiveness evidence for migalastat are limited and there are concerns about the design of both pivotal randomized controlled trials and the related open-label extension studies.[5] These concerns included:
- small populations and short trial durations
- imbalances in patient baseline characteristics between the trial arms in both randomized controlled trials and

- uncertainty as to how long individual patients had received migalastat because it was not reported how many patients were recruited to the open-label extension study from each arm of FACETS.[5]

Final NICE migalastat recommendations include:

1. Migalastat is recommended as an option for treating Fabry disease in people over 16 years of age* with an amenable mutation and only if enzyme replacement therapy (ERT) would otherwise be offered.[5] Criteria for starting and stopping ERT for Fabry disease are described in the United Kingdom Adult Fabry disease Standard Operating Procedures.[4]
2. The committee noted that there were important limitations and uncertainties in the evidence presented for migalastat, and that NICE has not evaluated ERT (agalsidase alpha or agalsidase beta) for treating Fabry disease.[5]

*FDA approval for migalastat is for adults, a specific age range is not referenced.[21]

Canadian Agency for Drugs and Technologies in Health

A 2018 report from the Canadian Agency for Drugs and Technologies in Health (CADTH) focused on the use of migalastat in treating Fabry disease.[6]
Migalastat is recommended for the long-term treatment of adults with a confirmed diagnosis of Fabry disease if the following criteria are met:

- For use in patients with an amenable mutation and who are otherwise eligible for enzyme replacement therapy for the treatment of Fabry disease.[6]
- Migalastat not to be used concomitantly with ERT.[6]
- Patients must be under the care of a clinician experienced in the diagnosis and management of Fabry disease.[6]

Due to the lack of large controlled studies in Fabry disease, most of the published guidelines regarding treatment are consensus based supported by data from observational trials and financially supported by manufacturer grants. For these reasons, 5 guidelines were excluded from this report.[28-31]

Randomized Controlled Trials:

A total of 128 citations were manually reviewed from the initial literature search. After further review, 128 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Drug Evaluation: Agalsidase beta (Fabrazyme®)

Agalsidase beta is a recombinant human AGAL-A enzyme approved for use in patients with Fabry disease to decrease Gb3 deposition in capillary endothelium of the kidney and other cell types.[20] Agalsidase beta is administered as an intravenous infusion once every 2 weeks at a dose of 1 mg/kg.[20] Agalsidase beta received accelerated FDA approval in 2003 due to its orphan drug status. The accelerated approval regulations provide that FDA may grant marketing approval on the basis of adequate and well-controlled clinical trials establishing that the product has an effect upon a surrogate endpoint that is reasonably likely to predict clinical benefit.[2] Approval under these regulations requires that the applicant study the product further to verify and describe the clinical benefit.[2]

Efficacy

The first published trial evaluating the safety and efficacy of agalsidase beta was a randomized, double blind, placebo-controlled trial in 58 patients with Fabry disease.[1] Patients received either 1 mg/kg of agalsidase beta or placebo every two weeks for five months (20 weeks) for a total of 11 infusions. All patients were pretreated with acetaminophen and an antihistamine to decrease or prevent infusion-associated reactions. Oral steroids were an additional option to the pretreatment regimen for patients who exhibited severe or recurrent infusion-associated reactions.[1] The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of Gb3 were cleared (reduced to normal or near-normal levels).[1] Microvascular deposits were graded

on an inclusion severity score ranging from 0 (normal or near normal) to 3 (severe inclusions).[1] After 20 weeks treatment with agalsidase beta resulted in clearance of Gb3 renal deposits in 20 of 29 (69%) treated patients compared with 0 patients in the placebo group (OR=0, p<0.001, CI not reported).[1] Patients in the agalsidase beta group also had decreased microvascular endothelial deposits of Gb3 in the skin (MD = 2.2, P<0.001, CI not reported) and heart (MD = 0.8, P<0.001, CI not reported) compared to placebo.[1] However, no differences between groups in symptoms or renal function were observed during the five-month trial.[1]

The FDA reviewers noted that accumulation of Gb3 within capillary endothelial cells is not a disease feature that is routinely assessed by physicians and validated for a relationship to clinically discernable consequences.[2] Thus, Gb3 accumulation does not constitute a clinically meaningful endpoint, and effects on intracellular Gb3 accumulation should not be regarded as substantial evidence of clinical efficacy.[2] In addition, the study was relatively short for a disorder where progression to renal failure may take many years.[2] It is also unknown which phase of the disease may be most amenable to demonstrating a clinical impact of treatment; so it is unknown if the most sensitive portion of the disease population was being studied in this first trial to evaluate the efficacy of agalsidase.[2]

Since agalsidase beta approval was based on data using a surrogate marker, the FDA required an additional trial to demonstrate clinical benefit.[2] The objective of the subsequent randomized, placebo-controlled trial was to evaluate the effect of agalsidase beta on disease progression in a composite analysis of renal, cerebrovascular, and cardiac events or death in patients with advanced Fabry disease and mild to moderate kidney disease (n=82).[3] Subjects were observed in the blinded portion of the study for 14 months and received open label treatment and follow-up for up to 35 months at 26 sites in 6 countries.[3] Thirteen (42%) of the 31 patients in the placebo group and 14 (27%) of the 51 patients in the agalsidase-beta group experienced composite clinical events including reduced renal function, cardiac events, stroke, or death.[3] In the composite assessment, agalsidase beta delayed the time to first clinical event compared to placebo (hazard ratio, 0.47; 95% CI, 0.21 to 1.03; P=0.06), but the results with not statistically signficant.[3] Individual assessments of each outcome (decreased renal function and incidence of cardiac and cerebrovascular events) were not significantly different between patients in agalsidase beta and placebo groups.[3]

Study limitations included a small sample size, only one third of the patients experienced clinical events, and some patients (n=6) withdrew before experiencing any event.[3] Eight patients had major protocol violations, including 5 patients who missed 22% to 87% of their infusions.[3] Nonsystematic errors introduced by protocol violations, such as missed treatments, could lead to bias toward treatment failure.[3] More information about both agalsidase beta studies is presented in **Table 5**.

A phase 4 post-marketing trial examined the clinical effects of agalsidase beta on the first occurrence of renal, cardiac or cerebrovascular events and serum creatinine over 10 years in 52 of the 58 patients included in the first RCT that evaluated agalsidase beta.[19] Severe clinical events were defined as chronic dialysis, kidney transplant, myocardial infarction, congestive heart failure, major cardiac procedures (i.e., implantation of a balloon pump, cardioverter-defibrillator or first pacemaker; or bypass surgery), stroke and death.[19] Eighty-one percent of patients (42/52) did not experience any severe clinical event during the treatment interval and 94% (49/52) were alive at the end of the study period.[19] Ten patients reported a total of 16 events.[19] The most frequent clinical event was stroke; five patients (9.6%) had a total of eight strokes.[19] Four patients (7.7%), all with high renal involvement at baseline, had a severe renal event.[19] Two cardiac events were reported; cardiac-related death at age 52 years and myocardial infarction at age 53.[19] Two patients with multiple strokes were in their 20's at the time of their first severe clinical event.[19] Renal and cardiovascular events occurred most frequently in patients older than 40 years of age.[19]

Safety

In clinical trials with agalsidase beta, approximately 50 to 55% of patients experienced infusion reactions during drug administration. The majority of infusion reactions were related to febrile reactions or pain symptoms. Most patients in clinical trials were pretreated with acetaminophen. According to the manufacturer, pretreatment with an antipyretic and antihistamine is recommended in patients experiencing infusion associated reactions.[20] A summary of common adverse reactions that occurred with agalsidase beta compared to placebo in clinical trials is presented in **Table 2.**

Table 3. Adverse Reactions Observed with Agalsidase Beta During Clinical Trials.[20]

Adverse Reaction	Agalsidase beta (n=80)	Placebo (n=60)
Upper respiratory infection	44%	30%
Chills	43%	12%
Pyrexia	39%	22%
Headache	39%	28%
Cough	33%	25%
Paresthesia	31%	18%
Fatigue	24%	17%
Peripheral Edema	21%	7%
Dizziness	21%	8%
Rash	20%	10%
Pain in Extremity	19%	8%
Nasal Congestion	19%	15%
Myalgia	14%	5%
Hypertension	14%	5%
Pruritus	10%	3%
Tachycardia	9%	3%
Burning Sensation	6%	0%
Anxiety	6%	3%
Depression	6%	2%
Wheezing	6%	0%
Hot Flush	5%	0%

Ninety-five of 121 (79%) of adult patients and 11 of 16 (69%) pediatric patients treated with agalsidase beta in clinical studies developed IgG antibodies to agalsidase beta.[20] Most patients who develop IgG antibodies do so within the first three months of exposure.[20] IgG seroconversion in pediatric patients was associated with prolonged half-life of agalsidase beta, a phenomenon rarely observed in adult patients.[20] Assessment of inhibition of enzyme uptake in cells has not been performed.[20] No general pattern was seen in individual patient reactivity over time.[20] The clinical significance of binding and/or inhibitory antibodies to agalsidase beta is not known with respect to efficacy of treatment or inhibition of enzyme activity.[20]

Look-alike / Sound-alike Error Risk Potential: No results reported.

Comparative Endpoints:

Clinically Meaningful Endpoints:

1) Improved renal function
2) Improved cardiac symptoms
3) Improved cerebrovascular symptoms
3) Mortality
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) Clearance of Gb3 renal deposits (surrogate endpoint)
2) Delay in progression of renal, cerebrovascular, and cardiac events

Table 4. Pharmacology and Pharmacokinetic Properties of Agalsidase[20]

Parameter	
Mechanism of Action	Agalsidase beta provides an exogenous source of alpha-galactosidase A in Fabry disease patients.
Oral Bioavailability	N/A – administered via intravenous route
Distribution and Protein Binding	Volume of distribution: 81-570 mL/kg
Elimination	N/A
Half-Life	45 to 102 minutes
Metabolism	Specific pathways are unknown

Abbreviations: N/A = not available

Table 5. Comparative Evidence Table for Agalsidase Beta

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Eng CM, et al.[1] MC, DB,PC N=58	1. Agalsidase beta 1 mg/kg IV every other week x 20 weeks 2. Placebo IV every other week x 20 weeks Followed by OL extension study for 6 additional months	Demographics: 1. Mean age: 28-32 yrs 2. Male: 97% 3. Race: White-92% Key Inclusion Criteria: 1. At least 16 years old 2. Subjects had enzymatically confirmed diagnosis of Fabry's disease 3. Subjects had a plasma level AGAL-A of < 1.5 nmol per/hr/mL OR < 4 nmol/hr/kg in leukocytes	ITT: 1.29 2.29 Attrition: 1. 0 2. 0	Primary Endpoint: Percentage of patients with reduced renal microvascular Gb3 deposits at 20 weeks 1. 20 (69%) 2. 0 (0%) OR = 0; P<0.001 Secondary Endpoints: Mean change in Gb3 deposits in myocardium specimen 1. -0.6 ± 0.7 2. 0.2 ± 0.8 P<0.001; 95% CI NR	 NA NA	Rigors 1. 14 (48%) 2. 0 (0%) P=0.004 Fever 1. 7 (24%) 2. 1 (3%) P=0.024 Headache 1. 5 (17%) 2. 2 (7%) P value NR	 NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Method of randomization not described. Baseline characteristics similar in both arms. Performance Bias: Unclear. Initial 20 weeks were double blinded, but method of blinding not stated. Detection Bias: Unclear. Pathologists who examined biopsy results were blinded to treatment arm. Methods for blinding not described. Attrition Bias: Low. No patients withdrew from the trial. Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Supported by NIH grant. Primary authors received grant support from Genzyme.

		Key Exclusion Criteria: 1. Scr > 2.2 mg/dl 2. Undergoing dialysis 3. Kidney transplant recipient		Mean change in Gb3 deposits in skin specimen 1. -2.1 ± 0.7 2. -0.1 ± 1.0 P<0.001; 95% CI NR Mean change in Gb3 deposits in kidney specimen 1. -1.6 ± 1.2 2. -0.1 ± 1.1 P<0.001; 95% CI NR	NA NA	Chills 1. 4 (14%) 2. 0 P value NR Hypertension 1. 3 (10%) 2. 0 (0%) P value NR Percentage of overall AEs, SAE & withdrawals due to AE NR	NA NA	**Applicability**: Patient: Applies to patients with confirmed Fabry disease diagnosis aged 16 yrs and older with normal renal function. Intervention: Agalsidase dosing evaluated in Phase 1 and 2 trials. Comparator: Placebo x 20 weeks followed by OL arm. Outcomes: Surrogate endpoint: Gb3 tissue concentrations from kidney, skin, and heart biopsies. Setting: 8 study sites: United States: 3 The Netherlands: 1 United Kingdom: 2 France: 2
2. Banikazemi M, et al.[3] DB, PC, MC, RCT N = 82	1. Agalsidase beta 1 mg/kg IV every other week x 35 months 2. Placebo IV every other week x 35 months	Demographics: 1. Mean age: 44 to 46 yrs 2. Male: 87.5% 3. Race: White -87.5% 4. Mean GFR = 53 mL/min Key Inclusion Criteria: 1. At least 16 years old 2. Subjects had enzymatically confirmed diagnosis of Fabry's disease 3. Subjects had a plasma level AGAL-A of < 1.5 nmol per/hr/ml OR AGAL-A < 4 nmol/hr/kg in leukocytes 4. Scr ≥1.2 mg/dL and < 3.0 mg/dL Key Exclusion Criteria: 1. Undergoing dialysis 2. Kidney transplant recipient 3. Patients with history of stroke, unstable angina, or myocardial infarction within 3 months of trial entry	ITT: 1. 51 2. 31 PP: 1. 43 2. 28 Attrition 1. 8 (16%) 2. 3 (10%)	Primary Endpoint: Proportion of patients with a clinical event (renal, cardiac, CVA, or death) 1. 14 (27%) 2. 13 (42%) HR = 0.47 (95% CI 0.21 to 1.03); P=0.06 Secondary Endpoints: Renal events (33% increase in serum creatinine level) 1. 10 (20%) 2. 7 (23%) HR=0.49 (95% CI 0.17 to 1.4); P=0.18 Cardiac events (arrhythmia, angina, MI) 1. 3 (6%) 2. 4 (13%) HR=0.42 (95% CI 0.058 to 2.7); P=0.42 Cerebrovascular events (stroke, TIA) 1. 0 (0%) 2. 2 (7%) HR=0 (95% CI 0 to 3.2); P=0.14 Death 1. 2 (2%) 2. 1 (0%) HR NR	NS NS NS NS NA	1. Treatment-related AEs 1. 31 (61%) 2. 10 (32%) 2. SAEs 1. 18 (35%) 2. 10 (32%) 3. AEs resulting in treatment termination 1. 4 (8%) 2. 1 (3%) P values and 95% CI NR for all	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Unclear. Randomized 2:1 treatment to placebo via computer generated program in block size of 3. Additional details about randomization strategy were not available for review. Baseline characteristics were balanced. Performance Bias: Low. Sponsor staff, investigators, and patients were blinded to treatment allocation using identical packaging. Detection Bias: Low. Agalsidase and placebo were packaged identically. Attrition Bias: Low. 2 subjects died, 3 withdrew consent, and 3 withdrew per protocol in active comparator arm. In placebo arm, 1 subject died and 2 subjects withdrew consent. Reporting Bias: Unclear. Protocol unavailable Other Bias: Unclear. Genzyme personnel were involved in the trial design, data management, and statistical analyses. **Applicability**: Patient: Fabry disease in patients over 16 yrs with mild to moderate renal impairment. Most patients were between 18 and 65 yo. Intervention: Agalsidase beta dose evaluated in Phase 1 and Phase 2 trials. Comparator: Placebo Outcomes: Composite endpoint of clinical events (renal, cardiac, cerebrovascular and death). Setting: 26 referral centers in 6 countries in Europe and North America

Abbreviations [alphabetical order]: AE = adverse events; AGAL-A = alpha-galactosidase A; ARR = absolute risk reduction; CI = confidence interval; CVA = cerebrovascular accident; DB = double blind; dL = deciliter; Gb3 = globotriaosylceramide; GFR = glomerular filtration rate; hr = hour; HR = hazard ratio; ITT = intention to treat; IV = intravenous; kg = kilograms; MC = multicenter; MI = myocardial infarction; mL = milliliters; N = number of subjects; NA = not applicable; nmol= nanomole; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OL = open label; OR = odds ratio; PC = placebo control; PP = per protocol; RCT = randomized clinical trial; SAE = serious adverse events; Scr = serum creatinine; TIA = transient ischemic attack; yo = years old; yrs = years

New Drug Evaluation: Migalastat (Galafold™)

The FDA granted accelerated approval of migalastat (Galafold™) in August 2018. Migalastat is an oral medicine for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene variant based on in vitro assay data.[21] The definition of an amenable mutation is one that increases activity of alpha galactosidase A in an in vitro cell culture system (human embryonic kidney [HEK] cells) by 1.2 times the baseline activity with an absolute value for enzyme activity of 3% or greater when compared with wild type values.[32] Migalastat is a pharmacological chaperone designed to bind selectively and reversibly to the active site of the enzyme AGAL-A.[8] This binding stabilizes AGAL-A in the endoplasmic reticulum facilitating its proper trafficking into lysosomes.[8] When in lysosomes, in an acidic pH and in a higher relative concentration of the relevant substrates, migalastat dissociates from AGAL-A, thereby allowing it to catalyze the breakdown of Gb3 and globotriaosylsphingosine (lyso-Gb3).[8] The accelerated approval was based on the surrogate endpoint of reduction in kidney interstitial capillary cell Gb3 substrate after 6 months of therapy.[21] As a condition of accelerated approval, the manufacturer will continue to study migalastat in a confirmatory Phase 4 program.[21] Migalastat is available as a 123 mg capsule and is dosed as 1 capsule every other day on an empty stomach.

Efficacy

The FDA approval of migalastat was based on data from a phase 3 study in 67 treatment-naïve patients with Fabry disease (FACETS).[7] Subjects were randomized in a 1:1 ratio to receive either migalastat 150 mg or a placebo every other day for the first 6 months of the study.[7] In the second 6 months, all patients were treated with open-label migalastat. The trial enrolled patients who had a "responsive" GLA variant using an in vitro assay, the CT HEK-293 assay.[7] As the CT HEK293 assay underwent validation in parallel with the phase 3 trial, 17 of the 67 enrolled patients were determined to have nonamenable GLA variants using the validated HEK assay.[7] Consequently, the final efficacy population was reduced from 67 to 50 patients.[7] Furthermore, among these 50 patients, only 45 had available histology data both at baseline and at month 6. The final population used for the analysis of efficacy consisted of 45 patients with amenable GLA variants and available histology data, of whom 29 were females and 16 were males.[7]

The primary efficacy outcome was a surrogate endpoint, the proportion of patients with 50% or greater reduction in the average number of GL-3 inclusions per kidney interstitial capillary (KIC) in biopsy samples. Both the ITT and the modified ITT (patients with amenable GLA variants and available histology) populations were assessed from baseline to month 6.[7] In the ITT population, which included 17 patients with non-amenable GLA variants, the primary efficacy outcome did not show a significant treatment effect, as a response was achieved in 13 of 34 (38%) migalastat-treated patients compared to 9 of 33 (27%) placebo-treated patients ($p = 0.3$, CI not reported).[7] In the modified ITT population with available histology data 13 of 25 (52%) patients on migalastat achieved the primary efficacy outcome compared to 9 of 20 (45%) patients on placebo (statistical data not reported).[7] Among the 29 females with amenable GLA variants, 8 of 18 (44%) in the migalastat group achieved the primary efficacy outcome versus 5 of 11 (45%) in the placebo group (statistical data not reported).[7] In contrast, among the 16 males with amenable GLA variants, 5 of 7 (71%) in the migalastat group achieved the primary efficacy outcome as compared to 4 of 9 (44%) in the placebo group (statistical data not reported).[7]

This clinical trial involved a small numbers of subjects with very mild disease manifestations and did not include patients with high levels of proteinuria which is a known risk factor for adverse cardiovascular and renal events in Fabry disease.[8] The trial was also of short duration. In addition, baseline imbalances in patient

characteristics were observed between the 2 groups. Notably, placebo patients had a two-fold higher baseline urine GL-3 concentration than migalastat patients, which is of unclear clinical significance as GL-3 concentration in urine cannot reliably be correlated with disease severity in Fabry disease.[8] In addition, at baseline, there was a large difference between males and females in terms of GL-3 inclusion burden.[8] Males started with a higher baseline GL-3 inclusion burden as compared to the females, which is indicative of more extensive substrate deposition in KIC and, thus, more severe disease on a histologic level.[8] There was also a higher amount of proteinuria in the placebo patients than in the migalastat patients, which may explain why more patients in the placebo group were treated with an ACE inhibitor or ARB during the trial.[8] Of note, baseline renal function (as measured by eGFR) was similar in both groups.[8] Published data are not yet available on the effects of migalastat in patients with more advanced disease or with duration of therapy beyond 2 years.[8]

Safety

During the phase 3 trial, there were no deaths or serious adverse events attributed to migalastat treatment.[21] The most frequently reported adverse events in patients treated with migalastat in the FACETS trial over the first 6 months (and with a higher incidence than placebo) included headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia.[7] Incidence of adverse effects compared to placebo is presented in **Table 6.** No clinically significant laboratory or vital sign changes were observed in migalastat-treated patients in the phase 3 trial.[21] Migalastat showed no effects on the QT interval and electrocardiograms performed during the phase 3 trial revealed no clinically significant changes from baseline during migalastat treatment.[21] Migalastat is not recommended in patients with severe renal impairment (eGFR < 30 mL/min/1.73m2).[21] No dosage adjustment in patients with mild or moderate renal impairment is recommended.[21]

Table 6. Adverse reactions reported with migalastat during the first 6 months of treatment[21]

Adverse Reaction	Migalastat (n=34)	Placebo (n=33)
Headache	35%	21%
Nasopharyngitis	18%	6%
Urinary tract infection	15%	0%
Nausea	12%	6%
Pyrexia	12%	3%
Abdominal pain	9%	3%
Back pain	9%	0%
Diarrhea	95	3%
Epistaxis	9%	3%

Look-alike / Sound-alike Error Risk Potential: Miglustat (Zavesca®) used to treat Gaucher disease

Comparative Endpoints:

Clinically Meaningful Endpoints:
1) Improved renal function
2) Improved cardiac symptoms
3) Improved cerebrovascular symptoms
4) Mortality
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Percentage of ITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months (surrogate endpoint)

Table 7. Pharmacology and Pharmacokinetic Properties of Migalstat[21]

Parameter	
Mechanism of Action	Pharmacologic chaperone designed to bind selectively and reversibly to the active site of AGAL-A enzyme which allows breakdown of Gb3
Oral Bioavailability	75%, food decreases absorption by 37 to 42%
Distribution and Protein Binding	Volume of distribution = 89 L, no protein binding detected
Elimination	Renal: 77% of dose
Half-Life	4 hours
Metabolism	Substrate of UDPGT

Abbreviations: AGAL-A = alpha-galactosidase A; Gb3 = globotriaosylceramide

Table 8. Comparative Evidence Table for Migalastat

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Germain DP, et al.[7] Phase 3 RCT, DB, PC, MC 6 months	1. Migalastat 150 mg orally every other day 2. Oral placebo every other day Initial 6 month DB stage (Stage 1) followed by 6 month OL phase (Stage 2) where all patients received migalastat	Demographics: 1. Mean age: 42 yo 2. Gender: Female 64% 3. Years since diagnosis: 6.3 4.ACE/ARB use: 42% 5.Prior ERT use: 22% 6.Suitable *GLA* mutation: 75% 7.Race: White 93% Key Inclusion Criteria: 1. Aged 16 to 74 yo with Fabry disease with mutation responsive to migalastat 2. No ERT treatment for 6 months before enrollment 3. GFR > 30 mL/min/1.73 m^2 4. If taking ACE/ARB must be on a stable dose for 4 weeks prior to study inclusion 5. Urine Gb3 concentration ≥ 4 times the ULN Key Exclusion Criteria: 1. Subject has undergone kidney transplantation or is undergoing dialysis 2. GFR < 30 mL/min 3.QTC ≥ 450 msec for males or ≥ 470 msec for females	ITT: 1. 34 2. 33 mITT (responsive mutation with histology data): 1. 25 2. 20 ITT Attrition: 1. 0 (0%) 2. 3 (9%)	Primary Endpoint: Percentage of ITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months 1. 13 (38%) 2. 9 (27%) P=0.30; 95% CI NR Secondary Endpoints: Percentage of mITT patients with a ≥ 50% reduction in Gb3 inclusions in kidney interstitial capillary at 6 months 1. 13 (52%) 2. 9 (45%) P=0.55; 95% CI NR Median change in Gb3 inclusions in kidney interstitial capillary from baseline at 6 months in ITT population 1. -40.8% 2. -5.6% P=0.10; 95% CI NR Mean change in Gb3 inclusions in kidney interstitial capillary from baseline at 6 months in mITT population 1. -0.25 2. 0.07 P=0.008; 95% CI NR	NS NS NS NA	Serious AE during first 6 months 1. 5 (15%) 2. 2 (6%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Subjects randomized 1:1 to each arm and stratified by gender using a central randomization system. Concurrent validation of migalastat-amenable mutation assay conducted during DB phase. 17 patients subsequently excluded due to mutation unresponsive to therapy. Baseline characteristics imbalanced. Performance Bias: Low. Placebo matched to active comparator in capsules similar in appearance and size. All subjects instructed to take medication on an empty stomach. Detection Bias: Low. All subjects, investigators, and sponsors blinded to treatment arm. Attrition Bias: Low. 3 subjects withdrew from the placebo arm in the first 6 mos due to pregnancy (1) and withdrawal of consent (2). Reporting Bias: Low. Protocol available online. Other Bias: Unclear. Funded by Amicus Therapeutics. Data collection and analyses included authors and manufacturer. Over 50% of authors report grants or other funding from the manufacturer. **Applicability**: Patient: Study conducted in males and females with Fabry disease and with a GLA mutation responsive to migalastat. Patients with severe renal impairment were excluded from the trial. Majority of enrolled patients were female. Intervention: Migalastat 150 mg dose evaluated in Phase 2 trials. FDA approved dose is 123 mg. Comparator: Placebo controlled trial Outcomes: Surrogate endpoint with unclear link to clinical outcomes Setting: International settings including 30 sites

Abbreviations [alphabetical order]: ACE/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ARR = absolute risk reduction; CI = confidence interval; DB = double blind; ERT = enzyme replacement therapy; Gb3 = globotriaosylceramide; GFR = glomerular filtration rate; ITT = intention to treat; MC = multicenter; mITT = modified; mL= milliliters; min = minute; intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = non-significant; OL = open-label; PC= placebo controlled; PP = per protocol; ULN = upper limit of normal; yo = years old

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Appendix 1: Specific Drug Information

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FABRAZYME safely and effectively. See full prescribing information for FABRAZYME.

FABRAZYME (agalsidase beta) for injection, for intravenous use
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------

Fabrazyme is indicated for use in patients with Fabry disease. Fabrazyme reduces globotriaosylceramide (GL-3) deposition in capillary endothelium of the kidney and certain other cell types. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is 1 mg/kg body weight given every two weeks as an intravenous infusion. (2.1)
- Administer antipyretics prior to infusion. (2.1)
- See the full prescribing information for the recommended infusion rate. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

For injection: 5 mg or 35 mg lyophilized cake or powder in a single-dose vial for reconstitution (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Life-threatening anaphylactic and severe allergic reactions have been observed in some patients during Fabrazyme infusions. If severe allergic or anaphylactic reactions occur, immediately discontinue administration of Fabrazyme and provide necessary emergency treatment. Appropriate medical support measures should be readily available when Fabrazyme is administered because of the potential for severe infusion-associated reactions. (5.1)
- Infusion-associated reactions occurred in 59% of patients during Fabrazyme administration in clinical trials. Some reactions were severe. In patients experiencing infusion-associated reactions, pretreatment with an antipyretic and antihistamine is recommended. If an infusion-associated reaction occurs, decreasing the infusion rate, temporarily stopping the infusion, and/or administrating additional antipyretics, antihistamines, and/or steroids may ameliorate the symptoms. (5.2)
- If severe infusion-associated reactions occur, immediate discontinuation of the administration of Fabrazyme should be considered and appropriate medical treatment should be initiated. Severe reactions are generally managed with administration of antihistamines, corticosteroids, intravenous fluids, and/or oxygen as clinically indicated. (5.2)
- Patients with advanced Fabry disease may have compromised cardiac function, which may predispose them to a higher risk of severe complications from infusion-associated reactions, and these patients should be monitored closely during Fabrazyme administration. (5.3)
- Readministration of Fabrazyme to patients who have previously experienced severe or serious allergic reactions to Fabrazyme should be done only after careful consideration of the risks and benefits of continued treatment, and only under the direct supervision of qualified personnel and with appropriate medical support measures readily available. (5.4)

----------ADVERSE REACTIONS----------

Most common adverse reactions (≥20% and >2.5% compared to placebo) are: upper respiratory tract infection, chills, pyrexia, headache, cough, paresthesia, fatigue, peripheral edema, dizziness, and rash. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Genzyme at 1-800-745-4447 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 12/2018

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use GALAFOLD safely and effectively. See full prescribing information for GALAFOLD.

GALAFOLD™ (migalastat) capsules, for oral use
Initial U.S. Approval: 2018

----------INDICATIONS AND USAGE----------

GALAFOLD™ is an alpha-galactosidase A (alpha-Gal A) pharmacological chaperone indicated 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. (1, 12.1)

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. (1)

----------DOSAGE AND ADMINISTRATION----------

- Select adults with confirmed Fabry disease who have an amenable *GLA* variant for treatment with GALAFOLD.
- 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). (2, 12.1)
- The recommended dosage regimen of GALAFOLD is 123 mg orally once every other day at the same time of day. (2)
- Take on an empty stomach. Do not consume food at least 2 hours before and 2 hours after taking GALAFOLD to give a minimum 4 hours fast. (2)
- Do not take GALAFOLD on 2 consecutive days. (2)
- If a dose is missed entirely for the day, take the missed dose only if it is within 12 hours of the normal time that the dose should have been taken. If more than 12 hours have passed, resume taking GALAFOLD at the next planned dosing day and time and according to the every-other-day dosing schedule. (2)
- Swallow capsules whole; do not cut, crush, or chew. (2)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 123 mg migalastat. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------ADVERSE REACTIONS----------

Most common adverse drug reactions ≥ 10% are: headache, nasopharyngitis, urinary tract infection, nausea, and pyrexia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amicus Therapeutics at 1-877-4AMICUS or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2018

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to June Week 3 2019; Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations 1946 to June 25, 2019

1. Fabry Disease	*2306*
2. alpha-Galactosidase	*1834*
3. Migalastat.mp	*94*
4. 2 or 3	*1888*
5. 1 and 4	*1148*

6. limit 5 to (english language and humans and (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial protocol or clinical trial or comparative study or controlled clinical trial or guideline or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")) 128

Fabry Disease

Goal(s):

- Ensure medically appropriate use of drugs for Fabry Disease

Length of Authorization:

Up to 12 months

Requires PA:

- Agalsidase beta (pharmacy and physician administered claims) and migalastat

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA approved indication?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for continuation of therapy?	**Yes:** Go to **Renewal Criteria**	**No:** Go to # 5
5. Is the provider a specialist in managing Fabry disease?	**Yes**: Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Is the request for migalastat?	**Yes:** Go to # 7	**No:** Go to # 10
7. Does the patient have a mutation that is amenable to migalastat therapy as confirmed by a genetic specialist?	**Yes**: Got to # 8	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
8. Is the patient currently receiving agalsidase beta?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to # 9
9. Is the patient 18 years of age or older?	**Yes**: Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness. Migalastat is only FDA-approved for use in adults.
10. Is the patient a male with diagnosis of Fabry disease confirmed by genetic testing or deficiency in alpha-galactosidase A enzyme activity in plasma or leukocytes?	**Yes:** Go to # 11	**No:** Go to # 12
11. Does the patient have end stage renal disease requiring dialysis?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months
12. Is the patient a female and a documented Fabry disease carrier confirmed by genetic testing with significant clinical manifestations of Fabry disease such as: • Uncontrolled pain that interferes with quality of life • Gastrointestinal symptoms that are significantly reducing quality of life and not attributable to other pathology • Mild to moderate renal impairment (GFR > 30 mL/min) • Cardiac disease (left ventricular hypertrophy, conduction abnormalities, ejection fraction< 50%, arrhythmias) • Previous stroke or TIA with retained neurologic function	**Yes:** Approve for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing provider and provider attests to patient's improvement in one of the following: • Renal function • Pain Scores • Quality of Life measurement • Cardiac function • Neurologic status • Growth and development in children	**Yes:** Approve for 12 months. Document baseline assessment and provider attestation received.	**No**: Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 9/19 (DM)
Implementation: 11/1/19