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Reimbursement Recommendation

Cipaglucosidase Alfa (Pombiliti) With Miglustat (Opfolda)

Indication: Cipaglucosidase alfa is indicated in combination with the enzyme stabilizer Opfolda (65 mg miglustat capsule) for the treatment of adult patients with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) weighing ≥ 40 kg. Miglustat is an enzyme stabilizer indicated in combination with Pombiliti (cipaglucosidase alfa) for the treatment of adult patients with late-onset Pompe disease (acid α-glucosidase [GAA] deficiency) weighing ≥ 40 kg. Cipaglucosidase alfa must be used in combination with 65 mg miglustat capsules.

Sponsor: Amicus Therapeutics Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Pombiliti With Opfolda?

Canada's Drug Agency (CDA-AMC) recommends that Pombiliti with Opfolda be reimbursed by public drug plans for the treatment of adult patients with late-onset Pompe disease (LOPD) weighing at least 40 kg if certain conditions are met.

Which Patients Are Eligible for Coverage?

Pombiliti with Opfolda should only be covered to treat patients who have a confirmed diagnosis of LOPD, are able to walk, and have a sitting forced vital capacity measurements of at least 30% of the predicted value for healthy adults. Pombiliti with Opfolda should not be covered to treat patients who have severe disease.

What Are the Conditions for Reimbursement?

Pombiliti with Opfolda should only be reimbursed if prescribed by a clinician experienced in treating lysosomal storage diseases or other types of neuromuscular diseases, it is not used in combination with other enzyme replacement therapies for Pompe disease, and the cost of Pombiliti with Opfolda is reduced.

Why Did CDA-AMC Make This Recommendation?

- One clinical trial demonstrated that Pombiliti with Opfolda was as good as Myozyme in the walking distance outcome and there was no difference to minimal improvement in the breathing outcome.
- There was not enough evidence to suggest that Pombiliti with Opfolda provided any advantage over Myozyme in addressing patients' unmet needs.
- Based on the CDA-AMC assessment of the health economic evidence, Pombiliti with Opfolda does not represent good value to the health care system at the public list price. The committee determined there is not enough evidence to justify a greater cost for Pombiliti with Opfolda compared with the least expensive enzyme replacement therapy reimbursed for treatment of patients with LOPD.
- Based on public list prices, Pombiliti with Opfolda is estimated to cost the public drug plans approximately an additional $349 over the next 3 years. However, the actual budget impact is uncertain, considering the varying reimbursement status of alglucosidase alfa across Canada, and it may reach $6 million over the next 3 years for those jurisdictions that currently do not reimburse alglucosidase alfa.

Summary

Additional Information

What Is LOPD?

LOPD is caused by a genetic error that allows complex sugars to build up in the cells of organs and tissues, especially in muscles, causing them to not function properly. Many people with Pompe disease have heart problems and breathing problems, and almost all have muscle weakness. Most patients will have to use wheelchairs and/or oxygen at some point. It is not known how many people in Canada have LOPD. A study using data from births between 1969 and 1996 in British Columbia estimated the incidence of Pompe disease to be 1 in 115,091 people. No updated prevalence or incidence data specific to Canada have been identified.

Unmet Needs in LOPD

There is a need for treatments that improve muscle strength and breathing and prevent disease progression. Patients may also benefit from treatments that are easier to take, have fewer side effects, have a longer duration of treatment effect, and are easier to access without having to travel.

How Much Does Pombiliti With Opfolda Cost?

Treatment with Pombiliti with Opfolda is expected to cost approximately $683,183 per patient per year for Pombiliti and $4,788 per patient per year for Opfolda, resulting in approximately $687,971 per patient per year for the combination of Pombiliti with Opfolda.

Recommendation

The Canadian Drug Expert Committee (CDEC) recommends that cipaglucosidase alfa in combination with the enzyme stabilizer miglustat be reimbursed for the treatment of adult patients with late-onset Pompe disease (LOPD) (acid alpha-glucosidase [GAA] deficiency) weighing 40 kg or more only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, double-blind, phase III, randomized controlled trial (RCT) (the PROPEL study; N = 123) that enrolled adult patients with LOPD who were either currently receiving alglucosidase alfa for more than 24 months (enzyme replacement therapy [ERT]-experienced) or had never received any ERT (ERT-naive) demonstrated that treatment with cipaglucosidase alfa in combination with miglustat is comparable to treatment with alglucosidase alfa plus placebo. There was little or no clinically meaningful difference in 6-minute walk distance (6MWD), for which the least square (LS) mean difference between treatment groups was 14.21 m (95% confidence interval [CI], −2.60 m to 31.0 m). Additionally, cipaglucosidase alfa in combination with miglustat likely results in no difference to minimal improvement in sitting percent predicted forced vital capacity (FVC), Patient-Reported Outcomes Measurement Information System (PROMIS)-Physical Function score, and PROMIS-Fatigue score when compared to alglucosidase alfa plus placebo. However, statistical testing for secondary outcomes were not controlled for type I error.

The sponsor submitted an indirect treatment comparison (ITC) to compare the efficacy of cipaglucosidase alfa in combination with miglustat against avalglucosidase alfa and alglucosidase alfa in adult patients with LOPD. Although the ITC provides some comparative insights, several methodological and transparency gaps weaken confidence in the findings.

Patients identified a need for treatments with fewer side effects that improve strength and breathing function and slow down disease progression without reaching a plateau. Other considerations that patients valued included a better mode of delivery and fewer side effects. There is insufficient evidence to suggest that cipaglucosidase alfa in combination with miglustat provides any advantage over alglucosidase alfa in addressing patients' unmet needs. However, the evidence is supportive of cipaglucosidase alfa in combination with miglustat as an additional treatment option for patients living with LOPD.

At the sponsor-submitted price for cipaglucosidase alfa in combination with miglustat and the publicly listed price for alglucosidase alfa, cipaglucosidase alfa in combination with miglustat was more costly than alglucosidase alfa. Because the evidence suggests that cipaglucosidase alfa in combination with miglustat is considered similar and with no specific advantage over alglucosidase alfa, the total drug cost of cipaglucosidase alfa in combination with miglustat should not exceed the total drug cost of alglucosidase alfa.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with cipaglucosidase alfa in combination with miglustat should be reimbursed when initiated in patients with all the following: 1.1. have a confirmed diagnosis of LOPD 1.2. are ambulatory 1.3. have a sitting FVC ≥ 30% of the predicted value for healthy individuals.	The evidence from the PROPEL trial supported the efficacy and safety of treatment with cipaglucosidase alfa in combination with miglustat for patients with the outlined clinical criteria.	The diagnosis of Pompe disease should be based on confirmed GAA enzyme deficiency or confirmed *GAA* genotyping Ambulation is defined as the ability to ambulate more than 75 m without stopping and without an assistive device in a clinical assessment setting. Use of an assistive device for community ambulation is allowed. Cipaglucosidase alfa in combination with miglustat could be initiated similarly to alglucosidase alfa as per the reimbursement criteria for each public drug plan for the treatment of LOPD. Feedback from the clinical experts suggested that certain patients with a sitting FVC < 30% of predicted value who are not permanently ventilated may benefit from treatment with cipaglucosidase alfa in combination with miglustat and therefore should not be excluded from receiving this therapy.
2. Treatment with cipaglucosidase alfa in combination with miglustat must not be reimbursed when initiated in patients with severe disease.	There is no evidence to support the efficacy of cipaglucosidase alfa in combination with miglustat in patients with severe disease.	Severe disease can be defined as loss of ambulation or the need for permanent invasive ventilation.
Renewal		
3. Assessment of treatment response should be conducted at 6-month intervals. Treatment with cipaglucosidase alfa in combination with miglustat can be renewed as long as the patient does not meet any of the discontinuation criteria.	This is aligned with clinical practice in Canada based on input by clinical experts.	Cipaglucosidase alfa in combination with miglustat could be renewed similarly to alglucosidase alfa as per the reimbursement criteria for each public drug plan for the treatment of LOPD.
Discontinuation		
4. Treatment with cipaglucosidase alfa in combination with miglustat must be discontinued if the patient develops any of the following: 4.1. severe untreatable infusion-related reactions 4.2. declining motor or	There is a lack of evidence that cipaglucosidase alfa in combination with miglustat would benefit patients who exhibit the outlined clinical presentations. This is aligned with Canadian guidelines for the diagnosis and management of Pompe disease.	Some infusion-related reactions can be managed clinically with pretreatment and desensitization. Loss of ambulation is defined as wheelchair dependence. Cipaglucosidase alfa in combination with miglustat could be discontinued similarly to alglucosidase alfa as per the

Reimbursement condition	Reason	Implementation guidance
respiratory function at a similar rate as before therapy 4.3. loss of ambulation or the need for permanent invasive ventilation.		reimbursement criteria for each public drug plan for the treatment of LOPD.
Prescribing		
5. The patient must be under the care of a clinician experienced in treating lysosomal storage diseases or other types of neuromuscular diseases.	Accurate diagnosis and management of patients with Pompe disease are important to ensure that cipaglucosidase alfa in combination with miglustat is prescribed to appropriate patients.	—
6. Cipaglucosidase alfa in combination with miglustat should not be used in combination with other enzyme replacement therapies for Pompe disease.	There is no evidence to demonstrate a beneficial effect of cipaglucosidase alfa in combination with miglustat when used in combination with other enzyme replacement therapies for the treatment of Pompe disease.	—
Pricing		
7. The price of cipaglucosidase alfa in combination with miglustat should be negotiated so that it does not exceed the drug program cost of treatment with the least costly enzyme replacement therapy for the treatment of patients with LOPD.	Evidence from the PROPEL study suggests that cipaglucosidase alfa in combination with miglustat may result in no difference to minimal improvement in 6MWD compared to alglucosidase alfa plus placebo. There is uncertainty about how cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa will affect long-term wheelchair and ventilation dependence and these outcomes were not included with the submitted evidence. As such, there is insufficient evidence to justify a cost premium for cipaglucosidase alfa in combination with miglustat over the least expensive enzyme replacement therapy reimbursed for treatment of patients with LOPD.	—
Feasibility of adoption		
8. The feasibility of adoption of cipaglucosidase alfa in combination with miglustat must be addressed.	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and the CDA-AMC estimate(s).	—

6MWD = 6-minute walk distance; CDA-AMC = Canada's Drug Agency; FVC = forced vital capacity; GAA = acid alpha-glucosidase; LOPD = late-onset Pompe disease.

Discussion Points

- **Unmet need:** CDEC acknowledged that, although this treatment may not address an unmet need for adult patients with LOPD compared to currently approved ERTs for the treatment of LOPD, it offers a potential alternative for those who have developed antibodies to existing ERTs. In such cases, the combination of cipaglucosidase alfa and miglustat may serve as a viable treatment option. CDEC further acknowledged the scarcity of treatment options for patients living with LOPD.
- **GRADE assessment:** CDEC discussed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment of selected outcomes from the PROPEL study and noted the certainty of the outcome of 6MWD for cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa plus placebo was low. CDEC also noted the certainty of the outcomes of sitting FVC, PROMIS-Physical Function score, and PROMIS-Fatigue score were considered moderate.
- **6MWD**: CDEC discussed that the results of the primary efficacy end point in the PROPEL trial — 6MWD at 52 weeks — which demonstrated that cipaglucosidase alfa plus miglustat may have no difference to minimal improvement compared to alglucosidase alfa plus placebo in improving motor function. Although the mean improvement of 20.56 m in 6MWD for the cipaglucosidase alfa with miglustat arm represented a clinically meaningful group-level improvement, the mean improvement relative to alglucosidase alfa of 14.21 m did not reach the minimally important differences (MID) threshold for a between-group difference.
- **Percent predicted FVC**: CDEC discussed the result for the first key secondary end point in the PROPEL trial — sitting percent predicted FVC at 52 weeks — was assessed as moderate using GRADE and suggested that cipaglucosidase alfa in combination with miglustat likely results in no to minimal additional effect on pulmonary function compared to alglucosidase alfa plus placebo. The certainty of evidence was lowered due to imprecision because the lower bound of the 95% CI for the difference in FVC included the possibility of little to no clinically significant benefit. In addition, the mean difference did not meet the clinical meaningfulness threshold, and statistical testing was stopped after cipaglucosidase alfa in combination with miglustat failed to show superiority compared to alglucosidase alfa plus placebo for the primary outcome.
- **Patients who previously received ERT:** CDEC discussed that the ERT-experienced group in the PROPEL study had been receiving alglucosidase alfa for a mean duration of 7.4 years and were then switched to the study drug. In this subgroup, there was no clinically or statistically significant difference in 6MWD for cipaglucosidase alfa in combination with miglustat versus alglucosidase alfa plus placebo. Although there was a clinical improvement in sitting percent predicted FVC for cipaglucosidase alfa in combination with miglustat versus alglucosidase alfa plus placebo in the ERT-experienced subgroup, an interaction test was not performed and the lower bound of the 95% CI for the difference in FVC included the possibility of little to no clinically important benefit.
- **Long-term evidence:** CDEC discussed the results from the open-label extension (OLE) study and noted that the efficacy effects observed in the PROPEL trial generally remained stable across the OLE period to week 104 of treatment. For patients receiving cipaglucosidase alfa plus miglustat in

the PROPEL trial and continuing treatment in the OLE study, 6MWD, sitting percent predicted FVC, manual muscle test (MMT), and PROMIS-Physical Function effects were sustained to week 104. However, there is still uncertainty about the long-term effect of cipaglucosidase alfa combined with miglustat on wheelchair and ventilation dependence because these outcomes were not included in the submitted evidence.

- **Use of miglustat in combination with ERT:** CDEC noted that miglustat capsules, an enzyme stabilizer, are indicated for use in combination with cipaglucosidase alfa for the treatment of LOPD in adult patients. The committee emphasized that miglustat must be used alongside cipaglucosidase alfa because there is no evidence supporting the use of cipaglucosidase alfa as monotherapy or in combination with a lower or higher dosage of miglustat. CDEC also highlighted that there is no evidence supporting the use of miglustat capsules with other approved ERTs for LOPD.
- **Indirect evidence**: CDEC discussed the results from the sponsor-submitted ITC that compared the efficacy of cipaglucosidase alfa in combination with miglustat against avalglucosidase alfa and alglucosidase alfa in adult patients with LOPD. CDEC noted that although the ITC provides some comparative insights, several methodological and transparency gaps in it weaken confidence in the findings. The limited model diagnostics, missing inconsistency testing, reliance on reconstructed data, and variability in methodological choices introduce a high degree of uncertainty in the results.
- **Economic evidence is uncertain:** CDEC discussed the sponsor-submitted economic analysis, in which the long-term efficacy was based on assumptions of slower disease progression while on treatment with cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa. CDA-AMC was unable to address several key limitations with the sponsor's economic submission. CDA-AMC was unable to validate the impact of extrapolations and long-term assumptions due to poor flexibility with the submitted model, and the magnitude to which long-term assumptions drive the sponsor's cost-effectiveness results is unclear. Therefore, whether any predicted clinical results from the submitted model will be realized in clinical practice is highly uncertain. In addition, CDEC noted that the sponsor-submitted economic analysis did not include patients who were younger than 18 years and that the cost-utility analysis in this patient population is unknown.
- **Budget impact is uncertain:** Given the varying reimbursement status of alglucosidase alfa across Canada, there is potential for a high budget impact in jurisdictions that do not currently cover alglucosidase alfa for adult patients with LOPD (assuming no drug costs are currently being incurred). CDEC further noted that the budget impact analysis submitted by the sponsor did not account for patients younger than 18 years. As a result, the budgetary implication for this subgroup is unknown.

Background

Pompe disease is a rare autosomal recessive disorder caused by pathogenic variants in the *GAA* gene, leading to dysfunctional GAA enzymes. This defect allows glycogen accumulation, which impairs cellular function and causes tissue damage. Patients with LOPD have 2% to 40% of normal enzyme activity, while those with infantile-onset Pompe disease have little to none. The diagnosis of Pompe disease can be a

challenge because symptoms resemble those of other neuromuscular disorders. Diagnosis is typically confirmed via molecular testing and/or enzymatic analysis of blood samples. Usually, both of these noninvasive tests are performed as part of the diagnostic process. In most cases, the combination of 2 pathogenic variants of the *GAA* gene, reduced enzyme activity, and the presence of a myopathic phenotype confirms a diagnosis of Pompe disease. Disease progression varies, with severity inversely correlated to residual enzyme activity and worsened by earlier symptom onset. Patients with untreated LOPD have a 5-year postdiagnosis survival rate of 95%, which drops to 40% at 30 years postdiagnosis. ERT improves survival, although death often occurs before age 60, especially with early diaphragm involvement leading to respiratory failure. Clinical features range from slowly progressive myopathy to rapid progression with wheelchair and ventilator dependence. Respiratory muscle involvement, particularly of the diaphragm, is a hallmark of Pompe disease and a major cause of morbidity and mortality. A study using data from births between 1969 and 1996 in British Columbia estimated the incidence of Pompe disease to be 1 in 115,091 people. No updated prevalence or incidence data specific to Canada have been identified.

Treatment is currently focused on targeted, disease-modifying therapy as well as supportive, adjunctive interventions. In Canada, ERT is currently standard of care for patients who are symptomatic and have not yet reached end-stage disease requiring 24/7 invasive ventilation. The first ERT, alglucosidase alfa, was approved by Health Canada in 2006. A newer form of a recombinant human GAA (rhGAA), avalglucosidase alfa, was approved in 2021 for patients with LOPD aged 1 year or older. However, avalglucosidase alfa is not currently available on public plans in Canada.

Cipaglucosidase alfa has been approved by Health Canada in combination with an enzyme stabilizer (65 mg miglustat capsule) for the treatment of adult patients with LOPD (a GAA deficiency) weighing 40 kg or more. Cipaglucosidase alfa must be used in combination with 65 mg miglustat capsules. Miglustat is an enzyme stabilizer indicated in combination with cipaglucosidase alfa for the treatment of adult patients with LOPD (a GAA deficiency) weighing 40 kg or more. Miglustat capsules must be used in combination with cipaglucosidase alfa.

The recommended dosage of cipaglucosidase alfa is 20 mg/kg body weight administered every other week as an IV solution over approximately 4 hours. The recommended miglustat dosage for patients weighing between 40 kg to 50 kg is 3 capsules of 65 mg (195 mg total) orally every other week; for patients weighing 50 kg or more, it is 4 capsules of 65 mg (260 mg total) orally every other week.

Cipaglucosidase alfa is an rhGAA that provides an exogenous source of GAA and degrades glycogen by catalyzing the hydrolysis of alpha-1,4- and alpha-1,6-glycosidic linkages of lysosomal glycogen. Miglustat is a pharmacokinetic enzyme stabilizer of cipaglucosidase alfa that binds selectively to cipaglucosidase alfa in blood during infusion, thereby stabilizing the conformation of cipaglucosidase alfa and minimizing the loss of enzyme activity while in circulation.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, randomized, multicentre, double-blind study that evaluated the efficacy and safety of cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa plus placebo in adults with LOPD; 1 long-term extension study; 1 ITC; and 2 studies proposed by the sponsor as addressing gaps in the systematic review evidence, 1 of which was an ongoing, open-label, phase I/II study evaluating long-term (up to 48 months) efficacy of cipaglucosidase alfa in combination with miglustat, and the other was a prospective, observational registry study evaluating real-world safety and effectiveness of cipaglucosidase alfa in combination with miglustat
- patients' perspectives gathered by 1 patient group, Muscular Dystrophy Canada
- input from public drug plans that participate in the reimbursement review process
- two clinical specialists with expertise diagnosing and treating patients with LOPD
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted by for the purpose of this review.

Patient Input

Input for this review was provided by Muscular Dystrophy Canada, a nonprofit group supporting individuals with neuromuscular disorders. Muscular Dystrophy Canada gathered information through surveys, interviews, and the Pompe Canadian Journey Mapping Project. A total of 41 patients (17 female; 24 male) and 15 caregivers contributed, representing a significant portion of Canada's approximately 60 patients with Pompe disease. None had experience with the drug under review.

Patients identified 5 key quality-of-life impacts: mobility, strength, balance, and energy; breathing; mental health; daily activities; and effects on family and caregivers. Many patients struggled with tasks requiring strength or endurance and relied on mobility aids that posed accessibility challenges. Breathing difficulties led to poor sleep and reliance on respirators. Social isolation was common due to limited participation in activities, stigma, and illness concerns. High stress, anxiety, and depression were frequently reported, worsened by unpredictable symptoms and caregiver burden.

Diagnosing Pompe disease was often a lengthy and frustrating process, with most patients facing years of misdiagnoses, multiple tests, and specialty referrals before confirmation via muscle biopsy. Most patients received ERT and physiotherapy, although many experienced treatment delays due to equipment shortages or lack of trained nurses. Although health care teams managed funding applications for ERT, patients who applied independently faced long processes and occasional denials. Patients emphasized the need for more tolerable treatments with better disease control to maintain independence, reduce medical interventions, and

improve quality of life. Key treatment priorities included improved strength and breathing, slowed disease progression without plateauing, and more convenient administration.

Clinician Input

Input From Clinical Experts Consulted for This Review

The clinical experts consulted for this review indicated that the unmet needs of patients with LOPD would be new treatments that substantially reverse limb muscle and respiratory muscle weakness rather than simply provide stabilization, earlier treatment to prevent substantial weakness, shorter infusion times, and the availability of additional therapies (currently only 1 ERT is available in Canada). According to the clinical experts, patients would benefit from the availability of cipaglucosidase alfa in combination with miglustat as an alternative treatment, including for those who experience adverse reactions to or no longer receive benefit from alglucosidase alfa. The clinical experts indicated that the patients best suited for cipaglucosidase alfa in combination with miglustat would be those who are exhibiting symptoms from unequivocally diagnosed LOPD. The experts highlighted that, in their local practice, they test for FVC, manual muscle strength, and sometimes 6MWD (which is not always practical), along with other measures every 6 to 12 months. The experts agreed that a clinically meaningful response includes stabilization of the disease. The clinical experts indicated that treatment with cipaglucosidase alfa in combination with miglustat should be discontinued if the patient experiences life-threatening or intolerable immune responses that cannot be overcome. The clinical experts noted that patients receiving cipaglucosidase alfa in combination with miglustat should be under the care of a specialist with expertise in the management of Pompe disease (e.g., inherited metabolic disease specialists, medical geneticists, neuromuscular neurologists, and physiatrists).

Clinician Group Input

No clinician group input was received for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a recommendation for cipaglucosidase alfa in combination with miglustat:

- relevant comparators
- considerations for initiation of therapy
- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues
- system and economic issues.

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Avalglucosidase alfa is not reimbursed in any jurisdiction, and some jurisdictions do not reimburse alglucosidase alfa.	This is a comment from the drug programs to inform CDEC deliberations.
Considerations for initiation of therapy	
Patients with LOPD needed a documented deficiency of GAA enzyme or *GAA* genotyping to be included in the trial. How is LOPD diagnosed in Canada? Is it standard to evaluate deficiency of GAA enzyme or *GAA* genotyping?	In Canada, it is standard to evaluate both deficiency of GAA enzyme and *GAA* genotyping. LOPD diagnosis can usually be confirmed with *GAA* genotyping, but the clinical experts would also confirm the diagnosis with GAA enzyme deficiency. All patients in Canada will get at least 1 of these investigations, and usually both. CDEC noted that diagnosis of Pompe disease should be based on confirmed GAA enzyme deficiency or confirmed *GAA* genotyping.
Patients were required to be ambulatory for the trial with a sitting FVC ≥ 30% of the predicted value. Should reimbursement criteria reflect this?	The clinical experts stated that they would treat patients with a sitting FVC < 30% of the predicted value if they are not permanently ventilated. The FVC value does not determine whether patients should be treated. According to the Canadian guidelines, patients who are not fully ventilated are eligible for ERT. CDEC recommended that to be eligible for treatment with cipaglucosidase alfa in combination with miglustat, patients must have a sitting FVC ≥ 30% of the predicted value for healthy adults, which aligns with the inclusion criteria of the PROPEL trial.
The trial included patients who were ERT-experienced (defined as currently receiving alglucosidase alfa at recommended dose and regimen for at least 24 months), or ERT-naive (never received ERT). For patients who have been receiving standard ERT for less than 24 months, would you expect a full 24-month trial of alglucosidase alfa before considering switching to cipaglucosidase alfa in combination with miglustat?	The clinical experts noted to CDEC that they often observe small improvements in respiratory and motor function with ERT, and then a long plateau of approximately 5 years. After approximately 5 to 7 years on ERT, patients would typically have a resumption of decline at which time the clinical experts would determine that the patients were getting reduced benefit from ERT and consider switching from alglucosidase alfa to cipaglucosidase alfa in combination with miglustat. The clinical experts also noted that it is not necessary to do a trial of 1 ERT, such as alglucosidase alfa, before switching to cipaglucosidase alfa in combination with miglustat, and that patients do not have to have a 24-month trial of alglucosidase alfa before considering switching to cipaglucosidase alfa in combination with miglustat.
What is the standard of care for patients with LOPD in Canada?	The clinical experts noted to CDEC that standard of care for patients with LOPD in Canada is ERT, and if ERT is not provided to patients in some jurisdictions, then patients would receive supportive care, such as exercise, maybe vitamin D supplementation, and ventilation.
The proportion of patients who were ERT-experienced in the trial was 77.2%. However, patients were not required to “fail” on current ERT to be eligible for the trial. Should patients switch to cipaglucosidase alfa in	The clinical experts noted to CDEC that if patients are responding well to treatment with ERT (e.g., avalglucosidase alfa or alglucosidase alfa) they would not switch therapy to cipaglucosidase alfa in combination with miglustat, and that patients should be switched to receive cipaglucosidase alfa in combination with miglustat if they experience

Implementation issues	Response
combination with miglustat even if they are responding well to treatment with ERT?	an IAR, anaphylaxis, or other serious adverse effect while receiving another ERT.
Considerations for continuation or renewal of therapy	
The primary end point of the trial was change in the 6MWT distance from baseline to week 52, and the key secondary end points were change in sitting FVC (% predicted) from baseline to week 52, change in MMT lower extremity score form baseline to week 52, change in 6MWT distance from baseline to week 26, change in PROMIS-Physical Function total score and PROMIS-Fatigue score from baseline to week 52, and change in the GSGC total score from baseline to week 52. Are any of these end points used to monitor patients with LOPD in clinical practice in Canada? If not, how are patients monitored for therapeutic response?	One clinical expert stated that the change in 6MWT distance and sitting percent predicted FVC were monitored in practice in part because they were required to report these end points for each patient to their ministry of health. The clinical expert did not use the PROMIS instruments but did use the Short Form (36) Health Survey in practice. The other clinical expert shared that the 6MWT is not always practical because it is difficult to find the space to do a proper test in a neurology clinic. The clinical experts preferred to use the Gower manoeuvre test of the GSGC and the TUG test in practice. The clinical experts noted that patients should continue receiving ERT unless they experience life-threatening and unsurmountable anaphylactic reactions. CDEC noted that sitting FVC is widely accessible, inexpensive, and easy to administer, whereas the 6MWT presents greater logistical challenges. It was also noted that the 2 assessments capture different aspects of disease activity — sitting FVC primarily reflects diaphragmatic function, while the 6MWT assesses skeletal and/or axial muscle performance.
Considerations for discontinuation of therapy	

The discontinuation criteria recommended by CDEC for avalglucosidase alfa is:
• treatment with avalglucosidase alfa must be discontinued if the patient develops any of the following:
  ◦ severe untreatable infusion-related reaction
  ◦ declining motor or respiratory function at a similar rate as before therapy to the point of loss of ambulation or the need for permanent invasive ventilation.
Should the discontinuation criteria for cipaglucosidase alfa in combination with miglustat align with that of avalglucosidase alfa?
	The clinical experts agreed that treatment with cipaglucosidase alfa in combination with miglustat should be discontinued if the patient develops any of the following:
	• a severe untreatable infusion-related reaction
	• the need for permanent invasive ventilation.
	Because the goal of treatment is to slow disease progression, declining motor or respiratory function at a similar rate as before therapy does not mean that the treatment is not working (i.e., function may have decreased at a faster rate without treatment).
	CDEC recommended that cipaglucosidase alfa in combination with miglustat must be discontinued if the patient develops any of the following:
	• a severe untreatable infusion-related reaction
	• declining motor or respiratory function at a similar rate as before therapy
	• loss of ambulation or the need for permanent invasive ventilation.

How would disease progression be defined in patients with LOPD?	The clinical experts noted to CDEC that disease progression in patients with LOPD would be defined based on the following: worsening on the 6MWT, on manual muscle testing, or in respiratory function (as measured by FVC); need for ventilation; or need for increasing ambulatory aids.

Implementation issues	Response
Considerations for prescribing of therapy	
Cipaglucosidase alfa requires administration by a trained health care professional to monitor and manage IARs and the potential for anaphylaxis.	This is a comment from the drug programs to inform CDEC deliberations.
Care provision issues	
Cipaglucosidase alfa needs to be administered in a clinic or hospital setting when first initiated to monitor for IARs, severe allergic reaction, and anaphylaxis. The sponsor states that cipaglucosidase alfa in combination with miglustat can be administered at home by a trained health care professional after the evaluation of the risk for infusion-associated reactions. Patients in the PROPEL trial were eligible for home administration, administered by a trained home-infusion nurse, after participating in the trial for 6 months.	This is a comment from the drug programs to inform CDEC deliberations.
Patients must be monitored for development of severe infusion-associated reactions and anaphylaxis.	This is a comment from the drug programs to inform CDEC deliberations.
Premedication with oral antihistamines, antipyretics, and/or corticosteroids may be required for infusion-associated reactions.	This is a comment from the drug programs to inform CDEC deliberations.
System and economic issues	
Given the rarity of LOPD, do you anticipate patients needing to travel to a larger centre to receive treatment?	Based on the clinical experts' experience, patients have been able to receive infusion services from the local hospitals in remote areas, and it has been working well for patients.
Alglucosidase alfa was reviewed before the creation of pCPA, so it is unclear whether jurisdictions have confidential negotiated prices.	This is a comment from the drug programs to inform CDEC deliberations.

6MWT = 6-minute walk test; CDEC = Canadian Drug Expert Committee; ERT = enzyme replacement therapy; FVC = forced vital capacity; GAA = acid alpha-glucosidase; GSGC = Gait, Stairs, Gower manoeuvre, and Chair; IAR = infusion-association reaction; LOPD = late-onset Pompe disease; MMT = manual muscle test; pCPA = pan-Canadian Pharmaceutical Alliance; PROMIS = Patient-Reported Outcomes Measurement Information System; TUG = Timed Up and Go.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 1 pivotal study. The PROPEL trial, a phase III, randomized, multicentre, double-blind study, evaluated the efficacy and safety of cipaglucosidase alfa in combination with miglustat compared with alglucosidase alfa plus placebo in adults with LOPD. The trial was conducted across 24 countries, including 2 sites in Canada, from December 2018 to December 2020. The study enrolled 123 participants who were either currently receiving alglucosidase alfa for more than 24 months (ERT-experienced) or had never received any ERT (ERT-naive). Participants were randomized 2:1 to receive either cipaglucosidase alfa 20 mg/kg IV infusion plus miglustat 195 mg or 260 mg oral capsules (depending

on body weight; n = 85) or alglucosidase alfa 20 mg/kg IV infusion plus placebo (n = 38) every 2 weeks for 52 weeks.

The mean age of patients was 47 years, and the mean age at diagnosis was 39 years. Most (77%) of the patients were ambulatory and 23% used assistive devices at baseline. In the ERT-experienced group, the average ERT treatment duration was 7.4 years and approximately 67% had 5 or more years of prior treatment with ERT.

Efficacy Results

Results for all efficacy outcomes are presented using the ITT population without a patient with outlier results (a patient in the ERT-naive subgroup in the alglucosidase alfa plus placebo arm). After the database was locked and treatment assignments were unblinded, the outlier data were identified in the baseline 6MWD results. It was likely affected adversely by the patient's use of ostarine powder, an investigational anabolic steroid, before study enrolment which resulted in a clinically implausible change at week 52. Furthermore, this patient admitted to intentionally underperforming during the baseline assessment to enter the study. Given the patient's admitted underperformance on the screening test and their clinically implausible 6MWD results (i.e., observed change from baseline to 52 weeks = 355 m), all efficacy analyses are reported without the outlier data from this patient.

6MWD at Week 52 (Primary Outcome)

The mean change from baseline to week 52 for 6MWD was 20.56 m (95% CI, 11.22 m to 29.91 m) for the cipaglucosidase alfa in combination with miglustat group and 8.02 m (95% CI, −5.71 m to 21.74 m) for the alglucosidase alfa with placebo group. The LS mean difference between treatment groups was 14.21 m (95% CI, −2.60 m to 31.0 m). The results of the sensitivity analyses supported the primary analysis. Overall, 6MWD did not vary by any of the subgroups (i.e., ERT status, ERT duration, baseline 6MWD, and age group).

Sitting Percent Predicted FVC (First Key Secondary Outcome)

The mean change from baseline to week 52 for sitting percent predicted FVC was −0.93% (95% CI, −2.29% to 0.42%) for the cipaglucosidase alfa in combination with miglustat group and −3.95% (95% CI, −5.58% to −2.32%) for the alglucosidase alfa with placebo group. The LS mean difference between treatment groups was 2.66% (95% CI, 0.37% to 4.95%). The results of the sensitivity analyses supported the primary analysis. FVC did not vary by baseline 6MWD and age group. In the ERT-experienced subgroup, sitting percent predicted FVC showed stabilization over time, with a mean improvement of 0.05% (standard deviation [SD] = 5.84%) from baseline in the cipaglucosidase alfa in combination with miglustat group, compared to −4.02% (SD = 5.01%) in the alglucosidase alfa with placebo group, resulting in an estimated treatment difference of 3.51% (95% CI, 1.03% to 5.99%). In the subgroup of patients on ERT for 5 years or more, the LS mean treatment difference was 3.71% (95% CI, 0.41% to 7.00%) in favour of cipaglucosidase alfa in combination with miglustat. Interaction tests to test if results differed statistically by subgroup were not performed.

MMT Lower Extremity Score

The mean MMT lower extremity score increased from baseline by 1.56 (SD = 3.78) in the cipaglucosidase alfa in combination with miglustat group and 0.88 (SD = 2.58) in the alglucosidase alfa plus placebo group, resulting in a LS mean treatment difference of 0.96 (95% CI, −0.48 to 2.40).

6MWD at Week 26

At week 26, the mean 6MWD increased from baseline by 17.44 m (95% CI, 9.80 m to 25.08 m) in the cipaglucosidase alfa in combination with miglustat group and 9.19 m (95% CI, −0.20 m to 18.59 m) in the alglucosidase alfa plus placebo group. The LS mean treatment difference was 8.17 m (95% CI, −4.24 m to 20.57 m).

Patient-Reported Outcomes Measurement Information System

The PROMIS-Physical Function score total score ranges between 20 and 100, with a higher score indicating better physical functioning. MIDs of 2.4 (anchor-based) and 4.2 (distribution-based) have been reported for a clinically important improvement in physical function in patients with LOPD.

Compared to baseline, the PROMIS-Physical Function score increased by a mean of 1.94 (95% CI, 0.31 to 3.57) in the cipaglucosidase alfa in combination with miglustat arm, whereas the mean improvement was 0.19 (95% CI, −3.42 to 3.80) for the alglucosidase alfa plus placebo arm. This translated to an LS mean treatment difference of 1.87 (95% CI, −1.51 to 5.25).

The PROMIS-Fatigue total score ranges between 8 and 40, with lower scores indicating less fatigue. A MID for the PROMIS-Fatigue instrument in patients with LOPD was not identified in the literature.

Compared to baseline, the PROMIS-Fatigue score decreased by a mean of 2.02 (95% CI, −3.26 to −0.77) in the cipaglucosidase alfa in combination with miglustat arm, whereas the mean decreased by 1.67 (95% CI, −3.88 to 0.54) for the alglucosidase alfa with placebo arm. This resulted in an LS mean treatment difference of 0.04 (95% CI, −2.12 to 2.20).

Percent Predicted 6MWD

The mean change from baseline to week 52 for the percent predicted 6MWD was 4.07% (95% CI, 2.56% to 5.59%) for the cipaglucosidase alfa in combination with miglustat group and 1.58% (95% CI, −0.42% to 3.58%) for the alglucosidase alfa with placebo group. The LS mean difference was 2.38% (95% CI, −0.26% to 5.03%) between treatment groups.

Gower Manoeuvre

The Gower manoeuvre is an individual functional test of the Gait, Stair, Gower manoeuvre, and Chair (GSGC). The Gower manoeuvre involves the patient lying down on the floor, then rising from the floor to a standing position. The time (in seconds) to perform the test is recorded. A MID for the Gower manoeuvre specific to patients with LOPD was not identified in the literature.

The mean change from baseline for the Gower manoeuvre was −0.26 seconds (95% CI, −1.74 to 1.22) and −2.19 seconds (95% CI, −5.04 to 0.66) for the cipaglucosidase alfa in combination with miglustat and

alglucosidase alfa with placebo groups, respectively. The LS mean difference between treatment groups was 1.60 seconds (95% CI, −1.48 to 4.68).

Timed Up and Go

The Timed Up and Go (TUG) test is a mobility test that assesses balance, gait speed, and functional ability. The TUG test measures the time a patient needs to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down, all at the regular pace. A MID for the TUG test specific to patients with LOPD was not identified in the literature.

The mean change from baseline on the TUG test was −0.30 seconds (95% CI, −2.24 to 1.65) for the cipaglucosidase alfa in combination with miglustat group and −0.13 seconds (95% CI, −1.11 to 0.85) for alglucosidase alfa with placebo group. The LS mean difference between treatment groups was −0.47 seconds (95% CI, −3.38 to 2.43).

MMT Total Score

The MMT total score was the sum of the lower extremity score and the upper extremity score. The total score ranged from 0 to 80, with lower scores indicating lower overall muscle strength. MIDs for MMT scores specific to patients with LOPD were not identified in the literature.

The mean change from baseline for the MMT total score was 3.07 (95% CI, 1.66 to 4.48) and 1.41 (95% CI, −0.12 to 2.94) for the cipaglucosidase alfa in combination with miglustat and alglucosidase alfa with placebo groups, respectively. The LS mean difference between treatment groups was 2.22 (95% CI, −0.09 to 4.53).

Harms Results

Adverse Events

A total of 118 of 123 (98.9%) patients experienced a treatment-emergent adverse event (TEAE) during the study. The overall incidence was similar between the cipaglucosidase alfa in combination with miglustat group and the alglucosidase alfa with placebo group (95.3% and 97.4%, respectively). The most common TEAEs were falls, headaches, and nasopharyngitis. Most TEAEs were mild or moderate in severity.

Serious TEAEs

Overall, 10 of 123 (8.1%) patients had a severe TEAE. Eight of 85 (9.4%) patients in the cipaglucosidase alfa in combination with miglustat group reported 13 severe TEAEs (abdominal pain, enteritis, vomiting, chills, anaphylactic reaction, accidental overdose, fall, heart rate irregularity, dyspnea, pruritus, urticaria, aortic aneurysm, and flushing), whereas 2 of 38 (5.3%) patients in the alglucosidase alfa with placebo group reported 3 severe TEAEs (diverticulitis, cerebrovascular accident, and glycosuria).

Withdrawals Due to Adverse Events

Two patients in the cipaglucosidase alfa in combination with miglustat group withdrew from the study due to an adverse event, which were anaphylactic reaction and chills, both deemed to be study drug related. In the alglucosidase alfa with placebo group, 1 patient withdrew due to a cerebrovascular accident unrelated to the study drug.

Mortality
No TEAEs leading to death were reported.

Notable Harms
IARs were reported in 21 of 85 (25%) patients in the cipaglucosidase alfa in combination with miglustat group and in 10 of 38 (26%) patients in the alglucosidase alfa with placebo group. Two patients (1 in each group) reported 11 to 19 IARs and 1 patient in the cipaglucosidase alfa in combination with miglustat group reported more 20 IARs. In the cipaglucosidase alfa in combination with miglustat group, the most common IARs were dizziness, abdominal distension, headache, chills, diarrhea, dysgeusia, dyspnea, flushing, pruritus, pyrexia, and rash. In the alglucosidase alfa with placebo group, the most common IARs were nausea, fatigue, dizziness, and headache.

Critical Appraisal

Internal Validity
The PROPEL trial was a well-designed phase III, multicentre, double-blind, randomized, placebo-controlled study assessing the efficacy and safety of cipaglucosidase alfa in combination with miglustat and alglucosidase alfa with placebo over 52 weeks in adult patients with LOPD. The trial utilized a 2:1 random allocation process, generated by a computer algorithm and centrally managed to maintain allocation concealment. Blinding was effective, and patients could not infer their treatment group due to the frequency of adverse events. Adherence was high, and protocol deviations were well-documented. Missing data were handled through sensitivity analyses, and the results were consistent with the primary analysis outcomes for the primary and key secondary outcomes. Outcome measures were validated and reliable, and both the reported outcomes and analysis plan adhered to the study protocol.

External Validity
Overall, the patients in the PROPEL trial were deemed representative of the adult population with LOPD in Canada, although patients with more severe symptoms may not be properly represented (e.g., patients with sitting FVC < 30% of the predicted value for healthy adults who do not require full ventilation support). However, the clinical experts considered that the impact on the generalizability of results is low, and the effects are still applicable to the target population for reimbursement.

GRADE Summary of Findings and Certainty of the Evidence
For the pivotal RCT identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform the expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Following the GRADE approach, evidence from RCTs started as high-certainty evidence and could be rated down for concerns related to study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias.

When possible, certainty was rated in the context of the presence of an important (nontrivial) treatment effect; if this was not possible, certainty was rated in the context of the presence of any treatment effect (i.e.,

the clinical importance is unclear). In all cases, the target of the certainty of evidence assessment was based on the point estimate and where it was located relative to the threshold for a clinically important effect (when a threshold was available) or to the null.

The reference points for the certainty of evidence assessment for 6MWD and FVC were set according to the presence or absence of an important effect based on thresholds informed by the clinical experts. The reference point for the certainty of the evidence assessment for PROMIS-Physical Function was set according to the presence or absence of an important effect based on thresholds informed by the literature. Due to the lack of formal MID estimates for PROMIS-Fatigue, severe TEAEs, and IARs, the targets of the certainty of evidence assessments were the presence or absence of any (non-null) effect for each outcome.

The selection of outcomes for the GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following are the outcomes that were assessed:

- efficacy outcomes (6MWD and FVC)
- health-related quality-of-life outcomes (PROMIS-Physical Function and PROMIS-Fatigue scales scores)
- harms outcomes (severe TEAEs and IARs).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for cipaglucosidase alfa in combination with miglustat compared to alglucosidase alfa plus placebo.

Table 3: Summary of Findings for Cipaglucosidase Alfa in Combination With Miglustat vs. Alglucosidase Alfa With Placebo for Late-Onset Pompe Disease

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Alglucosidase alfa with placebo	Cipaglucosidase alfa in combination with miglustat	Mean difference		
Efficacy Outcomes							
Change from baseline in 6MWD (m) Follow-up: 52 weeks	117 (1 RCT)	NR	8.02 (−5.71 to 21.74)	20.56 (11.22 to 29.91)	14.21 (−2.60 to 31.02)	Low[a,b]	Cipaglucosidase alfa in combination with miglustat may result in little or no clinically meaningful difference in 6MWD when compared to alglucosidase alfa plus placebo.
Change from baseline in sitting FVC, % predicted Follow-up: 52 weeks	121 (1 RCT)	NR	−3.95 (−5.58 to −2.32)	−0.93 (−2.29 to 0.42)	2.66 (0.37 to 4.95)	Moderate[c,d]	Cipaglucosidase alfa in combination with miglustat likely results in little or no clinically meaningful difference in sitting percent predicted FVC when compared to alglucosidase alfa plus placebo.
Health-Related Quality of Life							
Change from baseline in PROMIS-Physical Function score Follow-up: 52 weeks	121 (1 RCT)	NR	1.94 (0.31 to 3.57)	0.19 (−3.42 to 3.80)	1.87 (−1.51 to 5.25)	Moderate[e,d]	Cipaglucosidase alfa in combination with miglustat likely results in little or no clinically meaningful difference in PROMIS-Physical Function score compared to alglucosidase alfa plus placebo.
Change from baseline in PROMIS-Fatigue score	122 (1 RCT)	NR	−2.02 (−3.26 to −0.77	−1.67 (−3.88 to 0.54)	0.04 (−2.12 to 2.20)	Moderate[f,d]	Cipaglucosidase alfa in combination with miglustat likely results in little or no difference in PROMIS--

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	What happens
			Alglucosidase alfa with placebo	Cipaglucosidase alfa in combination with miglustat	Mean difference		
Follow-up: 52 weeks							Physical Function score compared to alglucosidase alfa plus placebo. The clinical magnitude of the effect is unclear.[f]
Harms							
Patients with ≥ 1 severe TEAE Follow-up: 52 weeks	123 (1 RCT)	3.6 (0.5 to 27.6)	1 of 38 (2.6%)	8 of 85 (9.4%)	6.8% (−5.4% to 15.8%)	Low[g]	Cipaglucosidase alfa in combination with miglustat may result in little or no difference in the occurrence of severe TEAEs compared to alglucosidase alfa plus placebo. The clinical magnitude of the effect is unclear.[g]
Patients with any IARs Follow-up: 52 weeks	123 (1 RCT)	0.9 (0.5 to 1.8)	10 of 38 (26.3%)	21 of 85 (24.7%)	−1.6% (−18.4% to 15.1%)	Low[g]	Cipaglucosidase alfa in combination with miglustat may result in little or no difference in the occurrence of IARs compared to alglucosidase alfa plus placebo. The clinical magnitude of the effect is unclear.[g]

6MWD = 6-minute walk distance; CI = confidence interval; FVC = forced vital capacity; IAR = infusion-associated reaction; PROMIS = Patient-Reported Outcomes Measurement Information System; RCT = randomized controlled trial; TEAE = treatment-emergent adverse event.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]Rated down 1 level for serious imprecision. Based on clinical expert input, 20 m could be considered a clinically meaningful threshold for between-group difference. The 95% CI included the possibility of benefit and little to no difference.

[b]Rated down 1 level for serious imprecision. The minimally important difference for 6MWD in patients with late-onset Pompe disease is very uncertain based on the varying and wide ranges of minimally important differences reported in the literature and per clinical expert input.

[c]Rated down 1 level for serious imprecision. Based on clinical expert input, 3% could be considered a clinically meaningful threshold for between-group difference. The 95% CI included the possibility of benefit and little to no difference.

[d]Statistical testing for this outcome was not adjusted for multiplicity in the trial and should be considered as supportive evidence.

[e]Rated down 1 level for serious imprecision. Based on the relevant literature, MIDs of 2.4 (anchor-based) and 4.2 (distribution-based) could be considered clinically meaningful thresholds. The 95% CI included the possibility of benefit and little to no difference.

[f]Rated down 1 level for serious imprecision. No minimally important difference was found; therefore, the null effect was used. The 95% CI included the possibility of benefit and little to no difference.

[g]Rated down 2 levels for very serious imprecision. There are very few patients with events captured. No minimally important difference was found; therefore, the null effect was used. The 95% CI included the possibility of benefit and little to no difference.

Source: PROPEL Clinical Study Report. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

ATB200-07 is an ongoing, phase III, international, OLE study to assess the long-term safety and tolerability of cipaglucosidase alfa in combination with miglustat following 104 weeks of treatment (i.e., 52 weeks in the PROPEL trial and 52 weeks in the OLE study) in adult patients with LOPD. Efficacy of the drug combination was also assessed as a secondary objective. Efficacy and safety outcomes in the ATB200-07 study were consistent with the PROPEL study. Patients enrolled in the OLE study who received cipaglucosidase alfa in combination with miglustat in the PROPEL study continued on study treatment (continued treatment), and those who received alglucosidase alfa with placebo were switched to cipaglucosidase alfa in combination with miglustat (treatment switched). No direct statistical comparisons between treatment groups were conducted, and results were descriptive only. Cipaglucosidase alfa in combination with miglustat was administered in the same manner as in the PROPEL study. The first infusion visit in the OLE study was scheduled approximately 2 weeks after the last study visit of the PROPEL study.

Efficacy Results

Six-Minute Walk Distance

For the cipaglucosidase alfa in combination with miglustat continued treatment group, the mean 6MWD was 373.1 m (SD = 124.23 m) at baseline in the ATB200-07 OLE study, with a mean change from baseline of −2.0 m (95% CI, −9.1 m to 5.1 m) at week 52. The treatment switched group mean 6MWD was 363.5 m (SD = 137.38 m) at baseline, with a mean change from baseline of −1.4 m (95% CI, −14.0 m to 11.1 m) at week 52.

Sitting Percent Predicted FVC

For the cipaglucosidase alfa in combination with miglustat continued treatment group, the mean sitting percent predicted FVC was 69.1% (SD = 19.41%) at baseline in the ATB200-07 OLE study and 67.9% (SD = 20.39%) at week 52, with a mean change from baseline of −0.2% (95% CI, −1.9% to 1.6%). The treatment switched group mean sitting percent predicted FVC was 63.8% (SD = 19.63%) at baseline and 64.2% (SD = 19.21%) at week 52, with a mean change from baseline of 0.0% (95% CI, −1.8% to 1.8%) at week 52.

MMT Total Score

For the cipaglucosidase alfa in combination with miglustat continued treatment group, the mean MMT total score was 62.2 (SD = 8.33) at baseline in the ATB200-07 OLE study and 65.7 (SD = 8.41) at week 52, with a mean change from baseline of 3.2 (95% CI, 1.7 to 4.8). The treatment switched group mean MMT total score was 62.7 (SD = 9.86) at baseline and 64.0 (SD = 10.93) at week 52, with a mean change from baseline of 1.4 (95% CI, −0.2 to 2.9).

PROMIS-Physical Function Total Score

For the cipaglucosidase alfa in combination with miglustat continued treatment group, the mean PROMIS-Physical Function total score was 68.8 (SD = 12.81) at baseline in the ATB200-07 OLE study and 69.7 (SD = 12.98) at week 52, with a mean change from baseline of 0.6 (95% CI, −0.6 to 1.8). The treatment switched

group mean score was 67.8 (SD = 16.74) at baseline and 67.4 (SD = 15.23) at week 52, with a mean change from baseline of −0.1 (95% CI, −2.5 to 2.2).

PROMIS-Fatigue Total Score

For the cipaglucosidase alfa in combination with miglustat continued treatment group, the mean PROMIS-Fatigue total score was 19.9 (SD = 7.50) at baseline of the ATB200-07 OLE study and 20.1 (SD = 7.13) at week 52, with a mean change from baseline of 0.2 (95% CI, −1.1 to 1.6). The treatment switched group mean score was 19.3 (SD = 6.72) at baseline and 21.0 (SD = 6.80) at week 52, with a mean change from baseline of 1.5 (95% CI, −0.6 to 2.6).

Harms Results

No new safety signals were identified during the ATB200-07 OLE study and commonly reported TEAEs associated with cipaglucosidase alfa in combination with miglustat treatment were consistent with the safety profile observed in the PROPEL study. Most TEAEs were considered mild or moderate in severity. Overall, the safety profile of cipaglucosidase alfa in combination with miglustat observed during the ATB200-07 study were consistent with the PROPEL study.

Critical Appraisal

The ATB200-07 study was designed as an OLE study to assess long-term safety and tolerability of cipaglucosidase alfa in combination with miglustat in adult patients with LOPD. This open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes and reporting of safety parameters due to unblinded exposure to the study medication during the treatment period. The ATB200-07 study population for this interim analysis consisted of patients who took part in the PROPEL study; therefore, it is reasonable to expect that the same strengths and limitations related to generalizability apply to the OLE study. Because patients needed to complete the PROPEL study before enrolling, the OLE study population is inherently enriched and introduces some selection bias due to inclusion of patients who continued into the open-label phase and those with potentially lower risk for adverse effects.

Indirect Comparisons

Description of Studies

The sponsor conducted an ITC using a network meta-analysis framework to compare the efficacy of cipaglucosidase alfa in combination with miglustat against avalglucosidase alfa and alglucosidase alfa in adult patients with LOPD. Given the absence of direct head-to-head clinical trials comparing all these treatments, the ITC was performed to estimate their relative effects based on available clinical trial data.

To address differences in study populations and baseline characteristics, the sponsor used a multilevel network meta-regression (ML-NMR) approach. An ML-NMR extends a standard network meta-analysis by integrating individual patient-level data if available (from the PROPEL study) and adjusting for key effect modifiers, such as prior ERT exposure, age, and baseline function. This approach attempts to account for treatment-effect heterogeneity by modelling covariate distributions across studies, potentially improving the validity of indirect comparisons.

The ITC included data from 6 studies: 2 RCTs, PROPEL and COMET, and 4 single-arm studies, including OLE trials. The inclusion of single-arm studies required statistical adjustments to match baseline characteristics with comparator arms in the RCTs. Two separate analyses were conducted:

- Network A: Limited to the 2 RCTs (PROPEL and COMET) to ensure comparability of treatment arms.
- Network B: Included single-arm trials and OLE trials to incorporate additional data, particularly from patients receiving avalglucosidase alfa who had previously been treated with ERT.

The primary efficacy outcomes evaluated were the change from baseline in 6MWD and sitting percent predicted FVC at 52 weeks.

Efficacy Results

Six-Minute Walk Distance

Network A (RCTs only): Cipaglucosidase alfa in combination with miglustat was associated with a mean increase in 6MWD of 14.64 m (95% credible interval [CrI], 7.07 m to 22.31 m) compared to alglucosidase alfa, and cipaglucosidase alfa in combination with miglustat was associated with a mean decrease in 6MWD of 10.02 m (95% CrI, –23.62 m to 4.00 m) compared with avalglucosidase alfa. Avalglucosidase alfa showed a mean increase in 6MWD of 24.66 m (95% CrI, 9.95 m to 39.55 m) compared to alglucosidase alfa.

Network B (full evidence): Cipaglucosidase alfa in combination with miglustat showed a 13.64 m (95% CrI, 8.73 m to 18.70 m) improvement over alglucosidase alfa and a 28.93 m (95% CrI, 8.26 m to 50.11 m) increase over avalglucosidase alfa.

Percent Predicted FVC

Network A (RCTs only): Cipaglucosidase alfa in combination with miglustat showed a mean increase of 2.53 percentage points (95% CrI, 1.38 to 3.67) compared to alglucosidase alfa and cipaglucosidase alfa in combination with miglustat showed a mean decrease of 1.45 percentage points (95% CrI, –3.01 to 0.07) compared with avalglucosidase alfa. Avalglucosidase alfa demonstrated a 3.98 percentage point (95% CrI, 2.40 to 5.64) improvement over alglucosidase alfa.

Network B (full evidence): Cipaglucosidase alfa in combination with miglustat increased FVC by 3.95 percentage points (95% CrI, 3.23 to 4.69) over alglucosidase alfa and 2.88 percentage points (95% CrI, 1.07 to 4.71) over avalglucosidase alfa.

Harms Results

The ITC did not include any formal analysis of safety outcomes.

Critical Appraisal

Although the ML-NMR approach is a methodological strength, several limitations impact the robustness of the findings. The data extraction process in the updated SLR relied on a single reviewer, increasing the risk of bias or missing data. Furthermore, the selection of treatment-effect modifiers was not fully justified because it excluded potentially relevant factors such as weight, muscle damage, and *ACE* genotype. The analysis also relied on applying adjustments based on individual patient-level data to aggregate-level data from other trials. The sponsor provided overall Pearson residuals which suggested a good fit of the

final ML-NMR model predictions to the observed study-level data. However, specific diagnostics were not available to assess the appropriateness or impact of the step involving the application of adjustments derived from individual patient-level data to the aggregate-level data from other trials. Additionally, inconsistency testing was not performed due to the network's structure, which limited the ability to verify whether indirect comparisons aligned with direct evidence.

The inclusion of single-arm trials and OLE trials in network B introduced heterogeneity and required matching techniques to align populations with appropriate comparator arms. This led to a notable shift in treatment rankings between network A (RCTs only) and network B (including single-arm studies). In network A, avalglucosidase alfa appeared more effective than the comparators, whereas in network B cipaglucosidase alfa in combination with miglustat showed to be superior. The difference suggests that ERT experience significantly influences treatment outcomes, but it also raises concerns about bias introduced by single-arm studies and the repeated use of comparator data, such as alglucosidase alfa, which could artificially increase precision.

Although the ITC provides some comparative insights, several methodological and transparency gaps weaken confidence in the findings. The limited model diagnostics, missing inconsistency testing, reliance on reconstructed data, and variability in methodological choices introduce a high degree of uncertainty in the results.

Studies Addressing Gaps in the Evidence From the Systematic Review

Two studies were proposed by the sponsor as addressing gaps in the systematic review evidence: the ATB200-02 study and the UK Early Access to Medicines Scheme (EAMS) registry study.

ATB200-02 Study

Description of Study

ATB200-02 (N = 29) is an ongoing, open-label, phase I/II study evaluating the long-term (up to 48 months) efficacy of cipaglucosidase alfa plus miglustat. Results from the ATB200-02 study were submitted to fill an evidence gap pertaining to the underrepresentation of patients without experience with ERTs in the PROPEL study and the common exclusion of patients who are nonambulatory from LOPD clinical trials. Efficacy outcomes assessed in the ATB200-02 study that were identified by clinical experts as important to this review were 6MWD, sitting percent predicted FVC, and MMT total score. The study included 4 cohorts based on ERT experience and ambulatory status: ERT-experienced (2 to 6 years) and ambulatory, ERT-experienced (≥ 2 years) and nonambulatory, ERT-naive and ambulatory, and ERT-experienced (≥ 7 years) and ambulatory. Patients were excluded from the ATB200-02 study if they had previously used any investigational therapy within 30 days or 5 treatment half-lives, required ventilatory support for 6 or more hours per day (except the nonambulatory cohort), or had a history of anaphylaxis to alglucosidase alfa and high sustained anti-rhGAA antibodies (except the ERT-naive cohort). Across all groups, 90% of patients were aged between 18 and 64 years, and the mean duration of ERT for patients with ERT experience ranged from 5.1 to 10.6 years. Study patients in both the ERT-experienced and ERT-naive groups showed they were significantly impacted by Pompe disease at study entry based on baseline 6MWD and sitting percent predicted FVC.

Efficacy Results

Six-Minute Walk Distance

Motor function was evaluated in all patients who were ambulatory using 6MWD. At month 48, 88.9% of patients in the ERT-experienced subgroup and 100% in the ERT-naive subgroup experienced an improvement in 6MWD from baseline. For patients in the ERT-experienced and ambulatory subgroup (cohorts 1 and 4), mean and percent change from baseline were 20.7 m (95% CI, −57.6 m to 99.0 m) and 3.9%, respectively, at month 48. For patients in the ERT-naive and ambulatory subgroup (cohort 3), mean and percent change from baseline were 52.2 m (95% CI, −21.9 m to 126.3 m) and 12.5%, respectively, at month 48.

Sitting Percent Predicted FVC

A meaningful change from baseline in sitting percent predicted FVC was defined as greater than or equal to 3% change in points from baseline. At month 48, the mean change from baseline in sitting percent predicted FVC was 1.0 (95% CI, 5.7 to 7.7) for patients in the ERT-experienced and ambulatory group (cohorts 1 and 4) and 8.3 (95% CI, −9.2 to 6.7) for patients in the ERT-naive and ambulatory group.

For patients who were nonambulatory (cohort 2), percent predicted sitting FVC data were available for 2 patients with ERT experience after 36 months of follow-up and 1 patient at 48 months of follow-up. After 36 months of follow-up, 1 patient improved and the other worsened compared with baseline. The patient with available data after 48 months of follow-up was generally stable compared to baseline.

MMT Total Score

Muscle strength was evaluated in all cohorts using the MMT total score, for which higher total scores indicate a reduced impact of disease on muscle function. For patients who were nonambulatory, the total score for MMT was based off the upper extremity score only. At month 48, mean change from baseline in MMT total score was 4.0 points (95% CI, 0.9 to 7.1 points) for patients in the ERT-experienced and ambulatory group (cohorts 1 and 4) and −1.3 points (95% CI, −9.2 to 6.7 points) for patients in the ERT-naive and ambulatory group.

Results at 48 months were not available for patients in the ERT-experienced and nonambulatory group (cohort 2), but at month 36, the change from baseline in MMT total score was −0.8 points (95% CI, −17.8 to 16.3 points).

Harms Results

Overall, no unexpected safety events were observed during the extended treatment period of the ATB200-02 study. TEAEs leading to study withdrawal occurred in 2 patients: 1 patient in cohort 1 had diffuse large B-cell lymphoma, which the investigator assessed as unrelated to treatment, and 1 patient in cohort 2 had a drug-related TEAE of urticaria, considered to be an IAR. The incidence of IARs was similar between the ERT-experienced (48%) and ERT-naive (50%) cohorts.

Critical Appraisal

The ATB200-02 study was designed as an open-label, phase I/II study to assess long-term efficacy of cipaglucosidase alfa in combination with miglustat in adult patients with LOPD. Although the ATB200-02 study was submitted to address the systematic review evidence gap pertaining to the exclusion of patients with LOPD who were nonambulatory from clinical trials, the small sample size makes it challenging to draw conclusions about long-term efficacy in this patient group. Efficacy data for pulmonary function and patient-reported outcomes in this group was limited to 1 and 2 patients, respectively. Additionally, statistical hypothesis testing was not part of the study design and there was no active comparator or placebo arm. The open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes and reporting of safety parameters due to unblinded exposure to the study medication during the treatment period.

UK EAMS Registry Study

Description of Studies

The UK EAMS registry study (N = 37) was a prospective, observational registry study evaluating real-world safety and effectiveness of cipaglucosidase alfa in combination with miglustat in patients with LOPD with ERT experience (≥ 2 years). This study was submitted to fill an evidence gap pertaining to a lack of real-world data in patients with LOPD. Reported efficacy outcomes that were identified by clinical experts as important to this review were 6MWD and sitting percent predicted FVC. Harms results were not reported for this study. Compared to the PROPEL study, patients included in this registry study were slightly older (mean = 53 years) at baseline, with a slightly longer mean ERT duration (11.1 years), and lower 6MWD and sitting percent predicted FVC measures.

Efficacy Results

Of all adults enrolled in the EAMS registry, 13 and 12 patients had both baseline and postbaseline assessments of 6MWD and percent predicted FVC, respectively; however, the time between these 2 assessments varied considerably, between 82 days to 1,401 days.

From baseline to postbaseline assessment, patients had a mean change in 6MWD of 10.2 m (SD = 33.9 m), and a mean change in sitting percent predicted FVC of 4.0% (SD = 9.1%).

Harms Results

Harms data were not reported for the UK EAMS registry study.

Critical Appraisal

At the time of submission, the available evidence was limited with no comprehensive details on methods and results, which may impact the ability to sufficiently review and critically appraise the evidence as well as the robustness of evidence and conclusions. Efficacy data were only available for one-quarter to one-third of patients, which, combined with the wide variation in time between baseline and postbaseline visits, limits the ability to draw firm conclusions about efficacy. Given that so few patients had both a baseline and post–follow-up measurement, the mean changes observed were likely from a highly select group and may not be representative of the entire study population. Additionally, the lack of reported harms limits the ability to assess the safety of cipaglucosidase alfa in combination with miglustat in real-world clinical practice.

Statistical hypothesis testing was not part of the study design and there was no active comparator or placebo arm. The open-label design could bias the magnitude of treatment effect for subjective efficacy outcomes. Additionally, because the EAMS study was based on data from a national UK registry, generalizability to the population of patients with LOPD living in Canada may be limited.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis State transition microsimulation model
Target population	Adult patients with LOPD
Treatments	Cipaglucosidase alfa in combination with miglustat
Dose regimens	Cipaglucosidase alfa: 20 mg/kg administered every other week Miglustat: 260 mg (4 tablets) for patients ≥ 50 kg or 195 mg (3 tablets) for patients weighing from ≥ 40 to < 50 kg, 1 hour before cipaglucosidase alfa infusion
Submitted prices	Cipaglucosidase alfa: $1,751.75 per 105 mg vial Miglustat: $46.04 per 65 mg capsule
Submitted treatment cost	Cipaglucosidase alfa: $683,183 per patient annually Miglustat: $4,788.42 per patient annually Total treatment cost: $687,971 per patient annually
Comparator	Alglucosidase alfa
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (approximately 23 years)
Key data source	PROPEL trial for both cipaglucosidase alfa in combination with miglustat, and alglucosidase alfa
Key limitations	• The comparative clinical effectiveness for cipaglucosidase alfa in combination with miglustat vs. alglucosidase alfa is uncertain. Patient input received by CDA-AMC noted the importance of therapies that help patients maintain their independency. However, there is uncertainty about how cipaglucosidase alfa in combination with miglustat will improve long-term wheelchair and ventilation dependency compared to alglucosidase alfa, and these outcomes were not included in the submitted evidence. Based on clinical expert feedback received by the sponsor, the sponsor assumed that patients treated with cipaglucosidase alfa in combination with miglustat would experience a 15% slower rate of subsequent annual disease progression after year 3 compared to alglucosidase alfa. However, in the absence of long-term data, the duration and magnitude of clinical benefit remains unknown and the predicted independency and survival benefits of cipaglucosidase alfa in combination with miglustat (i.e., 1.04 additional QALYs attributed to wheelchair or ventilation independency and 0.17 years of additional life) is uncertain. • The submitted model lacked stability and employed poor modelling practices that limited the model's flexibility to run reanalyses. At the submitted simulation count (i.e., 30,000 first order and 5 second

Component	Description
	order), the sponsor's model produced highly variable ICERs across multiple runs (i.e., ranging from $3,000 to $182,000 per QALY gained) due to the small but variable incremental clinical benefit estimated between runs. • The analysis was based on publicly available list prices. In jurisdictions where the price of alglucosidase alfa has been negotiated, the actual prices borne by payers will need to be considered.
CDA-AMC reanalysis results	• CDA-AMC was unable to address several key limitations with the sponsor's submission, including uncertainty regarding the comparative clinical data and long-term effectiveness of cipaglucosidase alfa in combination with miglustat. Specifically, concerns about model stability (i.e., results were too variable across model runs) precluded CDA-AMC from deriving a base case estimate of the cost-effectiveness of cipaglucosidase alfa in combination with miglustat.

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; LOPD = late-onset Pompe disease.

Budget Impact

CDA-AMC identified the following limitations in the sponsor's base case: use of claims-based approach to estimate market size introduces uncertainty with the anticipated budget impact, annual drug costs did not align with costs submitted in the cost-utility analysis, and the analysis was based on publicly available list prices. Based on the CDA-AMC base case, the incremental budget impact of funding cipaglucosidase alfa in combination with miglustat for the treatment of adult patients with LOPD was $53 in year 1, $120 in year 2, and $176 in year 3. Therefore, the 3-year incremental budget impact was $349. Due to the varying reimbursement status of alglucosidase alfa across Canada, CDA-AMC conducted scenario analyses in which the budget impact of reimbursing cipaglucosidase alfa in combination with miglustat was considered separately for jurisdictions confirmed to currently fund alglucosidase alfa, from those who do not (or no information is available or confirmed). Given the varying reimbursement status of alglucosidase alfa across Canada, the 3-year overall pan-Canadian budget impact of reimbursing cipaglucosidase alfa in combination with miglustat is $6,215,865 ($205 for those jurisdictions currently reimbursing alglucosidase alfa [i.e., British Columbia and Ontario]) and $6,215,660 across all the other jurisdictions that do not (assuming no drug costs are currently being incurred).

CDEC Information

Members of the Committee

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, Dr. Ran Goldman, and Dr. Peter Zed.

Meeting date: May 29, 2025

Regrets: Three expert committee members did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.