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CADTH

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CADTH Reimbursement Recommendation

Alpha$_1$-Proteinase Inhibitor (Human) (Zemaira)

Indication: Maintenance treatment in adults with severe alpha$_1$-proteinase inhibitor deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), or PiSZ) and clinical evidence of emphysema

Sponsor: CSL Behring Canada, Inc.

Final recommendation: Reimburse with conditions

Note: This document was initially posted on May 2, 2022 and subsequently revised on December 20, 2023 to correct an error in the definition of A_1-PI deficiency reported in the implementation guidance.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Zemaira?

CADTH recommends that Zemaira be reimbursed for the treatment of severe alpha$_1$-proteinase inhibitor (A_1-PI) deficiency if certain conditions are met.

Which Patients Are Eligible for Coverage?

Zemaira should only be covered to treat patients with severe A_1-PI deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ) and clinical evidence of emphysema who are nonsmokers for at least 6 months.

What Are the Conditions for Reimbursement?

Zemaira should only be reimbursed if prescribed by a respirologist and the cost of Zemaira is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that after 24 months of treatment, those who received Zemaira showed a slower decline in lung density compared with those who received placebo, which suggests that treatment with Zemaira might slow the underlying destruction of lung tissue.
- Zemaira may address some of the needs that are important to patients as it might slow decline in lung function in adult patients with severe A_1-PI deficiency.
- Based on public list prices, Zemaira is not considered cost-effective at a willingness-to-pay (WTP) threshold of $50,000 per quality-adjusted life-year (QALY) for the indicated population relative to current standard of care and would require a price reduction of at least 93% to ensure it is cost-effective at this threshold.
- Based on public list prices, the 3-year budget impact from the perspective of Canadian Blood Services is $165,249,851.

Additional Information

What is Severe Alpha$_1$-Proteinase Inhibitor Deficiency?

Patients with A_1-PI deficiency do not have enough A_1-PI, a protein that helps protect your lungs from inflammation, which can lead to progressive lung damage and emphysema. The progression of lung disease in patients with A_1-PI deficiency is typically gradual. The prevalence of the genotype associated with A_1-PI deficiency is generally considered to be around 1 in 5,000 people, but the combined presence of the A_1-PI deficient genotype and clinical evidence of emphysema is rare.

Unmet Needs in Severe Alpha$_1$-Proteinase Inhibitor Deficiency

There is a need for a treatment that would halt or slow a patient's decline in lung function.

How Much Does Zemaira Cost?

Treatment with Zemaira is expected to cost approximately $101,748 per patient annually.

Recommendation

The CADTH Canadian Plasma Protein Product Expert Committee (CPEC) recommends that A_1-PI (human) (Zemaira) be reimbursed for maintenance treatment in adults with severe A_1-PI deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ) and clinical evidence of emphysema only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

In 1 double-blind, randomized controlled trial in adults with A_1-PI deficiency, emphysema, and reduced lung function (the RAPID trial), Zemaira was associated with a reduced rate of decline in lung density after 24 months compared with placebo when CT scans were taken at full inspiration state (0.74 g/L; 95% confidence interval [CI], 0.06 to 1.42; 1-sided P = 0.017). This indicated that treatment with Zemaira might slow the underlying destruction of lung tissue as shown by CT scan densitometry. Patient input received for this review articulated that there is a need for a disease-modifying treatment that can halt or slow decline in lung function in adult patients with severe A_1-PI deficiency.

CADTH was unable to derive an economic base case given the limitations with the clinical information and the sponsor's model. CADTH performed an exploratory analysis to examine aspects of uncertainty with the model. Using the sponsor-submitted price for Zemaira and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for Zemaira plus standard of care was $664,549 per QALY compared with standard of care alone. At this ICER, Zemaira is not cost-effective at a $50,000 per QALY WTP threshold for patients with severe A_1-PI deficiency. A reduction in price of at least 93% is required for Zemaira to be considered cost-effective.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Zemaira should be reimbursed in adults with severe A_1-PI deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ) and clinical evidence of emphysema	In the RAPID study, treatment with Zemaira demonstrated a meaningful effect in adults (18 to 65 years of age) with A_1-PI deficiency, emphysema, and FEV_1 between 35% and ≤ 70%.	The clinical experts noted that severe A_1-PI deficiency is a confirmation of low serum levels of A_1-PI and evidence of COPD by spirometry or emphysema by CT scan. • A_1-PI deficiency is defined as serum A_1-PI levels < 11 µM/L or < 57 mg/dL before start of the treatment. • Serum samples with an A_1-PI levels < 11 µM must undergo genotype testing to document the presence of genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ, or other rare variants that are considered equivalent. • Clinically important emphysema is not defined by the presence of emphysema on a CT scan alone, though lung density assessments are having

Reimbursement condition	Reason	Implementation guidance
		an increasing role. Physiologically important emphysema is generally determined by routine clinical pulmonary function tests. One benchmark suggested by the Canadian Thoracic Society is obstruction (FEV_1/FVC below 0.70 and FEV_1 below 80% of predicted).
2. Patients must be nonsmokers for at least 6 months	In the RAPID study, the treatment benefit of Zemaira was demonstrated in patients who had ceased smoking at least 6 months before study inclusion.	—
Discontinuation		
3. Reimbursement of Zemaira should be discontinued in patients who receive a lung transplant	There is no evidence demonstrating a clinical benefit of Zemaira following lung transplant.	—
Prescribing		
4. Patient should be under the care of a respirologist	Accurate diagnosis and follow-up of patients with severe A_1-PI deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ) and clinical evidence of emphysema are important to ensure that Zemaira is prescribed to the most appropriate patients.	Virtual appointments could be considered acceptable to provide equitable access to Zemaira in communities without a respirologist.
Pricing		
5. A reduction in price	Based on the clinical evidence, the cost-effectiveness of Zemaira is highly uncertain. CADTH undertook a price reduction analysis based on the exploratory analysis. This analysis indicated that a price reduction of at least 93% is required to achieve an ICER of $50,000 per QALY.	—
Feasibility of adoption		
6. The feasibility of adoption of Zemaira must be addressed	At the submitted price, the budget impact of Zemaira is expected to be greater than $40 million in year 3, with a three-year total of $165,249,851 from a CBS perspective.	—

A_1-PI = alpha$_1$-proteinase inhibitor; CBS = Canadian Blood Services; COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume per second; FVC = forced vital capacity; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Discussion Points

- CPEC discussed that Zemaira was associated with a reduced rate in the validated primary outcome of decline in lung density after 24 months compared with placebo. This shows that treatment with Zemaira might preserve lung tissue in patients with severe A_1-PI deficiency; however, it is unknown how the decrease in lung density observed in the RAPID trial translate into improvement in patients' symptoms and the associated effect on their ability to perform daily activities. Though lung function as assessed by spirometry is used in clinical practice for following disease progression, the clinical experts consulted by CADTH noted that its use is driven by familiarity and availability rather than its accuracy in predicting future clinical outcomes in A_1-PI deficiency. Therefore, decline in lung density is likely an appropriate surrogate marker for assessing progressive disease.
- CPEC discussed that there are no statistically significant differences between Zemaira and placebo for clinical outcomes from the RAPID trial, such as symptoms and function, pulmonary function, exacerbation, and lung transplant and survival data, which could be due to the small sample size, the relatively short trial duration, and slow disease progression.
- The combined presence of the A_1-PI deficient genotype and clinical evidence of emphysema was acknowledged to be rare, and the gradual progression of lung disease was considered by CPEC when assessing the uncertainty in the available evidence.
- CPEC noted the clinical uncertainty in the sponsor's economic model, and noted that based on the sponsor's analysis, Zemaira leads to a survival gain of 7.74 years, while no survival benefit was observed based on the clinical trials. A price reduction of at least 93% would be required to achieve an ICER WTP threshold of $50,000 per QALY given the cost of the Zemaira.
- The clinical experts noted to CPEC that there might be some rare cases in which a change in dosage from 60 mg/kg once per week to 120 mg/kg once per 2 weeks is required to compensate for missed doses. CPEC discussed that reimbursement of Zemaira should not be associated with a limitation on dosing.

Background

A_1-PI deficiency, also known as alpha$_1$-antitrypsin deficiency (AATD), is a genetic disorder, with the prevalence of the genotype associated with A_1-PI deficiency generally considered to be around 1 in 5,000 people. A_1-PI deficiency is characterized by low serum concentrations of A_1-PI, a serine antiprotease produced in the liver but that appears to have its most important physiologic role in the protection of the lung parenchyma from endogenous elastases released by the neutrophil. A deficiency in endogenous A_1-PI may subject an individual to lifelong, progressive loss of lung tissue and predispose patients to early onset emphysema. There is, however, variable clinical expression and not all deficient individuals will develop overt disease. The clinical experts consulted by CADTH for this report indicated that the combined presence of the A_1-PI deficient genotype and clinical evidence of emphysema is rare. As it is seen with chronic obstructive pulmonary disease (COPD) unrelated to this deficiency, patients may present with breathlessness, cough, wheeze, decreased exercise tolerance, and impactful exacerbations.

The progression of lung disease in patients with A_1-PI deficiency is typically gradual. There is generally a delay in arriving at a specific diagnosis and patients are often treated as having asthma, non-alpha COPD, or are not recognized as having a significant pulmonary disorder. An appropriate diagnosis is achieved through genetic tests to confirm genotypes. Severe A_1-PI deficiency includes, but is not limited to, genotypes PiZZ, PiZ(null), Pi(null,null), and PiSZ. Failure to diagnose A_1-PI deficiency in a timely manner may prevent initiation of appropriate therapies and that delay can lead to a worsening of symptoms and deterioration of functional status, as well as a decreased life expectancy.

A_1-PI (human) (Zemaira) is a lyophilized preparation of highly purified human A_1-PI. Derived from pooled human plasma, it is administered once weekly via IV at the recommended dosage of 60 mg/kg of body weight. Zemaira has a Health Canada indication for the maintenance treatment of adults with severe A_1-PI deficiency and clinical evidence of emphysema. Severe A_1-PI deficiency includes, but is not limited to, genotypes PiZZ, PiZ(null), Pi(null,null), and PiSZ. Patients are to be under optimal pharmacologic and nonpharmacologic treatment and show evidence of lung disease, such as lower forced expiratory volume per second (FEV_1) predicted, lower diffusion capacity, impaired walking capacity, or increased number of exacerbations, as evaluated by a health care professional experienced in the treatment of A_1-PI deficiency.

Sources of Information Used by the Committee

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

- a review of 1 double-blind, randomized, placebo-controlled trial in individuals who are A_1-PI deficient and have emphysema and reduced lung function
- patients' perspectives gathered by 1 patient group, Alpha-1 Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- input from 2 clinical specialists with expertise diagnosing and treating patients with A_1-PI deficiency
- input from 1 clinician group, the Canadian Thoracic Society
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Alpha-1 Canada submitted the patient input for this review. Alpha-1 Canada is a national non-profit organization committed to advocating on behalf of Canadians affected by AATD and providing education and support to patients, caregivers, and the health care community. The submission was based on 2 virtual focus groups conducted in March 2021, 2 semi-structured interviews conducted over the phone in June 2021, 3 online surveys distributed between April 2021 and May 2021, and a single question survey emailed to respirologists working in Canada in May 2021. A total of 143 respondents (45 patients with AATD who were receiving augmentation therapy, 53 patients who were not receiving therapy, 16 caregivers, and 29 respirologists working in Canada) and 2 families living with AATD were included in the patient input.

Respondents indicated that the physical manifestation of AATD impacts many aspects of their lives, including employment, relationships, extracurricular activities, day-to-day tasks, to overall mental health. In areas where there is not publicly funded access to treatment, patients are weighing the steps they are willing to take to access therapy, such as continuing to work past retirement age to be eligible for private insurance, uprooting their lives to relocate to a province that offers coverage, or participating in clinical trials. Patients highlighted the costs to the health care system when they are unable to access treatment. They require inhalers to manage the symptoms of AATD, undergo frequent lung function tests, experience hospitalizations during exacerbations, and undergo lung transplant. The other major challenge patients with AATD face is the need to demonstrate deteriorated lung function before becoming eligible for augmentation therapy. Many felt they were doing additional damage to their lungs and compromising their quality of life while they waited to become eligible.

When patients with AATD are on augmentation therapy, they are able to stabilize their lung function. Patients perceive this as the most important outcome in effective treatment because it is associated with their ability to perform activities of daily living and fully participate in their communities and with their families. Patients with AATD did not feel that any disadvantages were worth noting in comparison to the possibility of augmentation therapy improving their quality and longevity of life.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

The clinical experts consulted by CADTH for the purpose of the review indicated that there is currently an unmet need, considering that none of the treatments other than A_1-PI replacement can prevent the loss of lung tissue. A_1-PI replacement is currently available in Canada mainly through private insurers and exceptional access programs. This treatment is considered disease modifying and would be a first-line treatment for any patient with emphysema and A_1-PI deficiency, and would be used in addition to standard of care for COPD. Because the drug is used to prevent rapid progression of emphysema, there are no specific outcome parameters to assess response to treatment, as there are not any factors that would be used as a stopping rule other than severe adverse events (AEs). As the goal of augmentation therapy is to prevent or decrease the rate of further tissue damage, it is expected that some patients will keep deteriorating despite treatment. However, it is very likely that these patients would have deteriorated even more without A_1-PI replacement, thus limiting the usefulness of lung function or number of exacerbations to assess response to treatment in this particular instance.

Clinician Group Input

One clinician group, the Canadian Thoracic Society, provided input that is in line with the input provided by the clinical experts consulted by CADTH. The meaningful impact of augmentation therapy and its potential role in clinical use has been acknowledged by Canadian Thoracic Society statements.

Drug Program Input

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

- considerations for initiation of therapy

- considerations for continuation or renewal of therapy
- considerations for discontinuation of therapy
- considerations for prescribing of therapy
- generalizability of trial populations to the broader populations in the jurisdictions
- care provision issues.

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

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Considerations for initiation of therapy	
Are lab tests to check serum AATD level available in all provinces?	CPEC agreed with the clinical experts confirmed that laboratory tests are easily available in all provinces.
Are genetic tests to confirm genotypes such as PiZZ, PiZ(null), or Pi(null)(null) needed to confirm eligibility for treatment? Are these genetic tests available in all the provinces?	CPEC agreed with the clinical experts that the genetic tests are needed to confirm genotypes should be done systematically, and that the technology is readily available. CPEC also agreed with the clinical experts that genetic tests are available in most provinces, but some provinces, such as Alberta, have continued to rely on outdated serum protein electrophoresis to determine, indirectly, the probable genotype. Buccal swab genotyping is readily available as sponsored by Grifols, the only company currently marketing augmentation therapy in Canada. The testing is done at Biocerna, a lab based in Maryland.
What defines "optimal pharmacological and non-pharmacological treatment"? Is it practical to put this in the treatment eligibility criteria?	CPEC agreed with the clinical experts that "optimal pharmacological and non-pharmacological treatment" in A_1-PI deficiency is the same as that for COPD. Sometimes, some interventions, such as pulmonary rehabilitation, may not be readily available to all patients. The clinical experts also noted to CPEC that it would be very difficult to operationalize the definition of having met "optimal pharmacological and non-pharmacological therapy." Prescription by a respiratory specialist would be the best way to operationalize the requirement of optimal therapy before starting A_1-PI. Therefore, no alternative treatments would need to be trailed. CPEC also agreed with the clinical experts that the only reasonable benchmark is to require that patients be cared for by a respiratory specialist and that they be nonsmokers for at least 6 months at the time they start treatment with A_1-PI (human).
If a patient has a confirmed genetic test suggesting severe AATD but no lung damage yet, should they be eligible for treatment with Zemaira or should they have to show clinical evidence of emphysema before being eligible?	CPEC agreed with the clinical experts that not all patients develop clinically important emphysema despite having a severe deficiency of alpha-1 antitrypsin. It was also noted that it is important to stipulate that clinically important emphysema should be present before initiating treatment with A_1-PI (human). Clinically important emphysema is not defined by the presence of emphysema on a CT scan but by physiologically important emphysema as determined by routine clinical pulmonary function tests. One benchmark suggested by the Canadian Thoracic Society is obstruction (FEV_1/FVC below 0.70) and FEV_1 below 80% of predicted.

Implementation issues	Response
Should smokers be eligible for A_1-PI?	CPEC agreed with the clinical experts that smoking cessation is an essential part of the treatment. There is no evidence that Zemaira would work in the presence of continued smoking.
If a patient with severe AATD has received a lung transplant, how long does this patient have to wait before being eligible for treatment with A_1-PI? Should these patients be eligible for A_1-PI?	CPEC agreed with the clinical experts that there is no data to inform this question. There have been no studies of augmentation therapy following lung transplant. The clinical experts suggested that current practice is not to perform augmentation therapy after lung transplant, as graft failure or death from other causes would likely occur before mortality from progressive lung disease in the transplanted lung.
About 90% of patients had the PiZZ genotype in the RAPID trial. Should patients with other genotypes be eligible for A_1-PI? Would patients with other genotypes receive similar clinical benefit (if confirmed) as patients with the PiZZ genotype?	CPEC agreed with the clinical experts that there is a lack of data in patients with an SZ or MZ genotype, and that Zemaira should be made available for patients with a null, ZZ, or SZ genotype with evidence of lung disease. Those with equivalent rare variant genotypes with evidence of lung disease should also be offered treatment.
Should reimbursement for Zemaira be limited to certain genotypes or all?	CPEC agreed with the clinical experts that reimbursement for Zemaira be limited to SZ, ZZ, and null genotypes, and also to some of the rare variants that are considered equivalent.
If a patient currently treated with Prolastin-C needed to transition to Zemaira, would they need to meet the eligibility criteria for Zemaira or would they become eligible for Zemaira by default?	CPEC agreed with the clinical experts that reimbursement criteria should be identical for both Zemaira and Prolastin-C. Patients should become eligible for Zemaira by default.
Does evidence confirm that slow decline in lung density translates into better clinical outcomes?	The clinical experts noted to CPEC that there is no direct clinical data; however, there is data based on extrapolation from observational studies of reduced mortality with augmentation therapy. In addition, there was a correlation between preservation of lung density and preservation of lung function tests as measured by spirometry (in the RAPID open-label extension).
How often should patients be followed up before they are approved to continue treatment?	CPEC agreed with the clinical experts that a follow-up should be done every 6 to 12 months; however, once the treatment is started, there is no reason to discontinue, except for issues around infusion problems or allergy, or in the case of a patient receiving a lung transplant.
Do you expect that all patients receiving Prolastin-C will switch to Zemaira once it becomes available?	The clinical experts noted to CPEC that they expect that many patients and physicians will stay with the current augmentation therapy used. CPEC agreed with the clinical experts that there are no head-to-head studies to suggest superiority of any augmentation formulation over another.
Considerations for continuation or renewal of therapy	
The primary end point in RAPID and the RAPID extension study was decline in lung density measured by CT scans. Keeping in mind the slow progression of AATD, the sponsor suggests that CT scan is the only possible end point that can be assessed in a study and acceptable by regulatory authorities. • Is CT scan a meaningful clinical outcome?	The clinical experts noted to CPEC that there is a good biologic plausibility that CT is an appropriate outcome, and that CT scan is meaningful in this setting. While tobacco-related COPD is common, and many respirologists know that the CT scan appearance is not helpful in many patients with COPD who have other pathologic mechanisms that obstruct in the absence of important emphysema. Alpha-1 antitrypsin deficiency is unique in presenting a relatively homogenous emphysema. This makes lung density a useful end

Implementation issues	Response
• What should be the frequency of CT scans? • Would patients in rural areas be able to access CT scans for monitoring of therapeutic response? • Are there any other tests or assessments required to monitor therapeutic effectiveness and safety?	point. The clinical experts indicated that once the treatment is started there is no need for repeat CT scans. CT scans are used to make a diagnosis of emphysema, not to follow clinical progression. CT scanning at baseline should be accessible to all Canadians with clinically important lung disease. The clinical experts noted to CPEC that they do not think there are any necessary follow-up tests because the objective of treatment is to prevent or delay loss of lung tissue.
Should the renewal criteria for Zemaira be similar to that of Prolastin-C?	CPEC agreed with the clinical experts that the renewal criteria for Zemaira should be similar to that of Prolastin-C.
How do you define loss of response or absence of clinical benefit?	The clinical experts noted to CPEC that there is no such thing as loss of response or absence of clinical benefit. Patients will be followed clinically with periodic assessment of symptoms and lung function. A treatment failure would be an accelerated loss of lung function. However, this would not prompt discontinuation of the augmentation therapy. The finding would prompt most clinicians to look for factors that account for the rapid decline.
Considerations for discontinuation of therapy	
Should the discontinuation criteria for Zemaira be similar to that of Prolastin-C?	CPEC agreed with the clinical experts that the discontinuation criteria for Zemaira can be similar to that of Prolastin-C; however, the clinical experts noted that they do not know of any sensible discontinuation criteria except perhaps intolerance of or severe allergy to the therapy or receipt of lung transplant. It was also noted that it may take up to several years to see the effects of the treatment and that once the treatment is started, it should not be discontinued.
Considerations for prescribing of therapy	
Do you expect that clinicians would increase the dose of A_1-PI to 120 mg/kg or increase the frequency with 60 mg/kg dosing? Is there a need to put caps on dosing and frequency?	CPEC agreed with the clinical experts that there might be some rare cases of increased dosage, but only to compensate for missed doses, such as using 120 mg/kg biweekly.
Infusion time for the 60 mg/kg body weight dose is 15 minutes. Are patients able to self-administer at home? Is there any training required?	The clinical experts noted to CPEC that the requirements for home infusion seem to be beyond the scope of most people. It was also noted that while self-administration is possible with training, it is seldom done in Canada.
Are there any concerns related to accessing specialists and lab requirements for therapeutic drug monitoring?	The clinical experts noted to CPEC that there are no concerns related to accessing specialists and lab requirements for therapeutic drug monitoring. Blood sample can be drawn anywhere, and telehealth can also be done from anywhere now. Care should be under the guidance of a respirologist.
Should the prescribing criteria for Zemaira be similar to that of Prolastin-C?	CPEC agreed with the clinical experts that prescribing criteria should be identical for both Zemaira and Prolastin-C.

Implementation issues	Response
Generalizability	
If patients were to switch from Prolastin-C to Zemaira, what should be the time frame for switching?	CPEC agreed with the clinical experts that there is no need for washout. Zemaira would be given at the time of the next scheduled dose of Prolastin.
Care provision issues	
Zemaira can be stored in the refrigerator or at room temperature (at 2°C to 25°C). It should not be frozen. It should be administered within 3 hours after reconstitution. Would ancillary supplies related to infusion be provided by a patient support program or is this expected to come from hospital transfusion services?	The clinical experts noted to CPEC that ancillary supplies related to infusion should be provided by the patient support program. The sponsor confirmed that ancillaries will be provided through the patient support program. The sponsor and clinical experts indicated that it is unlikely that Zemaira will be administered in an inpatient hospital setting. Support programs would not have a role in these settings. Because this is a long-term treatment without clear acute care indications, even missing doses in the hospital would be acceptable.
Are there any concerns with the development and management of A_1-PI antibodies?	The clinical experts noted to CPEC that there are no concerns related to the development and management of A_1-PI antibodies.
Would Zemaira reduce the use of other concomitant treatment required for the management of COPD or emphysema?	The clinical experts noted to CPEC that they do not expect any change in the use of other concomitant treatments required for the management of lung disease. However, it should delay the introduction of expensive interventions, such as long-term home oxygen and transplant, though there is no clinical evidence to support this statement.

A_1-PI = alpha$_1$-proteinase inhibitor; AATD = alpha$_1$-antitrypsin deficiency; COPD = chronic obstructive pulmonary disease; CPEC = Canadian Plasma Protein Product Expert Committee; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of Studies

One published, manufacturer-sponsored, double-blind randomized controlled trial was included in the systematic review: RAPID (n = 180) evaluated the superiority of Zemaira compared with placebo on the progression of emphysema in individuals who were A_1-PI deficient and had emphysema and reduced lung function. Disease progression was assessed by the decline of lung density, measured by CT. Zemaira was administered at a dosage of 60 mg/kg through IV infusion once weekly for 24 months.

Patients in the trial had a mean age of 53 years. All patients were white. The mean FEV_1 was 47% predicted. Mean duration of disease was between 5 and 6 years. The majority of patients had a medical history before baseline, as well as concurrent illness and concomitant medication.

Efficacy Results

Zemaira was associated with a reduced rate of decline in lung density after 24 months compared with placebo in individuals who were A_1-PI deficient and had emphysema and

reduced lung function when CT scans were taken at full inspiration state (0.74 g/L; 95% CI, 0.06 to 1.42; 1-sided P = 0.017). CT lung densitometry measurements have been validated as a primary clinical end point for clinical study designs in monitoring emphysema progression in AATD. According to patient input, stabilizing lung function is perceived as the most important outcome in effective treatment because it is associated with the ability to perform activities of daily living. However, lung density is not used in clinical practice to assess disease progression; therefore, it is unknown how the slower decrease observed in the RAPID trials in terms of lung density translates into better quality of life. In addition, interpretation of the findings is affected by the fact that it was not clear which specific inspiration state the measure was to be taken at for the primary analysis. Results using other inspiration states measures also showed a slower decline in lung density with active treatment compared with placebo over a 24-month period, but the differences between groups were of smaller magnitude and did not reach statistical significance. From a statistical perspective, this is a major limitation, especially given that the analysis was not controlled for multiplicity. However, according to the clinical experts consulted by CADTH, the most reliable way to measure lung density is at full inspiration state, which is referred to as total lung capacity. When full of air, there are more lungs to see on the CT scan image; therefore, the measurement obtained is considered more reliable.

Other important clinical outcomes such as exacerbations, symptoms, and function were reported as secondary outcomes; however, the differences between groups did not reach statistical significance for any of these outcomes other than FEV_1 and forced vital capacity (FVC), where the treatment difference for the percentage change from baseline (day 1) to month 24 in the FEV_1 divided by FVC ratio for observed values revealed a change of 4.24% (95% CI, −8.04 to −0.45; P = 0.029) in favour of placebo when compared with Zemaira; however, results from FEV_1 divided by FVC should be interpreted with caution due to the risk of inflated type I error.

Harms Results

Virtually all patients in both treatment groups experienced at least 1 AE; however, discontinuation due to AEs was low, suggesting the harm profile might be considered acceptable. Respiratory-related AEs were commonly reported and, in some cases, were numerically higher with Zemaira than with placebo; however, this might be a random fluctuation due to the small sample size. Serious AEs were frequently reported, and the incidence was similar between treatment groups. No cases of severe hypersensitivity were reported in the trial. One patient in the Zemaira treatment group died over the study period due to respiratory failure. In the placebo group, 3 patients died over the study period from sepsis, pneumonia, and metastatic breast cancer.

Critical Appraisal

Though the RAPID trial may be considered methodologically rigorous, interpretation of the findings is affected by the small sample size and by the fact that it was not clear which specific inspiration state the measure was to be taken at for the primary analysis. From a statistical perspective, this is a major limitation, especially since the analysis was not controlled for multiplicity. However, according to the clinical experts consulted by CADTH, the most reliable way to measure lung density is at full inspiration state, which is referred to as total lung capacity, where statistical significance is reached. The trial population appeared similar to patients seen in clinical practice by the clinical experts consulted by CADTH; however, due to the limitations such as small sample sizes, the real-world effectiveness of Zemaira in patients in Canada may vary from what was observed in the trial. The strength

of evidence was reduced by the lack of controlled long-term data on efficacy and safety, and the lack of trials comparing the clinical outcomes of Zemaira with the other active treatment available.

Other Relevant Evidence

Additional relevant evidence addressing important gaps in the evidence were considered. One open-label long-term extension study from the RAPID trial, RAPID-OLE (n = 140), collected long-term data on the safety and efficacy of Zemaira on the progression of emphysema in individuals who were A_1-PI deficient, had emphysema, and had completed the 2-year treatment and observation periods in the RAPID study. Despite the limitations associated with the open-label, uncontrolled trial design, the findings suggested that the efficacy of Zemaira was sustained in the long term.

A noninferiority biochemical efficacy trial, Study 2002 (n = 44), suggested that Zemaira was considered to be noninferior to Prolastin throughout a 10-week blinded phase based on the mean steady-state trough serum antigenic A_1-PI levels in adult patients with a diagnosis of A_1-PI deficiency and clinical evidence of emphysema.

One survival analysis evaluated the efficacy of A_1-PI plus standard therapy in the US compared to standard therapy alone in the UK on the outcomes of survival and lung transplant in adult patients with A_1-PI deficiency and evidence of lung disease. Findings suggested that A_1-PI treatment was associated with benefits in terms of survival and time to lung transplant; however, the several limitations inherent with the database study design and the differences between groups, especially in terms of the patient population included in the 2 treatment groups, highly affect the level of confidence in the evidence.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults with severe alpha$_1$-proteinase inhibitor deficiency and clinical evidence of emphysema
Treatment	Alpha$_1$-proteinase inhibitor (Zemaira) plus SoC
Submitted price	Zemaira, 1,000 mg vial: $390.00 Zemaira, 4,000 mg vial: $1,560.00 Zemaira, 5,000 mg vial: $1,950.00
Treatment cost	The annual cost of Zemaira is $101,748, based on a mean patient body weight of 76 kg (per the RAPID trial)
Comparators	• SoC: comprising treatments typically prescribed to emphysema and patients with COPD: long-acting and short-acting beta2-agonists, long-acting muscarinic antagonists, inhaled corticosteroids, short-acting anticholinergics, xanthine bronchodilators, phosphodiesterase

Component	Description
	type 4 inhibitors • Prolastin-C plus SoC
Perspectives	• Canadian Blood Services • Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (50 years)
Key data sources	• Various published sources were used to define baseline and rates of emphysema progression, as measured by FEV_1. • The efficacy of augmentation therapy on emphysema progression was based on a meta-analysis of trials by Chapman et al. (2009). • Mortality benefits of augmentation therapy were calculated using parametric models of digitized Kaplan–Meier (KM) data from a retrospective study by Ellis et al. (2019).
Key limitations	• While the RAPID trial and its extension were the only clinical studies provided as part of the sponsor's submission, most model parameters, including survival, disease progression, transition probabilities, number of exacerbations, and health state utilities, were derived from alternate published sources. • The need for these additional information sources arose because the clinical studies did not consider meaningful patient outcomes and, as such, deriving relationships between FEV_1 and these outcomes was required. There is a large amount of uncertainty associated with, and heterogeneity among, these additional publications. ◦ The survival data are biased in favour of augmentation therapy and the populations included in the studies used to define disease progression are not representative of the RAPID trial. ◦ The survival extrapolation for patients receiving Zemaira is overestimated and does not meet face validity or match clinical expert opinion. • The health state utility values for moderate to very severe emphysema were overestimated and did not align with clinical expert opinion. • There is uncertainty surrounding the availability of lung transplants, which was not addressed in the sponsor's analysis. • The inclusion of costs and disutilities associated with exacerbations is associated with uncertainty.
CADTH reanalysis results	• Due to the high degree of uncertainty and heterogeneity in the included clinical inputs, CADTH was unable to derive a base case. • An exploratory analysis was conducted to explore areas of uncertainty. The changes included alternate parametric survival extrapolations, increased mortality beyond the study period, decreased health state utility values, decreased probability of lung transplant, and exclusion of costs and utilities associated with exacerbations. Taken together, these changes resulted in an ICER of $664,549 per QALY, with a 0% probability of being cost-effective at a $50,000 per QALY willingness-to-pay threshold. To account for the clinical uncertainty in the sponsor's input parameters, a price reduction of at least 93% would be required to achieve cost-effectiveness at this threshold.

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume per second; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY = quality-adjusted life-year; SoC = standard of care.

Budget Impact

CADTH identified several limitations with the sponsor's analysis, including uncertainty regarding the derivation of the population size and underestimate of market uptake of Zemaira in British Columbia. CADTH reanalysis corrected a transcription error and also assumed 100% market uptake for Zemaira in British Columbia in each year. In the CADTH base case from a drug plan perspective, the budget impact is expected to be $23,729,027 in year 1; $33,924,828 in year 2; and $44,046,744 in year 3; with a 3-year total of $101,700,599, similar to what was reported by the sponsor. The 3-year budget impact from the Canadian Blood Services perspective was $165,249,851.

CPEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Irene Sadek, Dr. Andrew Shih, and Dr. Peter Zed.

Meeting date: February 24, 2022

Regrets: None

Conflicts of interest: None

CADTH

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