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Reevaluation of Takhzyro™ (lanadelumab injection) Hereditary angioedema

English summary

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

Direction de l'évaluation des médicaments et des technologies à des fins de remboursement

Québec

SUMMARY

Reevaluation of Takhzyro™ (lanadelumab injection)
Hereditary angioedema

Mandate

The Institut national d'excellence en santé et en services sociaux (INESSS) reassessed Takhzyro® (lanadelumab), a monoclonal antibody for subcutaneous injection every 2 weeks (with the option of reducing the frequency to every 4 weeks) indicated for the routine prevention of attacks of hereditary angioedema (HAE) in adults and adolescents 12 years of age and older. Takhzyro™ is not intended for the treatment of acute HAE attacks. In the initial evaluation, published in August 2019, INESSS recommended that Takhzyro™ not be added to the *Liste des produits du système du sang du Québec* (blood products list) since its therapeutic value had not been recognized, primarily for the following reasons:

- The evidence was still too immature to guarantee the longer-term safety of a product that is in a new class of therapeutic agents for the treatment of HAE;
- The extent of the clinical gain (efficacy) is difficult to determine in the absence of studies involving a direct comparison with products actively used in clinical practice.

The standard treatment available at the time was considered efficacious for the vast majority of patients with type 1 or 2 HAE, and its past use in the management of HAE pointed to a favourable safety profile.

Evaluation process

Literature data and data provided by the manufacturer were reviewed to document the efficacy, safety and economic aspects (cost effectiveness and budget impact) of lanadelumab. Experiential and contextual data from consultations with experts are presented. The data-gathering for capturing the patient perspective during the initial evaluation was supplemented with questionnaires.

Health need

Hereditary angioedema is a rare autosomal dominant genetic disease typically caused by a quantitative (type 1) or functional (type 2) C1-esterase inhibitor (C1-INH) deficiency. It is characterized by recurrent, transient, noninflammatory edema of the tissues of the face, limbs, upper respiratory tract, digestive system or urogenital system. HAE follows a painful, unpredictable and potentially fatal course and is associated with a decrease in quality of life due to the unpredictability and frequency of the attacks and the accompanying emotional and physical distress. The goal of management is to prevent attacks or reduce their frequency and severity and thus improve the patient's quality of life. Long-term prophylaxis is generally proposed to patients when on-demand therapies

are insufficient for achieving an acceptable quality of life. The therapies available in Québec include a plasma-derived C1-INH concentrate (Berinert™) on the *Liste des produits du système du sang du Québec* as a replacement therapy and a kinin-kallikrein pathway antagonist (Firazyr™) on the *Listes de médicaments - médicament d'exception* for the treatment of acute attacks. Since February 2020, Haegarda™ a plasma-derived C1-INH concentrate for subcutaneous administration is available and distributed in Québec.

In Québec, it is estimated that between 120 and 150 people have HAE and that about a hundred of them are diagnosed. Although the disease is generally well controlled, its therapeutic management is quite burdensome because of the administration of the treatment (e.g. venous access problems), the frequency and duration of the injections, or even the equipment that patients must carry with them when travelling.

Results

Efficacy

- The available data show that prophylaxis with lanadelumab at a dose of 300 mg every 2 weeks reduced the monthly angioedema attack rate in three clinical studies: by 73% to 87% compared to placebo in a 26-week pivotal randomized clinical trial; by 82% to 92% relative to baseline in the uncontrolled extension of the Phase 3 study; and [redacted]% relative to baseline in a French cohort study.
- Exposure to lanadelumab for approximately 18 months during the extension study, in addition to the 26 weeks of treatment in the pivotal study for certain patients, suggests that lanadelumab's efficacy in preventing hereditary angioedema attacks can be maintained over time. However, the risk of bias is high, and the extension study is still ongoing.
- This efficacy was similarly observed in the analysis of other endpoints, such as the use of on-demand therapy, the rate of moderate to severe attacks, and the rate of high-morbidity attacks (a decrease of 73% to 87% compared to placebo and of 91% to 96% relative to baseline). Lastly, a significant proportion of the patients in the different studies did not report any attacks (31% to 44%, excluding the French cohort study).
- An indirect comparative analysis submitted by the manufacturer and evaluating the efficacy of lanadelumab in parallel with that of the comparators [redacted] This analysis was not included because the choice of fixed-effects models reduces the plausibility of the indirect comparison results in that these models ignore the significant heterogeneity observed between studies.

Quality of evidence: low

Safety

- Most of the patients in the pivotal (91%) and extension (95%) studies have reported adverse events. Most of these adverse events were mild to moderate in severity and often injection site reactions.
- Hypersensitivity reactions, often mild and transient, have occurred in 3% to 5% of the patients in the pivotal and extension studies and have led to a total of 3 withdrawals. No anaphylactic reactions have been reported.
- Abnormal peak liver enzyme levels, [redacted] have been observed in clinical studies ([redacted]). The frequency of these abnormalities was comparable toplacebo in the pivotal study. [redacted], several were associated with comorbidities, and there were [redacted] study withdrawals.
- [redacted]. The impact of plasma kallikrein inhibition on aPTT testing was expected. [redacted]
- Anti-drug antibodies were detected in 10% to 12% of patients. These antibodies were considered neutralizing in 2.4% to 2.8% of the cases. The titers were mostly low, and, according to the manufacturer, these antibodies had no impact on the efficacy or safety of lanadelumab.
- A first pharmacovigilance report submitted to the EMA did not lead to any changes in the conditions for marketing.

Quality of evidence: low

Quality of life

- In the pivotal study, a clinically and statistically significant improvement in quality of life was reported for all the domains on the AE-QoL, a specialized instrument, [redacted] Statistical analyses are forthcoming for the extension study.
- The few patients interviewed who had tried lanadelumab in a clinical study reported that the treatment had a positive impact on their quality of life. They felt that subcutaneous administration and an injection frequency of every 2 weeks were major advantages.

Quality of evidence: very low

Experts' perspectives

- The experts consulted recognize the efficacy of lanadelumab in preventing attacks in patients with type 1 or 2 hereditary angioedema.
- All the experts deplored the weakness of the available data and agreed that, in the absence of comparative studies, it is difficult to compare the extent of lanadelumab's efficacy with that of other treatments used prophylactically.
- Given that all the products have all demonstrated superior efficacy to placebo, the experts agreed to recognize lanadelumab as having non-inferior efficacy to plasma-derived C1-INH concentrates.
- As for safety, some experts considered that lanadelumab's profile is reassuring and satisfactory, that it is characterized by a reasonable level of risk and that it does not raise any major concerns. Others mentioned that the product is non-physiological and that a longer history of use would help increase confidence. In comparison, there is longer experience with plasma-derived C1-INH, and it is physiological in nature. However, it is derived from blood donors.
- As regards the impact on health-related quality of life, some experts deplored the choice for comparison (placebo), which does not reflect clinical reality. Other experts ascribed an advantage to lanadelumab over its comparators because of the frequency of injection (2 weeks vs. 3-4 days), the route of administration (subcutaneous vs. intravenous) and the volume of product (2 ml vs. 9-15 ml). With similar efficacy and safety, these characteristics are likely to have a significant impact on the patients' quality of life, especially young ones.

Economic analyses

Cost effectiveness analysis

At the price submitted by the manufacturer, and given the average weight of the Québec population, long-term prophylaxis of HAE attacks with lanadelumab is not a cost-effective treatment option compared to the C1-INHs listed and distributed in Québec, namely, Berinert™ (intravenous administration) and Haegarda™ (subcutaneous administration).

Budget impact analysis

At the price submitted by the manufacturer, and given the average weight of the Québec population, adding lanadelumab to the *Liste des produits du système du sang du Québec* as a long-term option for HAE attack prophylaxis could result in an increase in costs in the range of $264,000 to $659,000 per year, for a total of $1.4 million over a 3-year period.

Deliberation on all the criteria

The majority of members of the Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription are of the opinion that the therapeutic value of lanadelumab (Takhzyro™) has been demonstrated for the routine prevention of hereditary angioedema attacks in adults and adolescents. Consequently, the majority of the members are of the opinion that it is responsible, fair and equitable to enter lanadelumab (Takhzyro™) on the *Liste des produits du système du sang du Québec*, provided that a measure to mitigate the economic burden is put in place.

Reasons for the majority position

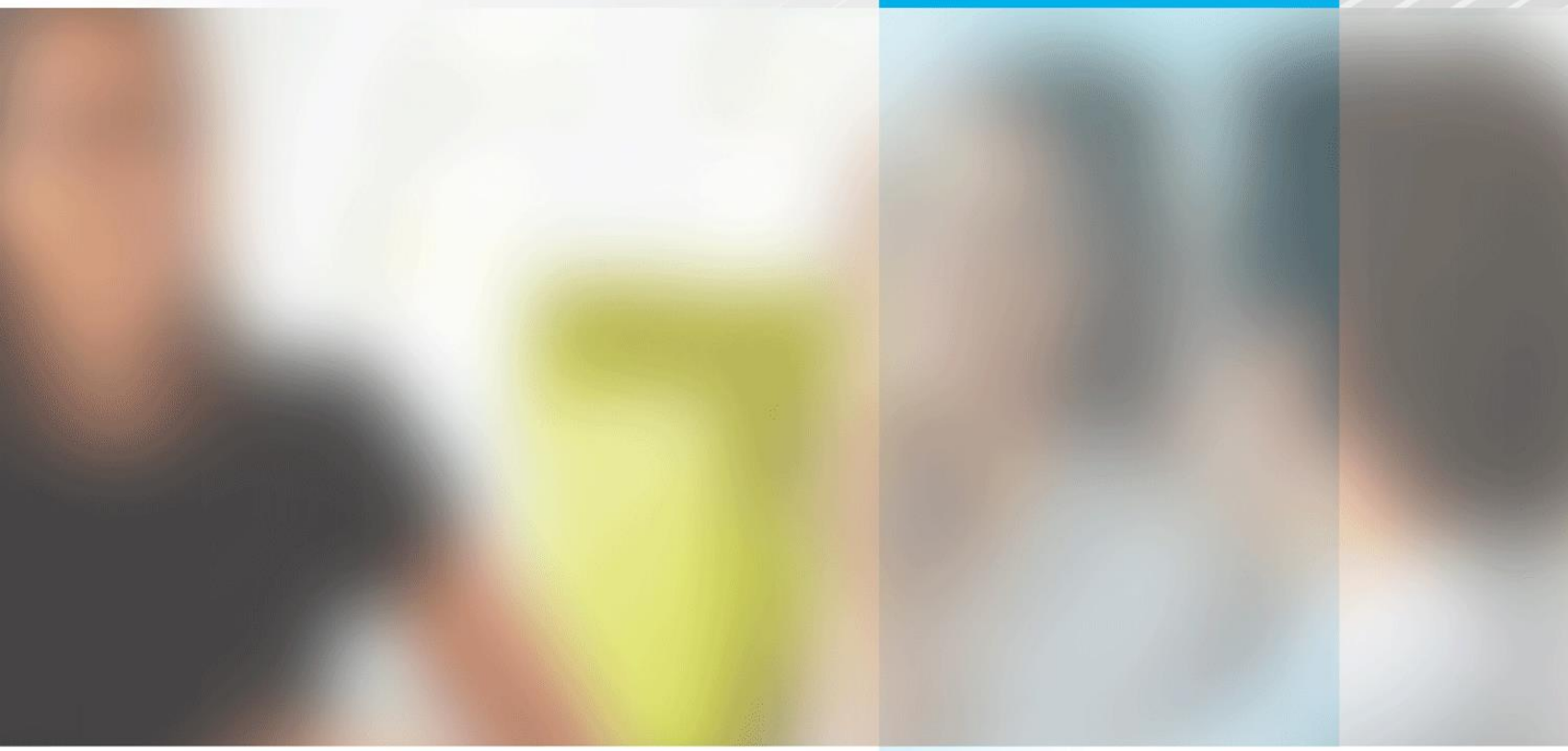
- In a randomized controlled study with patients with types 1 and 2 HAE, lanadelumab was more effective than placebo in preventing attacks. An extension study suggests that this effect could be maintained for up to 75 weeks.
- In the absence of comparative studies, the efficacy of lanadelumab is considered non-inferior to that of the plasma-derived C1-INH concentrates used in clinical practice.
- Lanadelumab is an additional treatment option whose therapeutic characteristics, such as the subcutaneous injection volume and frequency, would address a health need.
- The safety profile is acceptable. However, the members noted that certain elements, such as the liver profile and drug antibody development, while not alarming, should be monitored.
- At the price submitted by the manufacturer, long-term HAE attack prophylaxis with lanadelumab is not a cost-effective treatment option compared to its comparators listed and distributed in Québec.
- At the price submitted by the manufacturer, the net budget impact of introducing lanadelumab on the market would be an increase in costs, despite the therapeutic value being considered non-incremental.

Reasons for the minority position

- The weakness of the evidence presented, which is devoid, among other things, of comparative studies, makes it impossible to rule, beyond any doubt, on the risk-benefit ratio of lanadelumab.
- Criticism was expressed over the submission of new unpublished and non-peer-reviewed data.
- The cost of treatment is high relative to the health need, which is relatively well met.

The members of the deliberative committee also expressed the following concern about adding this product to the *Liste des produits du système du sang du Québec*:

Deliberation on all the criteria
The members are concerned about the high costs associated with managing these patients. In particular, they question the fairness of the price of these products and the equitableness of the use of the resources involved.
INESSS's recommendation - Takhzyro™
The **addition** of Takhzyro™ to the *Liste des produits du système du sang du Québec* for the routine prevention of hereditary angioedema attacks in all adults and adolescents with type 1 or 2 HAE. Takhzyro™ is not intended for the treatment of acute HAE attacks. **Condition** Mitigation of the economic burden.



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