CANADIAN COORDINATING OFFICE FOR HEALTH TECHNOLOGY ASSESSMENT
OFFICE CANADIEN DE COORDINATION DE L'ÉVALUATION DES TECHNOLOGIES DE LA SANTÉ

CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

AGALSIDASE BETA
(Fabrazyme® – Genzyme Canada)

Description:
Agalsidase beta (Fabrazyme®) is an enzyme replacement therapy used in the treatment of Fabry disease. Fabry disease is a rare, inherited glycosphingolipid storage disorder caused by deficient activity of the lysosomal enzyme, α-galactosidase A, resulting in the accumulation of globotriaosylceramide in tissues and thereby damaging internal organs such as the heart and kidneys. Clinical manifestations include chronic pain and acute pain crises, chronic kidney disease, heart disease and strokes. Agalsidase beta catalyses the hydrolysis of globotriaosylceramide, thereby reducing its accumulation in many cell types.

Recommendation:
CEDAC recommends that agalsidase beta not be listed.

Reasons for recommendation:
1. One 20-week randomized controlled trial (RCT) involving 58 people has been conducted with agalsidase beta. This trial and other less rigorous clinical trials failed to show the clinical benefit of agalsidase beta on a range of tests of neurologic, renal and cardiac function.
2. The lack of clinical benefit weakens confidence in the principal benefit seen in the RCT: reduced kidney interstitial capillary endothelial cell globotriaosylceramide levels. For example, despite reductions in kidney cell globotriaosylceramide levels, there was no change in renal function when all patients are included in the analysis. Baseline renal function (glomerular filtration rate) was not balanced between the treatment and control groups. Renal function improved for both placebo and agalsidase beta patient groups with no statistically significant difference between the groups.
3. There was no difference in pain control using a variety of assessment methods.
4. There were no significant improvements in any of the clinically oriented end points that were specified in the RCT protocol, including quality of life; and ophthalmological and cardiac end points. For example, there were no changes noted in cardiac conduction, ventricular size or echocardiographic measurements.
5. A large number of study results with agalsidase beta have been published since the original RCT was conducted. Many of these results appear to be analyses of subsets of patients who were part of the original RCT population. It is unknown how the subsets of patients were selected from the larger group of RCT patients; thus, the validity and generalizability of these data are difficult to assess.
6. Agalsidase beta is given by intravenous infusion once every two weeks. In clinical trials, infusion reactions occurred in 59% of patients. These reactions occurred despite pre-treating

some patients with nonsteroidal anti-inflammatory drugs and antihistamines and the concurrent use of systemic corticosteroids to manage these reactions.

7. Antibodies to agalsidase beta may develop over the course of therapy. Whether these antibodies impair the response to agalsidase beta or increase the risk of continued infusion reactions requires further study.
8. The per-patient treatment cost of agalsidase beta is high at $290,599 per year (excluding pharmacy mark-up) for a 70 kg person with Fabry disease. Despite this, there is no valid study supporting the cost-effectiveness of this agent.
9. In summary, it was CEDAC's opinion that although this medication affects certain surrogate markers, its impact on clinically meaningful outcomes has not been proven in randomized trials or observational studies to date.

Of Note:

1. Using conventional criteria, agalsidase beta has not been shown to be cost-effective, though this by itself, is only one of the factors that may be used in making any subsequent funding decision.
2. It is estimated that there are fewer than 300 people in Canada with Fabry disease, so this disease is rare.
3. To date, there is no treatment that alters the natural course of Fabry disease. Treatment is symptomatic or aimed at the disease's complications (e.g., dialysis for end-stage kidney disease).
4. The Committee recognizes that the small number of patients with Fabry disease makes the conduct of large randomized trials difficult. This makes it even more important than usual for the randomized and observational studies that are conducted to be of the highest possible quality. The available randomized trials were of extremely short duration and chose surrogate rather than clinically important outcomes as the primary outcomes. The Committee feels that it is both ethical and mandatory to conduct randomized trials with clinically important outcomes in rare diseases. As with most trials, an independent Data Safety Monitoring Board could be appointed, in order to ensure that the study is stopped when it is clear that a therapy has an impact upon clinically important outcomes that outweigh the therapy's side effects.

   The Committee found that the observational studies were of poor quality. In particular, given the brevity of the randomized trials, it would have been useful to follow all participants over many years to document progression of the Fabry disease and the occurrence of clinical outcomes while on treatment. Furthermore, the observational studies at present appear to report upon subgroups of patients, rather than all patients, thus raising concerns about why information from some patients was not provided. Nonrandomized trials should clearly describe the representativeness of the patients enrolled in the study, and should include measures of outcomes in all patients enrolled.
5. The above considerations raise ethical issues. Agalsidase beta has demonstrated a biological effect in a debilitating disease for which patients have no other options to treat their underlying disease. Agalsidase beta is costly and it has been argued that the costs of drugs to treat rare diseases are often high because of the relatively small number of patients for whom the drug is indicated. However, it is difficult to justify recommending reimbursement for such an expensive drug, which, at this time, has little evidence of effectiveness based on clinical endpoints. Reimbursement of agalsidase beta would raise questions about equity, since drugs that have not been shown to be cost-effective for other diseases are not generally reimbursed.
6. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.