Endocrinologic and Metabolic Drugs Advisory Committee

Questions to the Committee

January 13, 2003

BL 103979, Fabrazyme™ (agalsidase beta), Genzyme Corporation
- proposed for the treatment of Fabry's disease.

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1) The following are observations regarding Genzyme's studies of Agalsidase beta:

- The controlled study AGAL-002 conducted by Genzyme was designed with the primary objective of demonstrating a treatment associated effect on a histologic endpoint of "near-normalization" of substrate deposition in renal capillary endothelium on light microscopic examination. A robust effect was observed in reducing the deposition of substrate in the capillary endothelium. Reduced substrate deposition was also observed in several other, but not all, cell types examined in renal, cardiac and skin biopsies.

- Clinical efficacy was not observed. Among the secondary outcomes of Study AGAL-002 were the effect of the enzyme on pain and renal function. There were no changes in either group in renal function during the controlled study period, and there was no treatment-related difference in pain assessment. AGAL-002 was not specifically designed or powered to show an effect on these secondary outcomes. The eligibility criteria did not specifically focus on patients who might be likely to demonstrate an effect on these measures.

- Most patients developed antibody to agalsidase beta. Antibody formation has the potential to negate or lead to regression in the histologic findings prior to the time when clinically apparent decline in renal function would occur.

- Adverse effects were observed in association with drug infusion. Some adverse reactions were severe.

Genzyme has requested marketing approval under the accelerated approval framework. This requires a determination that the studied surrogate is "reasonably likely to predict clinical benefit."

a) Please discuss the relevance of the clinical measures studied and the importance of the observed results. To what extent should the results on these outcomes influence the assessment of potential efficacy as may be predicted by the histologic results?

b) Please discuss the quality and strength of the histologic data. Please include in your discussion the importance of substrate accumulation in the renal capillary endothelium to the pathophysiology of the kidney dysfunction, and the relative importance of substrate accumulation in other cell types.

c) Please discuss the ability to extrapolate the short-term histologic response data to the longer time frames when clinical benefit might be expected to occur.

d) Please discuss if capillary endothelium substrate deposition, specifically as assessed in Genzyme's study AGAL-002, is an appropriate surrogate for the purpose of accelerated approval.

That is, is "near-normalization" of renal capillary endothelium reasonably likely to predict a clinically meaningful effect?

e) Use of this product is associated with risks. It is difficult to balance the risks of definable adverse effects with efficacy that has not been directly observed, but may be only predicted from a finding on a surrogate endpoint. Please discuss how you balance risk with any benefit that may be inferred from these data.

2) Fabry disease is a life-long disease. The long term results (clinical safety and efficacy) from treatment with agalsidase beta are not known. Progression of disease during the course of the clinical studies conducted to date has not been observed. Antibody against agalsidase beta develops in a substantial number of patients. Antibody formation has the potential to limit the usefulness of the product, either by direct neutralization or by altering the pharmacokinetics and cellular/organ distribution of enzyme uptake. If this occurs, it is possible that administration of the enzyme early in the disease would result in antibody formation that eliminates any future potential clinical benefits. In this case, early administration of the enzyme to the asymptomatic or unimpaired patients might only serve to immunize the patients. Among patients who developed antibody, direct neutralization of the enzymatic activity was not observed, but there were alterations in pharmacokinetic parameters.

Longer-term bioactivity data are available from skin biopsies obtained from patients in Study AGAL-005. Genzyme observed that 6 of 20 patients who had near-absence of substrate deposition in skin deep vessel endothelium at 5 months of enzyme treatment had increased deposition after 23 months of enzyme treatments. A similar finding was seen in month 18 (or 23) superficial skin capillary histology in 5 patients, but the biopsies returned to the near–normal appearance in the 4 patients who underwent biopsy at later time points (range: months 24-35). Deep vessel endothelium biopsies are not presently available at similarly later time points. No longer-term biopsies were obtained in other tissues. No diminishment of treatment-associated response in urine or plasma substrate levels associated with antibody formation was discerned.

a) Please discuss your interpretation of these data. To what extent do these findings suggest a waning of enzyme activity?

b) In light of the need for long term, and likely life-long treatment, please discuss how important it is to obtain, and with what degree of rigor (e.g., degree of precision in ruling out a loss of activity) an evaluation of potential antibody-related loss of efficacy and/or activity.

c) If you view data assessing the long-term durability of efficacy or activity as a critical requirement,

i) Is it reasonable to permit these data to be generated and evaluated after marketing approval, or should the data be available and evaluated prior to market approval? Please bear in mind that controlled comparisons, particularly long-duration controlled comparison studies, may be more difficult in the post-marketing situation.

ii) Please discuss what types of outcomes would be most useful for assessing persistence or loss of enzyme activity related to antibody formation, and the time frame(s) for such assessments.

3) This product is intended for long term use by patients with Fabry Disease. If marketed on the basis of an accelerated approval, the product must be studied further to describe and verify the clinical benefit.

If the verification study were to yield inconclusive results, there would be uncertainty as to the clinical benefit of the product, and FDA would need to consider withdrawal of approval of a product that might, in fact, be beneficial.

a) Please discuss how FDA should approach verification studies, including the degree to which sensitivity to important, but small amounts of benefit should be sought.

b) Consider the situation of a post-marketing verification study where the result is inconclusive; e.g.,

i) an inability to complete the study as designed due inability to recruit or retain study subjects, or

ii) a study result that is not statistically significant but compatible with a worthwhile benefit smaller than the design goal.

Please discuss what issues FDA should consider in this circumstance and what actions you would advise FDA to take regarding the marketed product.

4) Genzyme is currently conducting a randomized, controlled study to provide the verification of clinical benefit that they believe the histologic measure predicts. Genzyme proposes to change this study design to a single arm, open label study of treatment with agalsidase beta. In order to support this proposal, they have provided a database of information on creatinine levels in patients with Fabry Disease. Genzyme proposes that this database can form an external, historical control group for comparison with the data in the proposed open label treatment study.

Genzyme initially proposed a method for analyzing the historical data to provide a historical disease progression rate. FDA reviewed the proposal and identified several areas of concern. Genzyme recently proposed a different method to analyze the historical data in order to provide a historical disease progression rate. This new proposal lacks sufficient methodological detail. FDA is unable to determine whether it is potentially suitable to provide a historical disease progression rate.

a) Please discuss the quality and strength of data in this historical database, particularly as regards the intended use as a historical control.

b) Please discuss, to the degree feasible, the advantages and disadvantages of the recent Genzyme proposal for a method to use the historical data.

c) Based on the information Genzyme has provided to FDA at this time, please discuss whether the new analysis method can be conclusively assessed to determine if it is suitable to provide a sufficiently accurate and precise prediction of the renal progression rate.

d) Please provide recommendations regarding how Genzyme and FDA should focus efforts to verify the potential clinical benefit of agalsidase beta. These efforts might include:

i. Completion of the verification study as a randomized, controlled study
ii. Renewed efforts to develop a more extensive historical database prior to developing analytic approaches to the historical data
iii. Further development of Genzyme's newly proposed analytic approach
iv. Other approaches the committee may wish to recommend