CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

AGALSIDASE ALFA
(Replagal™ – Transkaryotic Therapies Inc.)

Description:
Agalsidase alfa (Replagal™) 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 alfa catalyses the hydrolysis of globotriaosylceramide, thereby reducing its accumulation in many cell types.

Recommendation:
CEDAC recommends that agalsidase alfa not be listed.

Reasons for recommendation:
1. Published and unpublished clinical trials comparing agalsidase alfa with placebo in patients with Fabry disease were reviewed.
   - Study TKT003, was a six-month trial studying 26 patients with neuropathic pain. Pain scores improved in people in both treatment groups. There was no statistically significant difference between the two treatment groups in terms of area under the curve analysis for "pain at its worst" scores, while off pain medication (p=0.08). However, significant differences favouring the agalsidase alfa group over the control, for brief pain index (BPI) severity scores and BPI quality of life were observed. This study also reported an improvement in the proportion of normal glomeruli in patients treated with agalsidase alfa and a significant difference in renal function favoring the treatment group. This difference, however, was based on a precipitous fall in renal function in the control group between weeks 23 and 24, which was thought not to be physiologically plausible, and was no longer present by week 25.
   - Study TKT005, a six-month, placebo-controlled trial involving 15 patients, was published only in abstract form. The primary outcome was left ventricular (LV) mass measured using MRI. There was a 4.2% decrease in LV mass (agalsidase alfa) compared with an 8.8% increase in LV mass (placebo) (p=0.041). This study did not document any difference in clinically important cardiac outcomes between the two groups.
   - CEDAC also considered the results of one unpublished randomized trial, submitted by the manufacturer. The manufacturer has requested that these results remain confidential pursuant to the Confidentiality Guidelines of the Procedures for CDR.

2. Agalsidase alfa is given by intravenous infusion once every two weeks. In clinical trials, infusion reactions, occurred in 57% of patients. When the infusion time was increased from 20 to 40 minutes the rate of infusion reactions decreased to about 10%.
3. Antibodies to agalsidase alfa may develop over the course of therapy. Whether these antibodies impair the response to agalsidase alfa or increase the risk of continued infusion reactions requires further study.
4. In the absence of long-term randomized trials, the manufacturer presented data from the Fabry Outcome Survey, an observational database of 504 patients receiving treatment with agalsidase alfa. Unfortunately, the data for clinical outcomes such as renal function, quality of life, and left ventricular mass were presented only for small numbers of patients who were selected using unknown methods. As such, the validity and generalizability of these data are difficult to assess.
5. The per patient treatment cost of agalsidase alfa is $239,200 per year (excluding pharmacy markup) for a 70 kg person with Fabry disease. Despite this, the manufacturer did not provide a valid study supporting the cost-effectiveness of this agent.
6. 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 in subsequent observational studies to date.

Of note:

1. Using conventional criteria, agalsidase alfa 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 alfa has demonstrated a biological effect in a debilitating disease for which patients have no other options to treat their underlying disease. Agalsidase alfa 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 alfa 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.