INESSS
LE SAVOIR PREND FORME

JULY 2023

Zemaira™ – Congenital alpha$_1$-antitrypsin deficiency

English summary

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

Québec

SUMMARY

Zemaira™ – Congenital alpha$_1$-antitrypsin deficiency

Mandate

At the request of the manufacturer, CSL Behring Canada Inc., the Institut national d'excellence en santé et en services sociaux (INESSS) conducted an evaluation of the blood system product Zemaira™, a highly purified human alpha$_1$-proteinase inhibitor administered intravenously. In Canada, Zemaira™ is indicated for the maintenance treatment in adults with severe alpha$_1$-proteinase inhibitor deficiency (e.g. genotypes PiZZ, PiZ(null), Pi(null, null), PiS Z) and clinical evidence of emphysema. The indication requested for this evaluation is as follows: for the maintenance treatment of adults with severe alpha$_1$-proteinase inhibitor deficiency (e.g., PiZZ, PiZ[null], Pi[null, null], PiSZ or other deficiency-causing alleles) and presenting clinical signs of emphysema.

INESSS conducted simultaneous assessments of Prolastin™-C Liquid, Zemaira™ and Glassia™, all human plasma alpha$_1$-antitrypsin products. Recommendations for these 3 products were published at the same time.

Assessment Approach

A data review of the literature and those provided by the manufacturer was carried out to document the efficacy, safety, and cost-effectiveness of Zemaira™. Contextual and experiential data from expert consultation are also presented. Efficiency and budget impact analyses were developed by the INESSS.

Population Dimension

Alpha$_1$-proteinase inhibitor deficiency, or alpha$_1$-antitrypsin deficiency (DAAT), is a rare genetic condition with a variable presentation that can lead to severe pulmonary (emphysema, chronic bronchitis, and bronchiectasis) and hepatic symptoms, often with a slow progression. Due to the heterogeneous and often delayed clinical manifestations, and the discovery of new pathogenic variants associated with the disease, DAAT is an under-diagnosed condition. Usual treatments are aimed at alleviating respiratory symptoms and include inhaled medications, pulmonary rehabilitation and, for some patients, augmentation therapy consisting of weekly intravenous administration of plasma-derived alpha$_1$-antitrypsin (AAT). Augmentation therapy aims to slow the progression of emphysema in individuals with DAAT. Currently, only Prolastin™-C is available in Quebec, and public reimbursement is possible only through the “mesure du patient d’exception.”

Treatments that halt or slow the progression of emphysema and the deterioration of lung and liver function would meet current healthcare needs, especially if they were to improve the quality of life of sufferers and their families. Facilitating access to augmentation therapy is also desirable.

Clinical Dimension

Assessment of the therapeutic value of Zemaira™ is based on 1 randomized controlled trial (RAPID-RCT) and its extension (RAPID-OLE), as well as 1 bioequivalence trial with Prolastin™.

Efficacy

CT lung density quantification is a surrogate parameter deemed adequate by the experts consulted for evaluating emphysema progression, even if correlations with clinical manifestations of emphysema are weak.

In the RAPID-RCT study, treatment with Zemaira™ significantly slowed the loss of lung density at total lung capacity compared with the placebo group in individuals with alpha$_1$-proteinase inhibitor deficiency. Slower deterioration was also observed in the "delayed start" group of the RAPID-OLE extension. The results of the extension also suggest that the treatment effect can be maintained over a period of 4 years. Regarding effects on health-related quality of life, frequency of exacerbations and on respiratory function, Zemaira™ has not demonstrated any clinical benefit compared with a placebo.

Zemaira™ is considered bioequivalent to Prolastin™ in individuals with alpha$_1$-proteinase inhibitor deficiency.

Safety

The safety profile of Zemaira™ observed in the RAPID-RCT study is comparable to that of placebo. Moreover, no significant new safety findings were observed in the RAPID-OLE extension.

Organizational Dimension

Prolastin™-C is currently reimbursed by the RAMQ through the “mesure du patient d’exception” and private insurance plans. From now on, plasma AATs will have to be registered on the *Liste des produits du système du sang du Québec* and obtain a call for tenders from Héma-Québec before they can be distributed. With this change in management, it would be prudent to avoid treatment interruptions and minimize the consequences that could arise. At the moment, home administration of Prolastin™-C is not common practice in Quebec. It is generally administered in CLSCs or specialized clinics.

Economic Dimension

Efficiency Analysis

At the submitted price, Zemaira™ would provide savings of $[redacted] per week compared with Prolastin™-C, whose efficiency has not been evaluated prior to this assessment.

When compared to the use of best supportive care alone, Zemaira™, in addition to best supportive care, is not cost-effective. The incremental cost-utility ratio has been estimated at between $335,000 and $345,000 per QALY. A price reduction of 90% or 75% must be adopted to reach efficiency thresholds of $50,000 and $100,000 per QALY, respectively.

Budget Impact Analysis

Should Zemaira™ be added to the *Liste des produits du système du sang du Québec,* an increase in the number of patients can be expected due to patients currently using Prolastin™-C through private drug insurance plans to continue their AAT inhibitor treatment through the public plan. This increase in the number of people covered by the public system ([redacted] %) would translate into additional costs estimated at over $8 million over 3 years.

Socio-Cultural Dimension

In 2022, Quebec adopted a policy aimed at optimizing access to quality healthcare and services that are adapted to the specific needs of culturally sensitive patients and those with rare diseases. Some experts note that Quebec is at the forefront in the management of several rare diseases, including DAAT, compared to other Canadian provinces.

Therapeutic Value Decision
The members of the “Comité délibératif permanent – Remboursement et accès” unanimously recognize the therapeutic value of Zemaira™ for the maintenance treatment of adults with severe alpha$_1$-antitrypsin deficiency (e.g.,genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ or other deficiency-causing alleles) and presenting clinical signs of emphysema. **Reasons for the unanimous position** ▪ Members recognize the important health needs of this rare condition for the treatment of emphysema secondary to DAAT. ▪ Members recognize the slow progression of the condition and agree on the difficulty of testing DAAT therapy using clinical parameters considered beneficial to patients, such as lung function, quality of life or survival, within a randomized controlled study design. Thus:

- the lung density deterioration rate endpoint from the RAPID studies seems justified, and the results, although of low evidence level, allow a clinical benefit to be attributed to Zemaira™;
- some members appreciate the complementary real-life survival data from the *National Heart Lung and Blood Institute registry*, which suggest prolonged survival in patients on augmentation therapy.

- Zemaira™ is considered bioequivalent to the comparator Prolastin™. The magnitude and confidence intervals of the decreases in lung density loss observed in the respective pivotal studies (RAPID and EXACTLE), albeit in a naïve comparison, reassure some members about the conclusion of bioequivalence.
- In the opinion of the members, the safety profile of Zemaira™ is acceptable, given the comparable frequencies of adverse events between the groups in the RAPID studies.
- Some members expressed concern about the under-diagnosis of the condition and the potentially suboptimal management of a less severely affected population that could also benefit from treatment.

Overall Assessment

The members of the "Comité délibératif permanent – Remboursement et accès" unanimously recommend that Zemaira™ be added to the *Liste des produits du système du sang du Québec* for the maintenance treatment of adults with severe alpha$_1$-antitrypsin deficiency (e.g., genotypes PiZZ, PiZ(null), Pi(null,null), PiSZ or other deficiency-causing alleles) and presenting clinical signs of emphysema.

Reasons for the unanimous position

- The members recognize the therapeutic value of Zemaira™ since it provides clinical benefits, has an acceptable safety profile, and meets a health need deemed important in individuals with DAAT.
- Members reiterated that, although Zemaira™ is [redacted] than Prolastin™-C at the price submitted by the manufacturer, neither of these AATs is efficient compared to best supportive care, and that a significant reduction in economic burden, in the order of 90% or 75% of the asking price, is required to make it an efficient option by achieving ICERs of $50,000 and $100,000 per QALY, respectively.
- Members are sensitive to the significant increase in budgetary impact caused by individuals with DAAT moving from private insurance coverage to public management by Héma-Québec.
- The burden of administering a weekly intravenous product in specialized clinics is recognized by all members. The introduction of a home administration program for patients who so desire would be desirable and would improve their quality of life and reduce the use of dedicated resources.

- In a context of competitive tendering, the addition of Zemaira™ to the *Liste des produits du système du sang du Québec* represents a therapeutic alternative to other AAT products on the *Liste des produits du système du sang* for the population targeted by the indication.
- Members support the need to ensure overlap between the current administrative management by the RAMQ and the future administrative management by Héma-Québec, in order to avoid any interruption of treatment for these patients.
- Some members welcome Quebec's commitment to caring for patients with rare diseases. Others support *the listing of blood system products* to ensure greater equity of access within this patient population.
- Members stressed the importance of proper management and optimal use of human blood derivatives.

INESSS recommendation for Zemaira™

In light of the information available, INESSS recommends that Zemaira™ be added to the *Liste des produits du système du sang du Québec* for the maintenance treatment of adults with severe alpha$_1$-antitrypsin deficiency (e.g., PiZZ, PiZ(null), Pi(null,null), PiSZ or other deficiency-causing alleles) and presenting clinical signs of emphysema.

Recommendation Clarification

Considering the claims of bioequivalence between Prolastin™-C Liquid, Zemaira™ and Glassia™, reimbursement of Zemaira™ for the requested indication would be a responsible, fair, and equitable decision, if its cost were the lowest during the next call for tenders by Héma-Québec.

Clarification for Decision-Makers

In Héma-Québec's next call for tenders for AATs, the indications for the 3 products Prolastin™-C Liquid, Zemaira™ and Glassia™ could be grouped under the common indication “for the treatment of emphysema in adults with DAAT.”

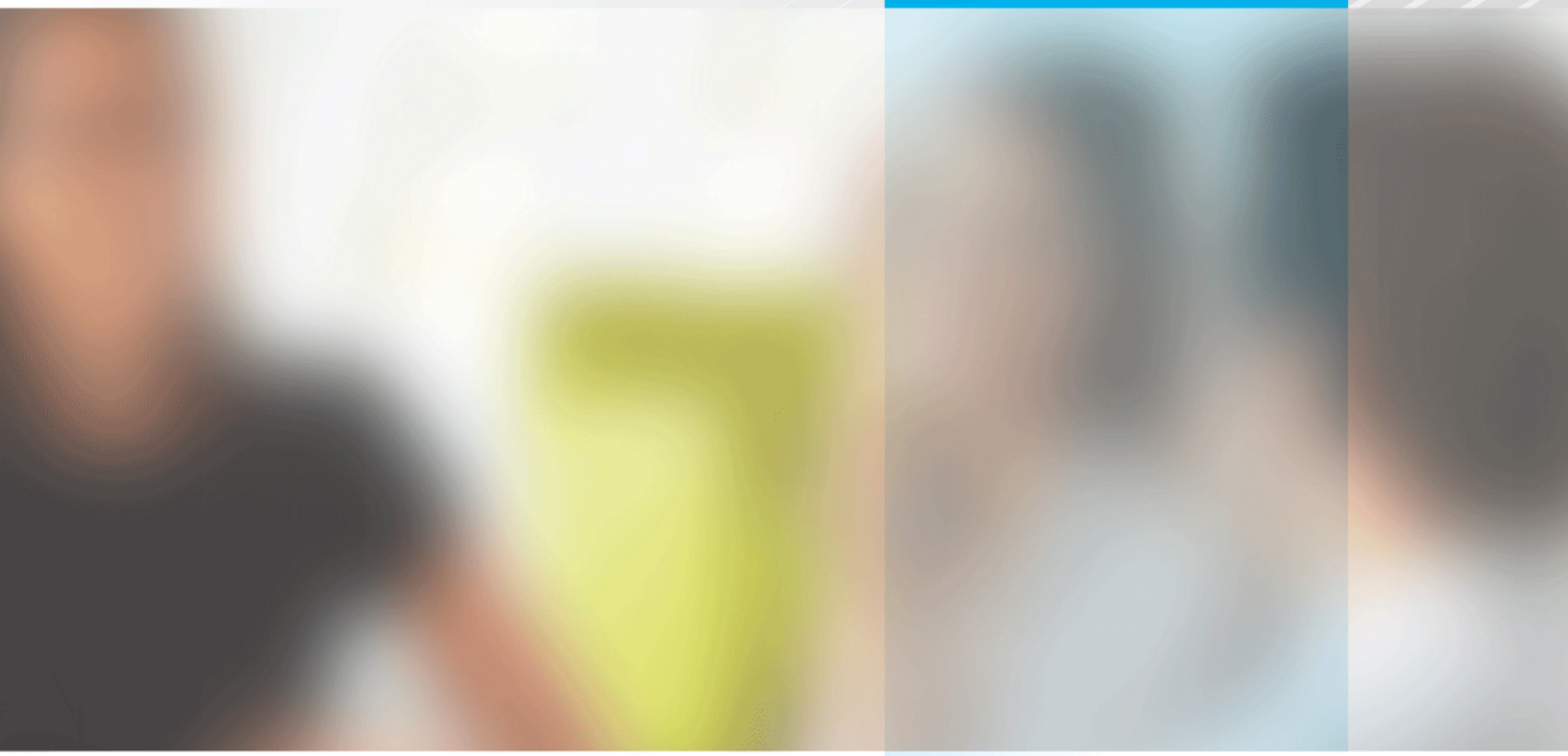
Consistent with the recommendations of the Canadian Thoracic Society, the historical access criteria of the “mesure du patient d’exception” for Prolastin™-C and the perspectives of the experts consulted, as well as in the interest of optimal use of human blood-derived products, the INESSS considers that plasma-derived alpha$_1$-antitrypsin on the *Liste des produits du système du sang* should be reserved for the following population:

- for the treatment of emphysema in adults:
  - with a clinical presentation of progressive lung disease;

    and,
  - with FEV$_1$ between 25% and 80% of predicted value;

    and,

- with demonstrated alpha$_1$-antitrypsin deficiency (plasma concentration ≤ 11 µmol/L or clinically relevant genotype);
  and,
- under optimal pharmacological and non-pharmacological treatment.



Siège social

2535, boulevard Laurier, 5e étage
Québec (Québec) G1V 4M3
418 643-1339

Bureau de Montréal

2021, avenue Union, 12e étage, bureau 1200
Montréal (Québec) H3A 2S9
514 873-2563
inesss.qc.ca

Institut national d'excellence en santé et en services sociaux
Québec