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Hemlibra® (emicizumab) – Hemophilia A with factor VIII inhibitors
Notice of inclusion on theListe des produits du système du sang du Québec

English summary

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

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

This is the English summary of the guidance entitled Hemlibra^{MC} (émicizumab) – Hémophilie A avec inhibiteurs du facteur VIII- Avis d'introduction à la Liste des produits du système du sang du Québec-published in April 2019.

The complete version of this guidance (in French) is available on the website of INESSS in the Publications section.

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SUMMARY

The Institut national d'excellence en santé et en services sociaux (INESSS) has evaluated Hemlibra® (emicizumab), a monoclonal antibody administered as a once-weekly subcutaneous injection indicated for hemophilia A (congenital factor VIII deficiency) patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

The comparators FEIBA® (activated prothrombin complex concentrate; aPCC) and NiaStase® (activated recombinant factor VII; rFVIIa), which are presently on the list, are the subject of INESSS recommendations as well.

Health needs

Hemophilia A patients with inhibitors are part of a subcategory of patients with a severe form of the disorder characterized by a factor VIII (FVIII) deficiency. This deficiency results in a prolonged clotting time, which leads to frequent, spontaneous bleeding in the joints or soft tissues, even in the absence of trauma. In patients with inhibitors (15% to 30% of patients with severe hemophilia A), first-line treatment, replacement with FVIII products, is ineffective because of the presence of inhibitors (antibodies) that inactivates them. An immune tolerance induction (ITI) protocol may be attempted; its efficacy is approximately 70%. Patients for whom ITI is not effective or not indicated will be treated with bypassing agents.

In Québec, most hemophilia A patients with inhibitors are treated with the bypassing agents aPCCs and rFVIIa. Through these products, hemostasis can be achieved via an alternative coagulation pathway. Prophylactic therapy with aPCC is rather burdensome for patients and their families because it requires the administration of several weekly or even daily intravenous doses. Furthermore, despite preventive therapy, breakthrough bleeding does occur, which has to be treated with additional aPCC or rFVIIa doses. Despite the available treatments, hemophilia A patients with inhibitors often require more aggressive and more frequent treatments than those without inhibitors.

Efficacy

Hemlibra®

- In adults, the annualized bleeding rate[1] with emicizumab is 3.2 compared to 26.2 with no prophylaxis (on-demand treatment); an 87% reduction according to the RCT HAVEN 1. The annualized bleeding rate[1] with emicizumab is 3.3 compared to 15.7 with bypassing agent prophylaxis; a 79% decrease according to the intra-patient comparison of the non-randomized arm in the HAVEN 1 study.

[1] Calculated by the study's authors using a linear regression model.

- In children, the mean annualized bleeding rate[2] with emicizumab is 0.24 compared to 19.66 with no prophylaxis; a 99% reduction according to unpublished results.

Low level of evidence for adults and very low level for children under 12 years of age

FEIBA[MC] and NiaStase[MC] (comparators)

- The hemostatic efficacy of FEIBA® and NiaStase® in the on-demand treatment of spontaneous bleeding episodes is approximately 80%.
- A randomized study comparing the efficacy of FEIBA® and NiaStase® did not find a statistically significant difference between these two products.
- Prophylactic therapy with FEIBA® decreases the number of spontaneous bleeding episodes by 60% to 75% compared to no prophylaxis (rates of 8 to 10 bleeds per year obtained).

Moderate level of evidence

Safety

Hemlibra®

- Most of the adverse events associated with emicizumab therapy are of mild to moderate intensity.
- The most common adverse events are local injection-site reactions of mild to moderate intensity.
- To reduce the risk of thrombotic events, the use of aPCCs should be avoided when treating spontaneous breakthrough bleeding.

Low level of evidence

FEIBA® and NiaStase® (comparators)

- The most common adverse events associated with treatment with FEIBA® or NiaStase® are considered minor and consist mainly of local injection-site reactions.
- The risk of thrombosis is approximately 4 events per 100,000 injections.

Moderate level of evidence

Quality of life

- More patients in the emicizumab group achieved improvements in their quality of life than in the control group.
- Experts consulted were of the opinion that emicizumab is simpler to use and involves less pain for patients.

[2] Mean calculated by INESSS using individual data on 13 patients provided by the manufacturer.

Cost-effectiveness

- Although prophylaxis with emicizumab is less expensive and more efficient than that with aPCC, it is not a cost-effective treatment, given that it has an estimated cost-utility ratio of$1 M/QALY. The cost-utility ratio of aPCC prophylaxis is more unfavourable ($3 M/QALY).

Budget impact

- The mean annual cost of emicizumab therapy is $[redacted], while for a patientreceiving aPCC prophylaxis, it varies from $[redacted] to $[redacted].
- Adding emicizumab to the*Liste des produits du système de sang du Québec*could lead to an annual cost reduction of about $14 M, for a total of close to $43 M over a 3-year time horizon.

Deliberation concerningHemlibra®

The members of the *Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription (CSEMI)*unanimously recognized the therapeutic value of emicizumab (Hemlibra®) for hemophilia A (congenital factor VIII deficiency) patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. Consequently, the members are of the unanimous opinion that the blood system product emicizumab (Hemlibra®) should be added to the *Liste des produits du système du sang du Québec*. However, the members stress that this addition should be accompanied by measures to reduce the economic burden, out of concern for equitable and reasonable access.

Reasons for the unanimous position

- The annualized bleeding rate is significantly lower with emicizumab prophylaxis than with no prophylaxis (on-demand treatment) or with aPCC prophylaxis (level of evidence considered low, although acceptable in the context of a rare disorder);
- The route of administration of emicizumab, subcutaneous injections, and its dosage regimen, which requires a once-weekly injection, could reduce the burden of treatment on patients and their families;
- Although the safety of emicizumab was deemed satisfactory, thrombosis may occur during the treatment of breakthrough bleeding with aPCC in patients receiving emicizumab prophylaxis;
- The mean annual cost of emicizumab therapy is significantly lower;
- Although prophylaxis with emicizumab is less expensive and more efficient than that with aPCC, it is not an efficient treatment. Nonetheless, given that patients are currently treated with a less efficient therapy, adding emicizumab to the list seems reasonable;
- Adding emicizumab to the *Liste des produits du système de sang du Québec* could lead to a considerable cost reduction.

Deliberation concerning FEIBA® (aPCC) and NiaStase® (rFVIIa)

The members of the *Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription (CSEMI)* unanimously recognized the therapeutic value of aPCC (FEIBA®) and activated recombinant factor VII (NiaStase®) for their respective Health Canada-recognized indications. Consequently, the members are of the unanimous opinion that the blood system products FEIBA® and NiaStase®should be kept on the *Liste des produits du système du sang du Québec*.

Reasons for the unanimous position

- The comparators evaluated are relevant in the treatment of spontaneous bleeding episodes and in the context of surgery;
- In patients with severe joint damage and very few bleeds, prophylactic therapy may not be indicated. In such cases, the use of an on-demand bypassing agent to treat bleeding episodes would be preferable;
- Despite prophylaxis with emicizumab, episodes of spontaneous breakthrough bleeding can occur, which would have to be treated with a bypassing agent.

INESSS's recommendation - Hemlibra®

Add the product **Hemlibra®** to the *Liste des produits du système du sang du Québec* for hemophilia A (congenital factor VIII deficiency) patients with factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

Stipulations attached to this recommendation

Given the current paucity of available data on the efficacy and safety of emicizumab and the absence of long-term follow-up data, Quebec's hemophilia centres should gather data on the clinical safety and efficacy of Hemlibra®for the purpose of monitoring them.

Given the very high cost-effectiveness ratio, measures to mitigate the economic burden should be put in place.

INESSS's recommendation - Comparators (FEIBA®and NiaStase®)

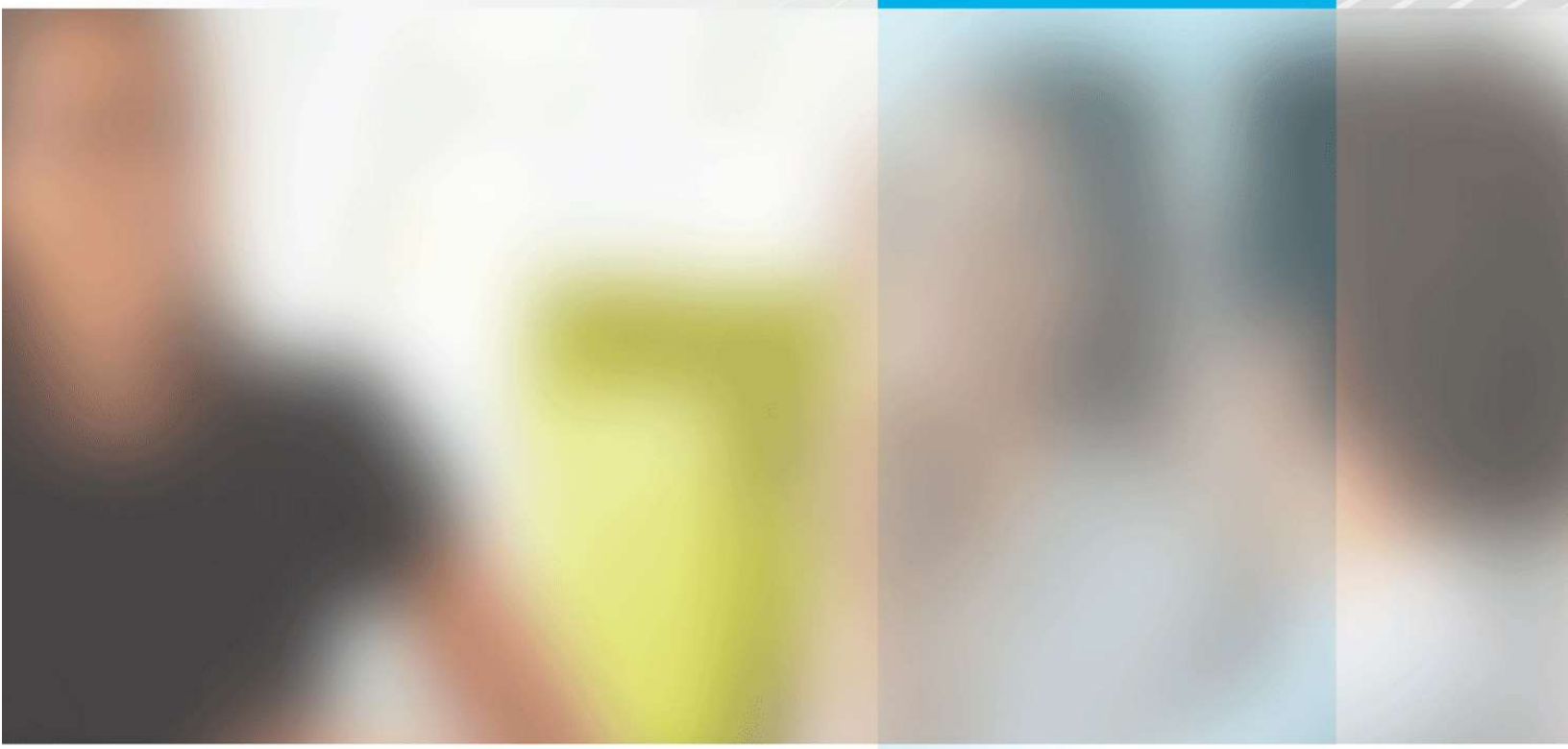
Keep the product **FEIBA®** on the *Liste des produits du système du sang du Québec* for the Health Canada-approved indication;

And

Keep the product **NiaStase®** on the *Liste des produits du système du sang du Québec* for the Health Canada-approved indication.

Stipulations attached to this recommendation

The use of the aPCC FEIBA® to treat spontaneous breakthrough bleeding during emicizumab prophylaxis should be avoided in order to prevent the risk of thrombosis.



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