INESSS
LE SAVOIR PREND FORME

MARCH 2021

Hemlibra™ (emicizumab) – Hemophilia A without inhibitor (re evaluation)

English summary

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

Québec

SUMMARY

Hemlibra™ (emicizumab) – Hemophilia A without inhibitor (re-evaluation)

Mandate

As requested by the manufacturer, the *Institut national d'excellence en santé et en services sociaux* (INESSS) proceeded to re-evaluat emicizumab (Hemlibra™), a bispecific monoclonal antibody indicated in Canada 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. The requested indication for the re-evaluation is as follows:

"For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients of all ages with hemophilia A (congenital factor VIII deficiency), graded as severe or moderate, without factor VIII (FVIII) inhibitors:

- Patients with severe hemophilia A who display trough FVIII levels of < 0,01 IU/ml or < 1% the normal concentration;
- Patients with moderate hemophilia A who display trough FVIII levels of < 0,01-0,05 IU/ml or 1-5% the normal concentration and experience at least 4 spontaneous bleeding events per year; AND
- Patients who cannot receive FVIII prophylaxis because of inappropriate venous access or an important limitation regarding adherence to FVIII prophylaxis."

Emicizumab was previously evaluated by INESSS (April and December 2019 reports) and is listed on the *Liste des produits du système du sang du Québe*c for the following indication : "For 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". This is the second evaluation for the population of type A hemophilia without inhibitors. In the previous evaluation, INESSS issued an unfavourable recommendation since the therapeutic value of emicizumab was not recognized for this population.

The recombinant FVIIIs Advate™, Adynovate™, Eloctate™, Esperoct™, 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.

Prophylactic treatment therefore imposes a considerable burden on certain patients and their families. In some patients, twice or thrice weekly or even daily doses of FVIII will be administered to achieve treatment goals. Venous access problems may require the use of a central venous access device, a situation that is particularly common among young children and obese individuals. These devices cause discomfort and carry an increased risk of infection and thrombosis in these populations. Arthropathies are a source of pain and disability that has a significant impact on their quality of life.

Patient perspective

The type A hemophiliacs consulted, by means of a survey conducted by the Canadian Hemophilia Society or INESSS as part of this evaluation, reported difficulties with the administration of the current treatments, which can affect their adherence to them. As well, some patients and parents of children with hemophilia indicated that therapeutic adherence is a source of stress and anxiety. While many said that they were satisfied with their current treatment (FVIII prophylaxis), they expressed a desire for a treatment that would be simpler and less invasive to administer, which would enable them to aspire to a better quality of life.

Results

Efficacy

Efficacy results come from two new studies as well as two studies reported in the previous evaluation.

- According to the network meta-analysis provided, the efficacy of emicizumab prophylaxis (both the every 7 and every 14 days regimens) to prevent treated bleeds is superior to FVIII prophylaxis. However, the weak methodological quality of the study, as well as the various biases make it impossible to assess this conclusion.

- Two intraindividual comparisons, both encompassing a non-interventional phase of FVIII prophylaxis, suggested that emicizumab offers a better protection than FVIII against bleeds. Considering the risk of bias of the non-interventional phase, it is not possible to assess the efficacy of emicizumab over FVIII.

Safety

New safety data were gathered from a post-market report and an unpublished manuscript. The safety data from the product monograph and clinical studies evaluated in the precedent evaluation were also considered.

- 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 linked to emicizumab have been reported.
- Since the FDA authorized emicizumab in 2018, severe adverse events (including deaths and thrombotic events) have been reported post-marketing.

Quality of life

No new quality of life data were provided. The data from the previous evaluation were considered.

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

Expert perspective

The experts consulted are unanimous in their opinion that the convenience of the route and frequency of administration of emicizumab is the main advantage of this treatment and that it has the potential to reduce the therapeutic burden associated with severe hemophilia A.

In their opinion, emicizumab appears to be effective in preventing bleeding. However, they point out that the studies submitted by the manufacturer for the purpose of this re-evaluation have designs of weak methodological quality and significant biases that preclude determining the extent of its impact and comparing it with the available treatments. Additionally, although a statistically significant reduction in the annualized bleeding rate (ABR) with emicizumab prophylaxis relative to FVIII prophylaxis has been observed in certain studies, the experts are of the opinion that it does not constitute a clinically significant benefit. Some maintain that replacement FVIII prophylaxis is effective and safe for treating hemophilia A patients in Québec and that FVIII infusions will still be necessary for treating breakthrough bleeding episodes for patients on emicizumab

The experts consulted feel that the adverse events seen in the HAVEN 1 to 4 clinical trials appear minor and do not call the safety of emicizumab into question. In their opinion, the complications that occurred during surgeries were minor. However, the experts expressed some concerns regarding certain U.S. post-marketing pharmacovigilance data reported by the manufacturer.

Deliberation on therapeutic value

The members of the *Comité scientifique permanent de l'évaluation des médicaments aux fins d'inscription* (CSÉMI) recognize the extent of the burden associated with managing this disease. They also note that subcutaneous administration and the lower frequency of injections could constitute significant advantages for a good number of patients and their families. Nonetheless, and given the main findings and uncertainties raised, most of the members are of the opinion that the therapeutic value of Hemlibra™ (emicizumab) has not been demonstrated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with moderate or severe hemophilia A (congenital factor VIII deficiency) without factor VIII (FVIII) inhibitors.

Reasons for the majority position

The data submitted for this re-evaluation are mainly from a network meta-analysis of weak methodological quality with numerous biases that prevent us from addressing the findings that led to the therapeutic value not being recognized during the first evaluation for patients without inhibitors. These findings mainly concerned the absence of a relevant comparator treatment in the Québec context, the fact that emicizumab only partially mimics FVIII coagulant activity, and certain long-term uncertainties.

The significant biases in the intra-patient comparison study preclude an assessment of the efficacy of emicizumab prophylaxis compared to that of FVIII prophylaxis.

The adverse events reported during the clinical trials do not call the safety profile of emicizumab into question.

The post-marketing pharmacovigilance data on emicizumab are of concern to the committee's members, even if no direct causal link has been established between the use of emicizumab and certain serious adverse events.

Considering the short patient follow-ups in the clinical trials, certain infrequent adverse events (such as those reported in the post-marketing surveillance data) may not yet have been observed.

Even if emicizumab could have a significant positive impact on quality of life and therapeutic adherence in hemophilia patients receiving FVIII prophylaxis, this promise of improvement is not supported by good-quality data. The members also stated that the demonstration of efficacy and safety takes precedence over the possibility of potential quality-of-life benefits.

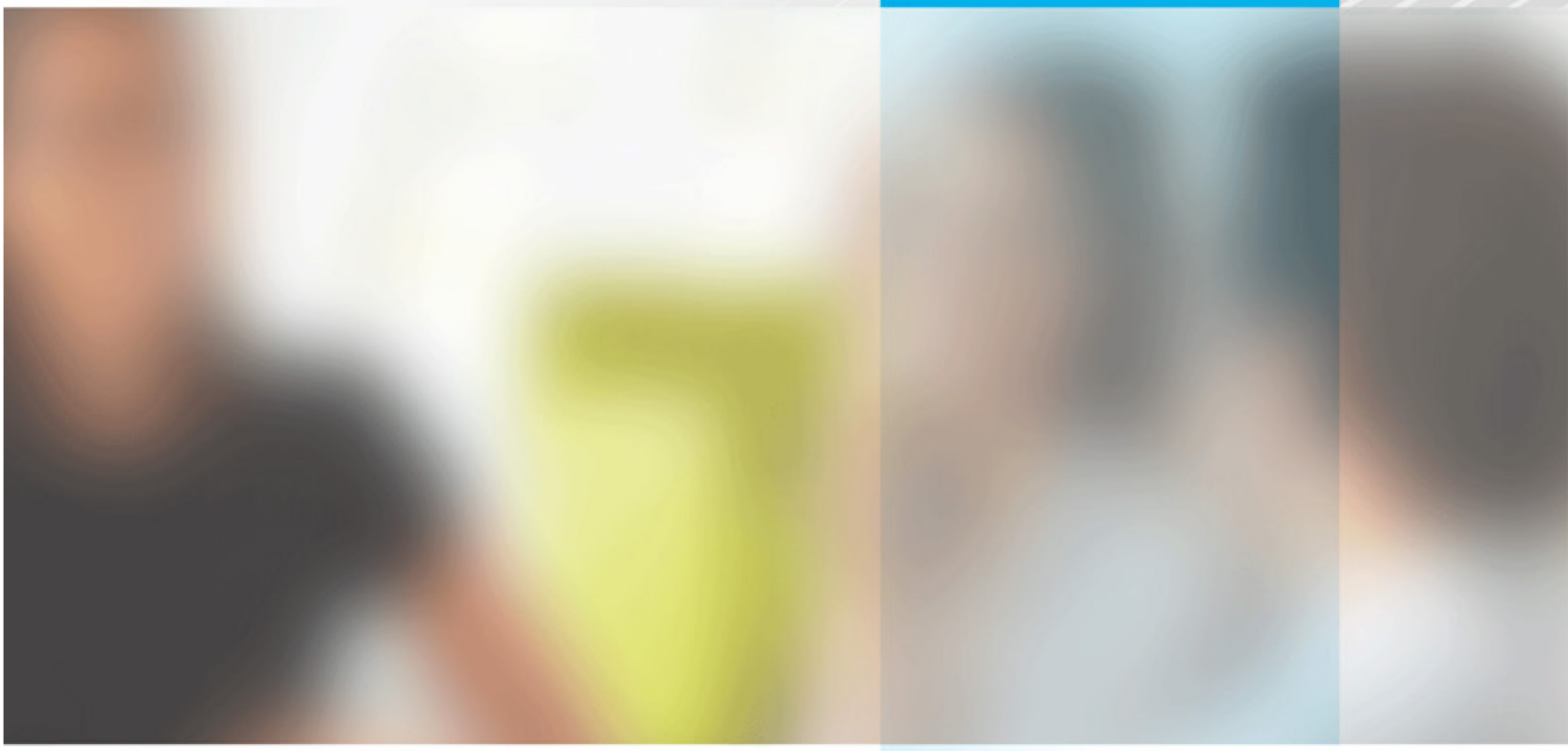
Reasons for the minority position

Emicizumab would constitute a therapeutic option whose features, such as its administration frequency and subcutaneous administration, could permit a significant reduction in the burden associated with the treatment of hemophilia.

Despite the scarcity of new data, certain members are of the opinion that emicizumab could prevent, at least in part, bleeding events and could constitute a therapeutic option for some patients after a risk-benefit assessment is performed by the healthcare team.

INESSS's recommendation regarding emicizumab

In light of the available data, INESSS cannot recognize Hemlibra™ for the following indication: routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with moderate or severe hemophilia A (congenital factor VIII deficiency) without factor VIII (FVIII) inhibitors. It therefore recommends that this indication not be included in the list of products for Québec's blood system. Comparative data of better methodological quality and relevant to the hemophilia context in Québec, and answers to the above-mentioned safety concerns raised are required to support the assessment of this drug's therapeutic value in the proposed indication.



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