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Hemlibra[MC] (émicizumab) – Hémophilie A

English summary

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Direction des services de santé et de l'évaluation des technologies

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Le présent rapport a été présenté au Comité scientifique permanent d'évaluation des médicaments aux fins d'inscription de l'Institut national d'excellence en santé et en services sociaux (INESSS) lors de sa réunion du 18 septembre 2019.

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SUMMARY

Hemlibra™ (emicizumab) – Hemophilia A

Mandate

The Institut national d'excellence en santé et en services sociaux (INESSS) evaluated emicizumab (Hemlibra™), a bispecific monoclonal antibody indicated for hemophilia A (congenital factor VIII deficiency) patient with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

Emicizumab was previously evaluated by INESSS and is listed on the *Liste des produits du système du sang du Québe*c for the following indication: routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients of all ages with hemophilia A (congenital factor VIII deficiency) with factor VIII (FVIII) inhibitors.

The recombinant FVIIIs Advate™, Adynovate™, Eloctate™, Kovaltry™, Nuwiq™, Xyntha™ (including Xyntha Solofuse™) and Zonovate™, all of which are listed on the *Liste des produits du système du sang du Québe*c, were used as comparators. Nuwiq™ and Zonovate™ are currently distributed by Héma-Québec, and Eloctate™ is available under an MSSS directive.

Evaluation process

Data from literature and provided by the manufacturer were reviewed to document the efficacy and safety of emicizumab. Experiential and contextual data from expert and patient consultations are also presented.

Health needs

Hemophilia A, caused by FVIII deficiency, manifests as longer-than-normal clotting times. In severe cases, FVIII deficiency leads to frequent bleeding episodes in joints (hemarthrosis) and soft tissues in the absence of trauma. Prophylaxis with plasma-derived or recombinant FVIII is the preferred treatment. Prophylaxis consists of several weekly or even daily intravenous injections to replace the missing FVIII.

In some patients, daily doses of FVIII will be administered to achieve treatment goals. Prophylactic treatment therefore imposes a considerable burden on certain patients and their families. In addition, venous access problems may require the use of a central venous access device, a situation that is particularly common among young children (up to about 12 years of age) and obese individuals. These devices cause discomfort and carry an increased risk of infection and thrombosis in these populations. In adult patients who have not received preventive treatment since childhood, polyarthropathy is a source of pain and disability that has a significant impact on their quality of life.

Patient perspective

Some of the persons living with hemophilia A who have been consulted report difficulties administering the current treatment, which may affect their adherence to the treatment. Some patients and family members indicated that therapeutic compliance is a source of

stress and anxiety. Patients also mentioned that frequent visits to a hemophilia centre or a hospital and missed days of work or school are major irritants that affect their quality of life. While a number of respondents expressed satisfaction with their current treatment (FVIII prophylaxis), they expressed a desire for a treatment with a longer half-life, better protection and a simpler, less invasive route of administration.

Efficacy

- Available data show that emicizumab prophylaxis at doses of 1.5 mg/kg per week and 3.0 mg/kg every 2 weeks could reduce annualized bleeding rates by 96% and 97%, respectively, compared to no prophylaxis (low level of evidence).
- However, in Quebec, patient management is based on well-established FVIII prophylaxis. An intra-patient comparison based on a non-randomized and non-interventional design reported that emicizumab prophylaxis (weekly dose of 1.5 mg/kg) reduced the annualized bleeding rate by 68% compared to FVIII prophylaxis. The risk of bias is very high. Some of the experts consulted pointed out that the bleeding rates observed during FVIII prophylaxis were higher than those observed in real-world care settings in Québec, which calls into question the external validity of these results (very low level of evidence).

Safety

- The most common adverse reactions (≥ 1%) observed in clinical studies were injection site reaction (21%), joint pain (16%), headache (14%), fever (6%), diarrhea (5%) and muscle pain (4%).
- Ever since the warning was issued concerning the use of high doses of activated prothrombin complex concentrate (aPCC) for the treatment of breakthrough bleeding in patients treated with emicizumab, no thrombotic events have been reported.

Quality of life

- The available data on FVIII prophylaxis is insufficient to determine the impact of emicizumab on quality of life.

Expert perspective

According to some of the experts consulted, emicizumab is probably at least as effective as its comparators, i.e., replacement FVIIIs. However, some regretted the absence of randomization in the groups, which would have permitted a direct comparison with FVIII prophylaxis. Hence, a non-inferiority conclusion cannot be drawn for this product. Some also pointed out that prophylactic treatment of hemophilia A with a replacement FVIII is very effective and safe for patients. However, they noted that the convenience associated with the subcutaneous administration of emicizumab at lower frequencies has the potential to reduce the therapeutic burden of severe hemophilia A.

Some of the experts consulted mentioned the following limitations in the event that emicizumab prophylaxis is introduced in Quebec:

- The use of FVIII will continue to be necessary for the treatment of breakthrough bleeding episodes;
- Considering the level of protection provided by emicizumab, the use of FVIII will still be necessary for perioperative management and when engaging in at-risk activities;
- The introduction of FVIII treatments in young children under emicizumab prophylaxis should be carefully planned to prevent the development of FVIII inhibitors.

Deliberation concerning emicizumab

The members of the Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription (CSEMI) are unanimously of the opinion that the therapeutic value of Hemlibra™ (emicizumab) as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes for hemophilia A (congenital factor VIII deficiency) patients without inhibitors has not been demonstrated.

Reasons for the unanimous position

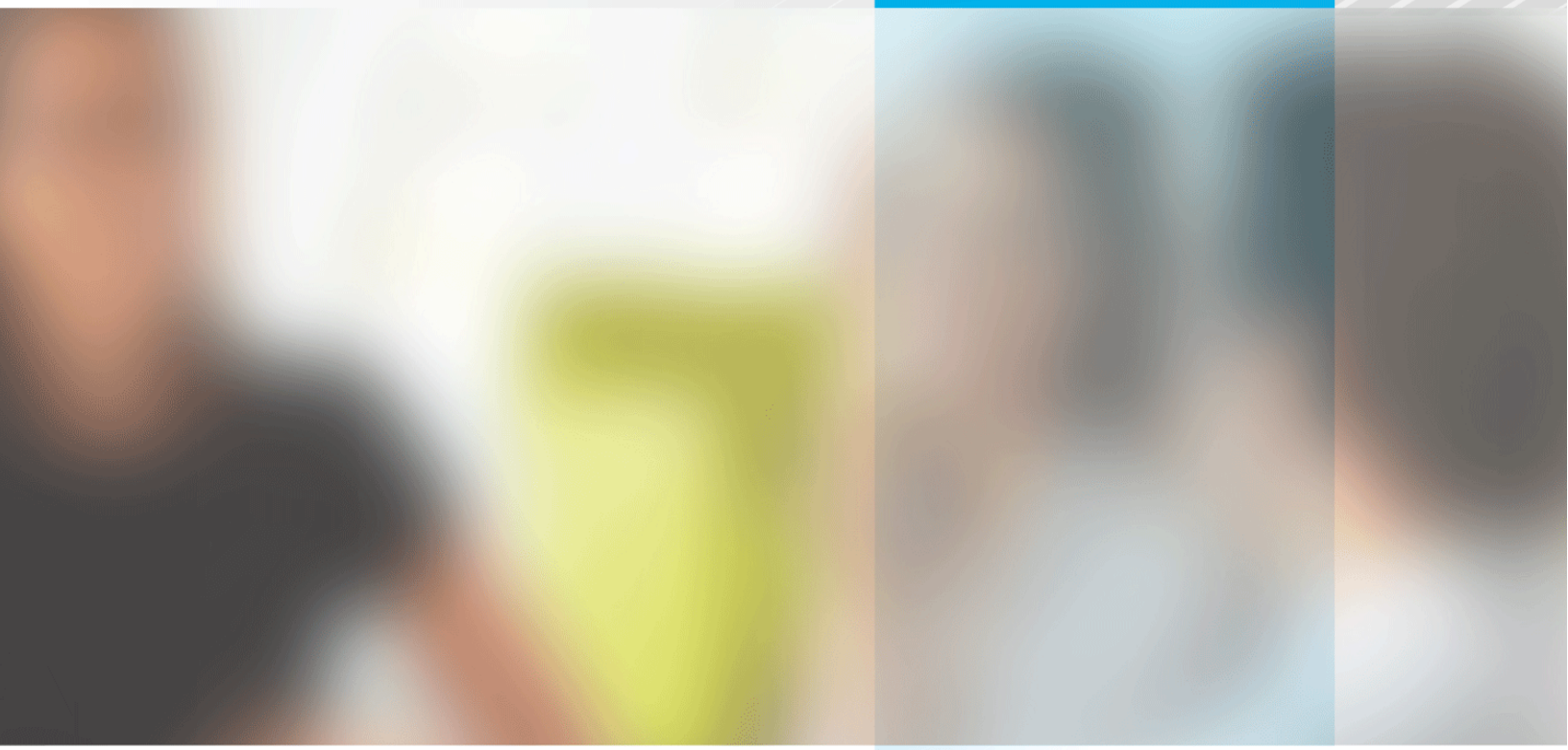
The Committee's members recognized the burden associated with managing the disease. They also recognized that subcutaneous administration and less frequent injections are significant benefits. Nevertheless, after a careful examination of all the evidence, the following observations were made:

- The treatment currently available to patients with severe hemophilia A (without FVIII inhibitors), replacement FVIII prophylaxis, is effective and safe. On the basis of the available studies, it cannot be ensured, in the event that emicizumab is distributed for the proposed indication that Quebec patients will have access to a therapy that is non-inferior to those currently available.
- The absence of a comparator treatment relevant to the Quebec context (FVIII prophylaxis) in the phases of the study where the subjects were randomized, and the small number of subjects make it difficult to weigh the potential benefits and risks. The available data, which are at high risk for bias, do not take all the potential confounding factors into account. The proposed study designs might have been considered acceptable in the context of a disorder or disease whose prevalence is significantly lower or of very significant unmet needs.
- Emicizumab only partially reproduces the coagulant activity of FVIII.
- Injecting factor VIII will continue to be necessary and will require weighing, on a daily basis, the risks and benefits of using a given product. In addition, patients' familiarity with intravenous injections may be affected, which makes it difficult to assess the long-term impact on patients and the organization of care.
- The uncertainty associated with the risk of developing antibodies to the drug and their clinical significance in the medium and long term are still a concern.

- Overall, the safety of emicizumab seems acceptable, and its adverse effects are considered minor.
- Considering that emicizumab constitutes a therapeutic alternative to replacement FVIIIs, whose historical use bears out their efficacy and safety, in accordance with the principle of do no harm, the Committee's members consider it essential that the decision be based on more robust evidence that demonstrates the non-inferiority of this product.

INESSS's recommendation regarding emicizumab

In light of the available data, INESSS recommends that Hemlibra™(emicizumab) should not be offered as a treatment option for patients with hemophilia A without factor VIII (FVIII) inhibitors. Additional data are required to support the therapeutic value for the proposed indication.



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