Formulary Drug Monograph

Fabrazyme®
agalsidase beta
[Genzyme Corporation]

Date of Review: June 2004

Reason for Review: Manufacturer submission of clinical data for formulary consideration.

THERAPEUTIC ALTERNATIVES

Fabrazyme is indicated for use as enzyme (α-galactosidase A) replacement therapy in patients with Fabry disease. Fabrazyme (agalsidase beta) is currently the only FDA-approved therapy for the treatment of Fabry disease. Prior to the availability of Fabrazyme, treatment for Fabry disease in the United States was limited to symptomatic and palliative management strategies. Chronic pain therapy includes membrane stabilizers such as gabapentin, carbamazepine and phenytoin. ACE inhibitors and antihypertensives are used to delay progressive loss of renal function. Kidney transplants can stay free of glycosphingolipids as a result of enzyme production from the graft. However, the graft's enzyme production is not sufficient to prevent progression of systemic disease. Cardiovascular disease may require antiarrhythmic medications, artificial pacemakers, and coronary-artery bypass grafting. Heart transplant has also been successfully performed in these patients.

In Europe, Replagal (agalsidase alfa) is also approved for use as enzyme (α-galactosidase A) replacement therapy for Fabry disease. Although these products indirectly appear to be similar clinically, Replagal is approved for use at a much lower dose than Fabrazyme there.

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EXECUTIVE SUMMARY

Key Questions/Issues and Results of Investigation

Issue 1: Does this agent provide greater efficacy than formulary or other therapeutic alternatives?

Prior to the availability of Fabrazyme, in the U.S., treatment for Fabry disease was directed at managing patients' symptoms and ameliorating complications associated with the disease.

The safety and efficacy of Fabrazyme was assessed in one multicenter, randomized, double-blind, placebo-controlled study of 58 Fabry patients (56 hemizygotes and 2 heterozygotes). The primary efficacy endpoint was the percentage of patients free of microvascular endothelial deposits of globotriaosylceramide (GL-3) in renal-biopsy specimens (a score of 0). A score of 0 was achieved in 20 of 20 (69%) of patients treated with Fabrazyme compared to 0 of 29 treated with placebo (intent-to-treat analysis, $P<.001$).[1] Notably, the percentage of patients with clearance of microvascular endothelial deposits of GL-3 in the endomyocardium (a secondary endpoint) increased from 67% after 20 weeks to 82% after 6 months of open-label treatment. This suggests that the clearance of GL-3 may be tissue specific and dependent on the dose, duration of treatment, level of enzyme uptake, and degree of substrate accumulation.

The safety and efficacy of Replagal was evaluated in one single-center, randomized, double-blind, placebo-controlled study in 29 Fabry hemizygotes. The primary efficacy endpoint was Brief Pain Inventory (BPI) score. At baseline, the placebo group had higher pain scores than did the treatment group, and this difference was maintained. This suggests a confounding effect, as a divergence in scores between treatment groups would be expected if there was an effect on pain perception.

For numerous reasons, the results of these trials cannot be easily compared. Both drugs have demonstrated clearance of GL-3 from plasma and histologic evidence of improvement on a tissue level. This makes it very likely that α-galactosidase A replacement therapy will be an effective treatment to delay or slow progression of the disease.

Issue 2: Is this agent relatively safer than formulary or other therapeutic alternatives?

Enzyme replacement therapy for Fabry Disease is associated with a relatively high risk for allergic reactions. However both Fabrazyme and Replagal were generally well tolerated.

In the pivotal clinical trial for Fabrazyme, infusion reactions were the only treatment related adverse events that occurred significantly more frequently in the Fabrazyme group than in the placebo group. Rigors occurred in 48% of Fabrazyme-treated patients and in none of the placebo-treated patients ($P=.004$) and fever occurred in 24% and 3% of patients, respectively ($P=.024$). Reducing the infusion rate and/or administering preventive medications controlled infusion-associated reactions. Eighty-eight percent (51/58) patients developed detectable IgG. These antibody titers tended to decrease with time, suggesting tolerization. One patient became skin-test and IgE positive to recombinant α-galactosidase A after his eighth infusion during the 6-month extension of the study, and treatment was discontinued.

The sensitivities of the various assays for IgG antibodies were not described in either the Fabrazyme or the Replagal pivotal clinical trials. As a result, it is not possible to directly compare the frequency of immunoglobulin positivity.

Issue 3: Does this agent provide any economic advantage compared with formulary or other therapeutic alternatives?

No economic modeling was supplied by the manufacturer. The monthly and annual Redbook AWP cost for drug only is $18,240 and $218,880, respectively for a 16-70 kg patient. It should be noted that AWP costs may vary significantly based on pricing source.

RECOMMENDATIONS TO THE COMMITTEE

Fabry disease is a rare autosomal recessive, chronic, progressive, debilitating, and life-threatening lysosomal disorder. Previously, most treatments for the condition were symptomatic and palliative and did not address the underlying cause of or halt progression of the disorder. Kidney failure was the primary cause of mortality in Fabry patients prior to availability of dialysis and kidney transplant. Fabrazyme offers a treatment alternative that addresses the underlying cause of the condition, reducing substrate accumulation in end organs, delaying but not necessarily reversing damage.

Patient subtypes in whom benefit remains to be established include female heterozygotes without classic clinical manifestations and absent or low α-galactosidase activity, and dialysis or kidney transplant patients.

Fabry patients are managed by both primary and specialty providers. Albeit a very costly therapy, Fabry disease is a rare condition and Fabrazyme is a very specific therapy unlikely to be used for other indications. There is potential for use in subpopulations for whom benefit has not been established. There are also published opinions that higher doses of enzyme replacement therapy might be warranted to reverse end organ damage, particularly in the kidney and heart. Therefore, **it is recommended this drug be covered with medical policy guidance**.

ISSUE 1: Does this agent provide greater efficacy than formulary or other therapeutic alternatives?

- One larger pivotal clinical efficacy and safety trial was conducted and published in the clinical development of this product. This was a 20-week, multicenter, randomized, double-blind, placebo-controlled study in 58 Fabry patients (56 hemizygotes and 2 heterozygotes). The study's primary efficacy endpoint was the percentage of patients free of microvascular endothelial deposits of GL-3 in renal-biopsy specimens (a score of 0). A score of 0 was achieved in 20 of 29 (69%) of patients treated with Fabrazyme compared to 0 of 29 treated with placebo (ITT, $P<.001$).
- Patients in the Fabrazyme treatment group also had decreased microvascular endothelial deposits of GL-3 in the skin (ITT, $P<.001$) and heart (ITT, $P<.001$) after 20 weeks of therapy.
- Following the 20-week, double-blind trial, all patients were enrolled in a 6-month, open-label extension study and received Fabrazyme infusions every other week. After the 6-month time period, 98% of patients in whom a biopsy was performed (42 of 43) had a score of 0 on histological analysis of microvascular endothelial deposits of GL-3 in kidney specimens, 96% (45 of 47) had such results for skin specimens, and 75% (24 of 32) had such results for heart specimens.
- A competitive product, Replagal (agalsidase alfa) is available in Europe, but there are no head-to-head clinical trials with therapeutic alternatives available at this time.
- The safety and efficacy of Replagal was evaluated in one single-center, randomized, double-blind, placebo-controlled study in 29 Fabry hemizygotes.[2] The primary efficacy endpoint was Brief Pain Inventory (BPI) score. At baseline, the placebo group had higher pain scores than did the treatment group, and this difference was maintained. This suggests a confounding effect, as a divergence in scores between treatment-groups would be expected if there was an effect on pain perception. Other study endpoints included renal histology and function and plasma and urine globotriaosylceramide.
- Indirect comparison of the results of these trials is impossible because of differences in study designs and conduct, as well as reporting. However, both drugs have demonstrated clearance of GL-3 from plasma and histologic evidence of improvement on a tissue level. This makes it very likely that α-galactosidase A replacement therapy will be an effective treatment to delay or slow progression of the disease.

Table 1. Summary of Published Pivotal Clinical Trial for Fabrazyme

Citation LOE	Design	Treatment	No. of Patients	Inclusion/Exclusion Criteria	Endpoints	Results/Comments
Eng CM et al. LOE: 1	R, DB, PC, PG 20-weeks + open-label 6-month extension US Clinical evaluations were performed at baseline, before each infusion, after week 20 of the DB study, and after 6 months of open-label treatment.	• DB study: Fabrazyme 1mg/kg IV QOW or PBO QOW • OL extension study: Fabrazyme infusion 1mg/kg QOW	58 (n=29 for Fabrazyme and n=29 for PBO) + all 58 continued in extension study	• Enzymatically confirmed diagnosis of Fabry disease (α-galactosidase A level activity <1.5nmol/hr/ml) • ≥16 years old • SCr <2.2mg/dl • No dialysis patients • No history of kidney transplant <u>Demographics</u> • Mean age 30 years (range 16-61 years) • 56/58 male • SCr = 0.8 ± 0.2 mg/dl • Plasma GL-3 = 14.5 ng/ml	<u>Primary</u> • Percentage of patients free of microvascular endothelial deposits of GL-3 in renal-biopsy specimens (a score of 0) • Adverse effects <u>Secondary</u> • Composite score for endothelial deposits of GL-3 in the heart, kidney, and skin • Change from baseline in kidney and urine concentrations of GL-3 • Level of pain by McGill Pain Questionnaire (scoring range 0-45, with higher scores indicating more severe pain)	***Efficacy:*** • A score of 0 was achieved in 20 of 29 (69%) of patients treated with Fabrazyme compared to 0 of 29 treated with placebo (ITT, *P*<.001) for clearance of GL-3 in renal capillaries. • Patients in the Fabrazyme treatment group also had decreased endothelial deposits of GL-3 in the skin (ITT, *P*<.001) and heart (ITT, *P*<.001). • At completion of the 6-month extension study, 98% of patients in whom a biopsy was performed (42 of 43) had a score of 0 for GL-3 endothelial deposits in kidney specimens, 96% (45 of 47) for skin specimens, and 75% (24 of 32) for heart specimens. • Median changes in kidney and urinary concentrations of GL-3 were decreased significantly more in the Fabrazyme-treated group compared with the placebo-treated group. • There were no significant changes in pain scores between groups, and baseline pain was relatively low for both. • Following the 6-month extension, in those whom a biopsy was performed, 42/43 (98%) had a score of 0 for endothelial GL-3 deposits in the kidney, 45/47 (96%) for skin deposits, and 24/32 (75%) for heart deposits. ***Safety:*** Rigors (48% and 0, *P*=.004) and fever (24% and 3%, *P*=.024) were the only treatment-related AEs that occurred more frequently in Fabrazyme-treated patients compared with PBO-treated patients, respectively. IgG antibodies developed in 88% of patients, but these appeared to decrease over time and did not affect efficacy endpoints. One patient was skin-test and IgE positive to recombinant α-galactosidase A after his 8th infusion during the 6-month extension of the study, and treatment was discontinued.

LOE= level of evidence; No.= number; R=randomized; DB=double-blind; PC= placebo-controlled; PG= parallel-group; US=United States; QOW=every other week; OL=open-label; PBO=placebo; SCr=serum creatinine; GL-3= globotriaosylceramide ITT=intent-to-treat analysis; AEs=adverse events.

ISSUE 2: Is this agent relatively safer than formulary or other therapeutic alternatives?

- In a multicenter, randomized, double-blind, placebo-controlled study, infusion reactions were the only treatment related adverse events that occurred significantly more with the Fabrazyme group than in the placebo group. Rigors occurred in 48% of the Fabrazyme-treated patients and in none of the placebo-treated patients (*P*=.004) and fever occurred in 24% and 3% of patients respectively (*P*=.024). Other infusion reactions included chest tightness, hypertension, hypotension, pruritus, myalgia, dyspnea, urticaria, abdominal pain, and headache. Reducing the infusion rate and/or administering preventive medications controlled infusion associated reactions.
- One patient was IgE and skin-test positive to recombinant alpha-galactosidase A after his eighth infusion during the 6-month extension of the study, and treatment was discontinued.
- IgG seroconversion occurred in 51 of the 58 (88%) patients who received Fabrazyme during the study. This did not appear to affect the primary or secondary efficacy endpoints.

ISSUE 3: Does this agent provide any economic advantage compared with formulary or other therapeutic alternatives?

- No pharmacoeconomic modeling was supplied.

- The monthly and annual Redbook AWP cost for drug only is $18,240 and $218,880, respectively for a 16-70 kg patient. It should be noted that AWP costs may vary significantly based on pricing source.

BACKGROUND INFORMATION

DISEASE BACKGROUND

Disease Burden

Fabry disease is an X-linked recessive disorder that predominantly affects males. It affects all ethnic groups with estimates of incidence ranging from 1 in 40,000 to 60,000 males. Females can also be affected because of random X-chromosomal inactivation,[3] and typical disease manifestations are frequently exhibited with increasing age. Diagnosis is confirmed by low or absent α-galactosidase activity in plasma or serum, leukocytes, tears, biopsied tissues, or cultured skin fibroblasts.

Pathophysiology

Fabry disease is a rare inherited lysosomal storage disorder caused by the partial or complete deficiency of the lysosomal enzyme α-galactosidase. This leads to the progressive accumulation of globotriaosylceramide and glycosphingolipids in the vascular endothelial lysosomes of the kidneys, heart, skin and brain. In patients with the classic form of the disease, the clinical onset is in childhood and is characterized by intermittent pain in the extremities (acroparesthesias); episodic "Fabry crises" of acute pain lasting hours to days; characteristic skin lesions (angiokeratomas); corneal opacity that does not affect vision; hypohidrosis; heat, cold, and exercise intolerance; mild proteinuria; and gastrointestinal problems. By the third to fifth decade of life, microvascular disease of the kidneys, heart, and brain progresses resulting in end-stage renal disease, congestive heart failure, myocardial infarction, strokes and ultimately death. Prior to the treatment of uremia, the average lifespan of affected males was about 40 years. With renal dialysis or transplantation, the average lifespan is about 50 years.

Clinical manifestations in carrier females range from asymptomatic disease to disease severity similar to that seen in affected males.[3]

PHARMACOTHERAPY

Until recently, no disease-specific treatments have been available for U.S. patients with Fabry disease. Traditionally, patients have been managed with supportive, nonspecific treatments. For pain management, diphenylhydantoin, carbamazepine, or gabapentin are administered prophylactically. Pancrelipase or metoclopramide are used to decrease gastrointestinal symptoms. Antiplatelet agents or anticoagulants are used for patients who have had transient ischemic attacks or stroke. Valve replacement is often required in cardiovalvular disease. ACE inhibitors and antihypertensives can help delay progression of end-stage kidney disease. For patients with advanced renal disease, dialysis or transplantation can prolong life as renal failure is the most frequent cause of death in classic Fabry disease.

PRODUCT BACKGROUND

Pharmacology

Fabrazyme provides an exogenous source of alpha-galactosidase A, the deficient enzyme in Fabry disease. It has the same amino acid sequence as the native enzyme.

Pharmacokinetics

The pharmacokinetic profile of Fabrazyme was studied at 0.3, 1.0 and 3.0 mg/kg in 15 patients with Fabry disease. The area under the curve (AUC) and clearance did not increase proportionately with increasing doses, following non-linear pharmacokinetics. The terminal half-life was dose independent with a range of 45 – 102 minutes.

In 11 patients with Fabry disease, Fabrazyme was administered at 1.0 mg/kg every 2 weeks for a total of 11 infusions. The pharmacokinetic responses with repeat dosing fell into three categories. In some patients, pharmacokinetic responses were maintained with repeated dosing, whereas in other patients, pharamacokinetic values decreased at infusion seven relative to baseline and returned to baseline values by infusion 11. In the remaining patients, AUC decline and failed to return to baseline by infusion 11. In these patients, the average AUC was 25% of its baseline level.

Adverse Effect Profile from the Clinical Trials
In the phase 3, randomized, double-blind, placebo-controlled study, no significant changes from baseline in echocardiograms, electrocardiograms, or other safety assessments were seen after 20 weeks or following the 6-month, open-label extension study. Infusion reactions were the only treatment-related adverse event that occurred significantly more frequently in the Fabrazyme group than in the placebo group. Rigors occurred in 48% of the Fabrazyme-treated patients and in none of the placebo-treated patients (P=.004) and fever occurred in 24% and 3% of these patients respectively (P=.024). Other infusion reactions reported included chest tightness, hypertension, hypotension, pruritus, myalgia, dyspnea, urticaria, abdominal pain, and headache. Transient mild-to-moderate infusion-associated reactions occurred in 59% of patients (34 of 58) during the double-blind or open-label studies. Reducing the infusion rate and/or administering preventive medications controlled infusion-associated reactions. Skeletal pain was the only other adverse event that occurred more frequently among the Fabrazyme-treated patients during the double-blind study, but was considered not to be related to recombinant α-galactosidase A therapy (P=.02).

One patient had a positive skin-test to recombinant alpha-galactosidase A after his eighth infusion during the 6-month extension of the study, and treatment was discontinued. IgG seroconversion occurred in 51 of the 58 (88%) patients who received Fabrazyme during the study. This did not affect the primary or secondary efficacy endpoints.

Drug Interactions[4]
No drug interaction studies have been performed.

No *in vitro* metabolism studies were performed.

Precautions
Patients should be given antipyretics prior to infusion. If an infusion reaction occurs, regardless of pre-treatment, decreasing the infusion rate, temporarily stopping the infusion, and/or administration of additional antipyretics, antihistamines and/or steroids may ameliorate symptoms. Because of the potential for severe infusion reactions, appropriate medical support measures should be available when Fabrazyme is administered.

Patients with advanced Fabry disease may have compromised cardiac function which may predispose them to a higher risk of severe complications from infusion reactions.

Dosage and Administration[4]
The recommended dosage of Fabrazyme is 1.0 mg/kg body weight infused every 2 weeks by intravenous infusion. The initial IV infusion rate should be no more than 0.25 mg/min. The infusion rate may be slowed in the event of a reaction. After patient tolerance to the infusion is well established, the infusion rate may be increased in increments of 0.05 to 0.08 mg/min each subsequent infusion.

Patients should receive an antipyretic prior to infusion.

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REFERENCES

[1] Eng CM, Guffon N, Wilcox WR, et al. Safety and efficacy of recombinant human alpha-galactosidase A replacement therapy in Fabry's disease. *N Engl J Med.* 2001;345(1):9-16.
[2] Schiffmann R, Kopp JB, Austin HA, et al. Enzyme replacement therapy in Fabry disease: a randomized controlled trial. *J Am Med Assoc*. 2001:285:2743-2749.
[3] Desnick RJ, Brady R, Barranger, et al. Fabry disease, an under-recognized multisystemic disorder: expert recommendations for diagnosis, management, and enzyme replacement therapy. *Ann Int Med*. 2003;138:338-346.
[4] Package Insert, Fabrazyme (algalsidase beta). Genzyme Corporation, April 2003.