INESSS
LE SAVOIR PREND FORME

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Prolastin™-C Liquid – Congenital alpha$_1$-antitrypsin deficiency

English summary

Une production de l'Institut national
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Québec

SUMMARY

Prolastin™-C Liquid – Congenital alpha$_1$-antitrypsin deficiency

Mandate

At the request of the manufacturer, Grifols Therapeutics Inc., the Institut national d'excellence en santé et en services sociaux (INESSS) conducted an evaluation of the Prolastin™-C, a highly purified human alpha$_1$-proteinase inhibitor administered intravenously. In Canada, Prolastin™-C Liquid is indicated for chronic replacement therapy in people with congenital alpha$_1$-proteinase (alpha$_1$-antitrypsin deficiency) related to the PiZZ, PiZ (null), Pi (null)(null), PiSZ genotypes, or any other deficiency allele, and clinically diagnosed emphysema. The intended indication for this evaluation is as follows: for the treatment of alpha$_1$-antitrypsin deficiency related to the PiZZ, PiZ (null), Pi (null)(null), PiSZ genotypes, or any other deficiency allele, in adult patients with clinical emphysema AND an alpha$_1$-antitrypsin level ≤ 11 μmol/L AND FEV_1 of 25-80 %.

INESSS conducted simultaneous evaluations of Prolastin™-C Liquid, Zemaira™ and Glassia™, all human plasma alpha$_1$-antitrypsin products. Recommandations 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 Prolastin™-C Liquid as well as previous Prolastin™ and Prolastin™-C formulations. 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 variable presentation that can lead to severe pulmonary (emphysema, chronic bronchitis, and bronchiectasis) and hepatic symptoms, often with 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 Prolastin™-C Liquid was based on 1 randomized controlled trial (EXACTLE study) and 2 bioequivalence studies between Prolastin™, Prolastin™-C and Prolastin™-C Liquid.

Efficacy

- In the EXACTLE exploratory study, Prolastin™ appeared to reduce emphysema progression compared with placebo in individuals with DAAT.
  - Whole-lung lung density, assessed by CT scan, was used as a surrogate endpoint for the evaluation of emphysema progression. Although this parameter is considered adequate, it only partially correlates with observable manifestations of emphysema.
  - Regarding effects on health-related quality of life, frequency of exacerbations and respiratory function, the use of Prolastin™ did not demonstrate any clinical benefit compared with placebo.
- Human plasma AAT products Prolastin™, Prolastin™-C and Prolastin™-C Liquid are considered bioequivalent in individuals with DAAT.

Safety

- The safety profile of Prolastin™ observed in the EXACTLE study is considered acceptable.
- Although evaluated over shorter periods, the safety profiles of Prolastin™-C and Prolastin™-C Liquid appear comparable to that of Prolastin™.

Organizational Dimension

Coverage for human plasma AATs is currently provided 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. During this change of management, it would be prudent to avoid treatment interruptions and minimize the consequences that could be associated with them.

Economic Dimension

Efficiency Analysis

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

When compared to the use of best supportive care alone, Prolastin™-C Liquid, in addition to best supportive care, is not cost-effective. The incremental cost-utility ratio was estimated at $327,000 to $337,000 per QALY. A price reduction of 86% or 70% must be adopted to reach efficiency thresholds of $50,000 and $100,000 per QALY, respectively.

Budget Impact Analysis

Should Prolastin™-C Liquid 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 the private drug insurance plan continuing 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" are unanimously of the opinion that the therapeutic value of Prolastin™-C Liquid is recognized for the treatment of alpha$_1$-antitrypsin related to the PiZZ, PiZ (null), Pi (null)(null), PiSZ genotypes, or any other deficiency allele, in adult patients with clinical emphysema AND an alpha$_1$-antitrypsin level ≤ 11 μmol/L AND FEV$_1$ of 25-80 %.

Reasons for the unanimous position

- Members recognize the importance 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 on clinical parameters considered beneficial to patients, such as lung function, quality of life or survival, by a randomized controlled study design. Thus:
  - the use of the slowing of lung density loss endpoint in the EXACTLE study seems justified, and the results, although of low evidence level, allow a clinical benefit to be attributed to Prolastin™;
  - 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.
- Prolastin™-C Liquid is considered bioequivalent to Prolastin™ and Prolastin™-C.
- In the opinion of the members, the safety profile of Prolastin™, Prolastin™-C and Prolastin™-C Liquid are acceptable given the comparable frequencies of adverse events between the groups in the EXACTLE study and the bioequivalence 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 Prolastin™ -C Liquid be added to the *Liste des produits du système du sang du Québec* for the treatment of alpha$_1$-antitrypsin deficiency related to the PiZZ, PiZ (null), Pi (null)(null), PiSZ, or any other deficit allele, in adult patients with clinical emphysema AND an alpha$_1$-antitrypsin level ≤ 11 μmol/L AND FEV$_1$ of 25-80 %.

Reasons for the unanimous position

- The members recognize the therapeutic value of Prolastin™ 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 Prolastin™-C Liquid 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, of the order of 86 or 70% of the asking price, is required to make it an efficient option in 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 Prolastin™-C Liquid 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 Prolastin™-C Liquid

In light of the information available, INESSS recommends that Prolastin™-C Liquid be added to the *Liste des produits du système du sang du Québec* for the treatment of alpha$_1$-antitrypsin related to the PiZZ, PiZ (null), Pi (null)(null), PiSZ genotypes, or any other deficiency allele, in adult patients with clinical emphysema AND an alpha$_1$-antitrypsin level ≤ 11 μmol/L AND FEV$_1$ of 25-80 %.

Recommendation Clarification

Considering the claims of bioequivalence between Prolastin™-C Liquid, Zemaira™ and Glassia™, reimbursement Prolastin™-C Liquid 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$_1$-antitrypsine 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;

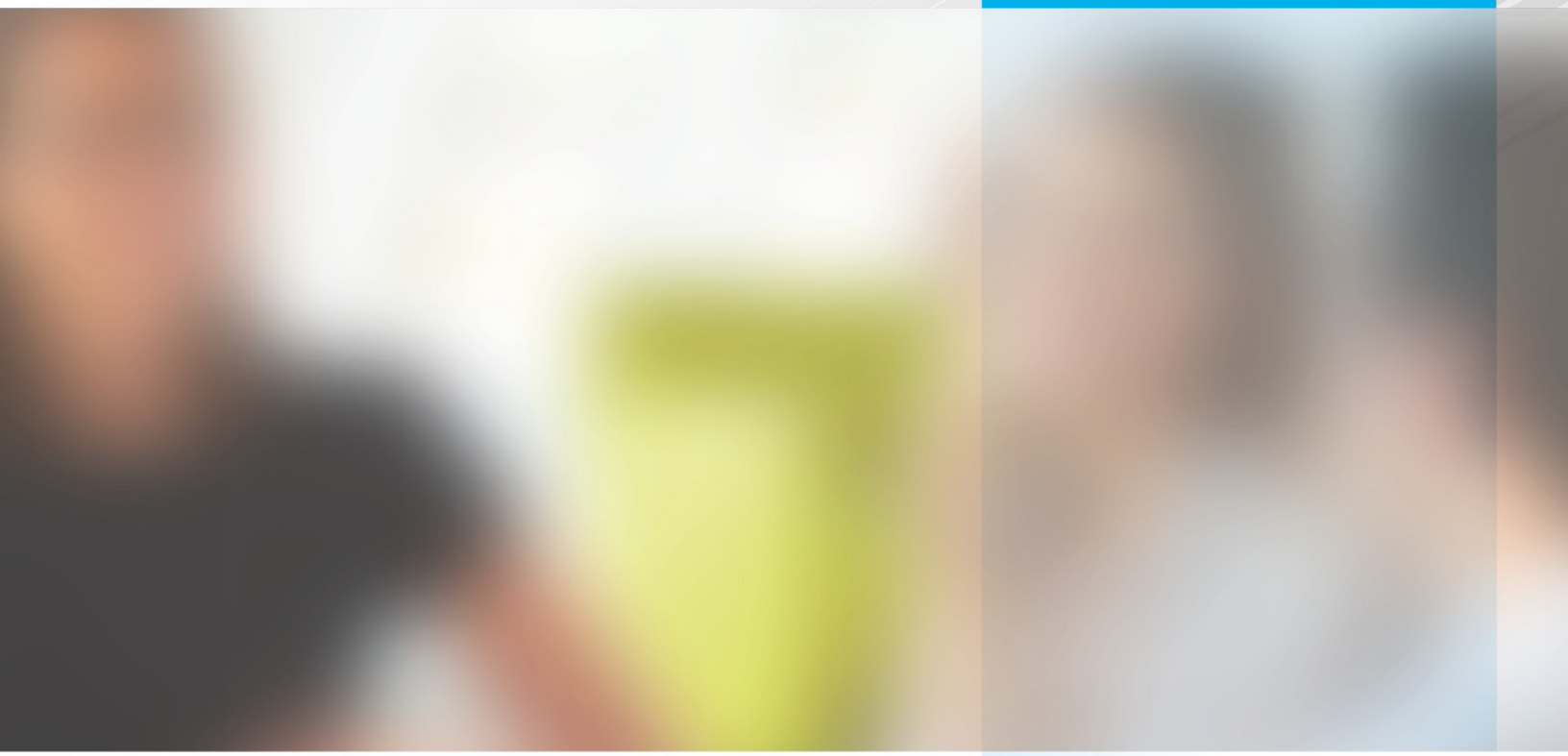
    and,
  - with FEV$_1$ between 25 % and 80 % of predicted value;

    and,

- with demonstrated alpha$_1$-antitrypsin deficiency (plasma concentration ≤ 11 µmol/L or clinically relevant genotype);

  and;

- under optimal pharmacological and non-pharmacological treatment.



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