

Alglucosidase alfa

Product:

ALGLUCOSIDASE ALFA
(Myozyme®) 50 mg/vial injection

Class of drugs:

Enzyme replacement therapy

Indication: Treatment of Pompe disease (lysosomal glycogen storage disease type II [GSD II])

Manufacturer: Genzyme Canada Inc.

CED Recommendation

The CED recommended that alglucosidase alfa (Myozyme) be funded through the Ontario Public Drug Programs via the Exceptional Access Program for the treatment of infantile/early onset Pompe disease, according to specific criteria. The Committee acknowledged that Pompe disease is rare and it is difficult to generate adequate data to clearly demonstrate clinical benefit and value for money. In the absence of a pan-Canadian policy for drugs for rare diseases, the CED's recommendation was made on the basis of the high fatality rate in untreated infants with early onset disease, the reported early survival benefits and reduction in ventilator dependence observed in the limited clinical trials, coupled with the lack of treatment options available.

The CED also reviewed the available evidence for adult/late onset Pompe disease and recommended no reimbursement. When the initial review for alglucosidase alfa (Myozyme) for the treatment of infantile and adult/late onset was done, the Drugs for Rare Diseases (DRD) evaluation framework was not in place.

After the DRD evaluation framework was developed, the adult/late onset indication was reviewed under the DRD evaluation framework. For additional information on the review and reimbursement guidelines for the adult/late onset indication, please see: http://www.health.gov.on.ca/english/providers/program/drugs/pdf/myozyme_reimbursement_adult.pdf

For additional information on the review and reimbursement guidelines for the infantile/early onset indication, please see: http://www.health.gov.on.ca/english/providers/program/drugs/pdf/myozyme_reimbursement_infantile.pdf

Executive Officer Decision

Based on the CED's recommendation the Executive Officer decided to fund alglucosidase alfa (Myozyme) through the Ontario Public Drug Programs via the Exceptional Access Program for the treatment of infantile/early Pompe disease, according to specific criteria.

Status

Funding is available through the Exceptional Access Program according to specific criteria.

For further information, please see http://www.health.gov.on.ca/english/providers/program/drugs/eap_criteria.html

Highlights of Recommendation:

- ◆ The Committee noted that the evidence submitted for infantile/early onset Pompe disease does not meet conventional standards for public drug funding reviews, but acknowledges that the rarity of the disease makes it difficult to produce strong clinical evidence and value for money. The observed survival benefits and reduction in ventilator dependence seen in the small numbers of infant patients who have received treatment is compelling.
- ◆ Long term evidence is required to evaluate the true clinical benefit, safety profile, and quality of life improvements for this product.
- ◆ Treatment with this product is very expensive, with an estimated a cost of \$155,000 per year for a child with infantile/early onset disease. A full cost analysis was not provided by the manufacturer; therefore value for money of this product could not be determined by the Committee.
- ◆ The available information for adult/late onset Pompe disease was also reviewed. The Committee noted the available evidence in this population was more immature and difficult to interpret; therefore, recommended against reimbursement. At the time the initial review was done for the adult/late onset indication, Ontario's DRD evaluation framework was not in place. After the DRD evaluation framework had been established, this indication was reviewed through the DRD evaluation framework where funding was recommended, according to specific criteria.

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- ◆ Overall, the Committee acknowledged that Pompe disease is a rare disease and therefore difficult to produce adequate data to demonstrate clinical benefit and value for money. In the absence of a pan-Canadian policy for drugs for rare diseases, given the high fatality rate in untreated infants with early onset disease, the lack of treatment options, and the compelling survival benefits and reduction in ventilator dependence observed in the limited clinical trials data available, the Committee recommended that alglucosidase alfa (Myozyme) not be approved for listing in the Formulary/CDI but be considered for reimbursement on an Exceptional Access basis according to specific criteria for infant/early onset Pompe Disease.

Background:

Pompe disease (lysosomal glycogen storage disease type II [GSD II]) is caused by the buildup of excess amounts of glycogen in the muscles including the heart. Glycogen is a form of stored carbohydrate that is used by muscles as an energy source. Patients with Pompe disease are lacking an enzyme that is needed to break down and convert glycogen to sugars that can be used properly by muscle tissue.

Pompe disease is rare. The predominant form of Pompe disease affects adults and results in gradual muscle weakness often leading over many years to ventilator-dependency for breathing later in life. The heart is typically not consistently affected in patients with adult/late onset of the disease. The less common but more severe form affects infants and can be diagnosed as early as several weeks after birth and almost always affects the heart muscle. Most cases of infantile/early onset Pompe disease result in death before the age of 18 months due to heart failure.

There is no standard treatment for Pompe disease at this time; current treatments are generally supportive in nature, assisting with breathing and heart problems and providing nutritional supplementation. Alglucosidase alfa (Myozyme) is an enzyme replacement therapy to provide patients with the missing enzyme.

Infants with Pompe disease may require lifelong treatment with alglucosidase alfa (Myozyme). Due to the rare nature of this disease and the very high likelihood of death in the infantile-onset type, it is difficult to know the long-term effects of the drug and whether or not treatment will produce a normal lifespan or reduce long-term outcomes.

Detailed Discussion:

- ◆ The manufacturer, Genzyme Canada Inc., asked the Ministry of Health and Long-Term Care to list alglucosidase alfa (Myozyme) on the Ontario Drug Benefit Formulary. Due to the high fatality rate in infantile onset type Pompe disease and the promising results in small groups of patients, the Committee approved the drug for Rapid Review. At that time, Ontario's DRD Evaluation Framework had not been established.
- ◆ The CED first reviewed alglucosidase alfa (Myozyme) for reimbursement consideration in December 2006. During this review, the Committee reviewed two trials related to infantile/early onset disease.
- ◆ Study AGLU01602 was an open label study of 18 patients less than six months of age with a historical control group. Although the trial had a few number of patients and was short in duration, the Committee found the evidence compelling in terms of improvement in survival and reduction in ventilator dependence. However, because the data available was short term, the Committee questioned how long the benefits of alglucosidase alfa (Myozyme) treatment could be maintained. It was further noted that alglucosidase alfa (Myozyme) does not cross the blood brain barrier and the Committee questioned whether long-term treatment in young patients will be curative or simply slow the progression of disease.
- ◆ Study AGLU01702 was an open label study of 21 patients between 6 months to 36 months of age. This study showed evidence of improvement in cardiac function, particularly in those patients who were less affected from a motor perspective. The data for survival in this group was not as well established as for the early infantile form; however there was an improvement in survival and fewer than expected children required ventilator support.
- ◆ The most common adverse effects to alglucosidase alfa (Myozyme) are hypersensitivity reactions which have ranged in severity from mild to life-threatening, including anaphylaxis.

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- ◆ No formal pharmacoeconomic analysis was submitted by the manufacturer; therefore, value for money could not be determined.
- ◆ Treatment is very expensive with alglucosidase alfa (Myozyme) with an estimated a cost of \$155,000 per year for a child with infantile/early onset disease (*assuming 17.5 kg body weight*). A full cost analysis was not provided by the manufacturer; therefore value for money of this product could not be determined by the Committee. The budgetary impact was difficult to predict. The Committee noted that diagnoses of Pompe disease may increase with the availability of active treatment and better screening for the disease.
- ◆ After a review of the clinical and economic evidence, the Committee noted that alglucosidase alfa (Myozyme) did not meet the conventional criteria for value for money. However, given the invariable risk of death in the first 12-18 months in the untreated infantile/early onset population, the evidence for benefit due to alglucosidase alfa (Myozyme) in this population is compelling. It was also noted that the evidence provided is from small, short term trials and longer term data is required in order to understand impact on disease and patient quality of life.
- ◆ In light of the policy and evidentiary issues highlighted by the CED, a subcommittee of clinicians including an expert in metabolic disease and genetics was convened in February 2007. The mandate of this subcommittee was to identify a niche population where reimbursement of alglucosidase alfa (Myozyme) therapy might be clinically beneficial.
- ◆ Upon review of the available evidence, and in consultation with several clinical experts from across the country, the subcommittee recommended start and stop criteria for endorsement by the CED.
- ◆ In June 2007, the CED reviewed and endorsed the subcommittee's recommendation on funding criteria for alglucosidase in the treatment of infantile/early onset Pompe Disease (*i.e. onset of generalized weakness before 12 months of age*). In the absence of a pan-Canadian policy for drugs for rare diseases, the CED's recommendation to fund treatment was based on the high

fatality rate in untreated infants with infantile/early onset disease, the lack of treatment options available, and the compelling survival benefits and reduction in ventilator dependence observed in the limited clinical trial evidence.

CEDAC Recommendation:

(<http://www.cadth.ca/index.php/en/cdr/recommendations>)

The Canadian Expert Drug Advisory Committee (CEDAC) recommended that alglucosidase alfa (Myozyme) be listed in patients with infantile-onset Pompe disease, as demonstrated by onset of symptoms and confirmed cardiomyopathy within the first 12 months of life. The CEDAC also recommended that drug plans develop specific criteria for monitoring and stopping alglucosidase alfa (Myozyme), in consultation with experts in the management of lysosomal storage diseases.

In September 2007, the Advisory Committee on Pharmaceuticals (ACP) supported the incorporation of Ontario's funding criteria when jurisdictions implement the CEDAC recommendation.



Ministry of
Health and Long-Term Care
 Ontario Public Drug Programs

For more information, please contact:

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