Canadian Hemophilia Society
Help Stop the Bleeding
Société canadienne de l'hémophilie
Arrêtons l'hémorragie

Response to medical/scientific and economic reviews of emicizumab

Prepared by the Canadian Hemophilia Society Blood Safety and Supply Committee

February 18, 2019

Medical and Scientific Review of Hemlibra

The Medical and Scientific Review of Hemlibra (emicizumab) was produced by Canadian Blood Services (CBS) on August 24 but only provided to the Canadian Hemophilia Society (CHS) on February 14 with three working days to respond. The CHS agrees with the unanimous recommendation of the CBS Internal Review Team:

Based on the unanimously favourable medical and scientific review, the Internal Review Team recommends that HEMLIBRA® (emicizumab) be added to the plasma protein products considered for distribution by Canadian Blood Services.

The review states: *Reviewers uniformly foresaw HEMLIBRA® becoming the standard of care for prevention of bleeding in hemophilia A patients with inhibitors*. This is already the case in the U.S. and in many countries in Europe. Canada is lamentably slow in introducing this life-changing therapy, internationally recognized as standard of care, for this vulnerable population.

Emicizumab should be made available to all patients with hemophilia A and inhibitors immediately.

CADTH Economic Review Report

Consultation process

This 53-page report was released by the Canadian Agency for Drugs and Technologies in Health (CADTH) in December 2018 but not shared with the CHS until February 14, and with a February 18 deadline for comments. This is unacceptable. Nor did this short window for comments provide the time necessary for the Association of Hemophilia Clinic Directors of Canada (AHCDC) to provide their valuable input.

The CHS was told that the report we received is "final" and that no comments or corrections suggested by the CHS will change the report. It will be presented as is to CBS senior management and then eventually to the Provincial/Territorial Blood Liaison Committee no matter what CHS' comments are. This is also unacceptable. This goes against CADTH's own principles of welcoming feedback from key stakeholders, including patient organizations, on its draft reports.

While the CHS accepts that certain information, for example, confidential pricing and current market share, be redacted from the report, other non-proprietary information and/or assumptions made by CADTH that are essential to understanding the conclusions are unnecessarily redacted, for example:

- The percentages of inhibitor patients assumed by the manufacturer to switch to emicizumab in Years 1, 2 and 3;
- Assumptions of pediatric and adult;
- The percentages of non-inhibitor patients assumed by the manufacturer to switch to emicizumab in Years 1, 2 and 3;

- Assumptions of wastage;
- Assumptions by CADTH of percentages of pediatric and adult patients currently treated with BPAs prophylactically or on-demand;
- Assumptions by CADTH of the percentages of moderate and severe pediatric and adult on prophylactic and on-demand regimens;
- The manufacturer's assumptions on the proportion of the inhibitor population adopting emicizumab;
- The manufacturer's assumptions on the proportion of the non-inhibitor population adopting emicizumab;
- The manufacturer's estimate of patient numbers.

Emicizumab for patients with hemophilia A AND inhibitors

The CADTH economic review confirms the CHS analysis submitted to CBS in June 2018 that conservatively predicted 33% lower costs for the treatment of inhibitor patients with coagulation therapies including emicizumab compared to current standard of care and annual savings of $15,000,000 to $20,000,000. Indeed, CADTH states: *CADTH reanalysis estimated the following budget impact associated with treating hemophilia A with inhibitors with emicizumab: cost savings of $32,920,731 in year 1; $34,750,021 in year 2; and $36,545,226 in year 3*. The CHS submits that these savings will be even larger following price negotiation with the manufacturer.

We dispute the attempt by CADTH (page 7, line 162) to distinguish between prophylaxis and on-demand therapies with bypassing agents for patients with inhibitors (these protocols are often situational) if this is to lead to a decision to provide emicizumab to one group of patients with inhibitors and not to the other. As agreed by the reviewers, emicizumab is of great benefit to all patients with inhibitors and is "dominant" (higher quality-adjusted life year [QALYs], lower costs) when provided to the entire population of approximately 80 people.

The CADTH review regarding patients with hemophilia A and inhibitors contains enough unredacted information (patient numbers, patient uptake of emicizumab, comparative costs, evidence of fair comparisons between the *reference scenario* and the *new treatment scenario* using the international list price for emicizumab and the PMPRB prices for BPAs, which we know to be quite similar to real-world prices) such that we are able to understand and support its conclusions. Emicizumab undeniably "dominates" bypassing agents both in terms of value for patients and reduced health care costs, even before price negotiation.

The medical benefits of emicizumab and the cost savings for the health system were already demonstrably evident on August 2, 2018, the day the therapy was approved by Health Canada. Using CADTH-generated numbers, CBS and the health system have seen / will see …

- $2,743,394 in foregone savings each month of delay in introducing emicizumab ($32,920,731 in costs for emicizumab divided by 12 months, from CADTH Table 1);
- $16,460,365 in foregone savings to date;
- $30,000,000 in foregone savings if emicizumab is not made available until June or July, as the CHS has been informed by CBS.

There is enough evidence from the Medical and Scientific Review, the CADTH Economic Review, the U.S. ICER Health Technology Assessment and the CHS submission to decide immediately to make emicizumab available to all patients with hemophilia A and inhibitors. Further delay is unacceptable.

Thus our questions are:

- When will CBS recommend the introduction of emicizumab for inhibitor patients to the P/TBLC?
- Why is CBS waiting for a decision from the P/Ts before starting to negotiate a contract with the manufacturer so that emicizumab can be made available immediately? (The CHS is convinced that given the positive medical/scientific recommendation and the favourable budget impact, a positive decision is inevitable; it is only a question of time.)
- Are CBS and the Provinces/Territories not concerned that a licensed therapy, internationally recognized as the new standard of care, remains unavailable, leaving the blood system open to public criticism and, in the event of an avoidable adverse outcome, potentially liable?

Emicizumab for patients with hemophilia A WITHOUT inhibitors

The CHS contends that all references with regard to patients with hemophilia A without inhibitors should be struck from the economic review.

CBS conducted its Medical and Scientific Review before the publication of HAVEN 3, the pivotal study on emicizumab in the non-inhibitor population, published in the New England Journal of Medicine on August 30, 2018. CADTH conducted its analysis in the complete absence of any information on the value of the therapy to patients, for example, improved prevention of bleeding, increased adherence and higher quality of life. An economic review of a drug therapy without considering health benefits is of little value.

The CHS believes that CADTH Economic Review of emicizumab for non-inhibitor patients was conducted prematurely and based on inaccurate and incomplete information and we reject its budget impact conclusions. It was carried out without proper consultation of stakeholders. The assumptions made by CADTH are opaque and the conclusions, in some cases, completely wrong.

The CADTH scenario compares the *international list price* for emicizumab to the *negotiated prices* for a standard half-life FVIII (Xyntha) and an extended half-life FVIII (Adynovate). These two products are known to be two of the least costly FVIIIs on the Canadian market and do not represent the actual average cost of current therapies. CADTH is comparing apples and oranges: the price of emicizumab before any negotiation with the manufacturer, and FVIII prices representing only the lowest cost products in the current FVIII market. This distorts the calculations.

For the last year, the CHS has recommended an initial expedited analysis of emicizumab for patients with inhibitors and a subsequent analysis for the non-inhibitor population when research, marketing information and real-world data were available. This flawed report proves our approach to have been the correct one.

CADTH reanalysis of the non-inhibitor population estimated a budget increase of $238,690,523 in Year 1. The CHS is convinced this conclusion is unrealistic.

Here are some calculations that show the CADTH economic review to be in error. Based on contacts with patients and physicians around the world, the CHS believes that no more than 12.5% to 25% of patients with severe hemophilia A, and 5% to 10% of patients with moderately severe hemophilia A, would switch to emicizumab in Year 1. Many would be children. We estimate the international list price for emicizumab to be $400,000 CDN (average price for all weights, based on total cost for emicizumab in CADTH Table 1, divided by 81 patients). This compares well with what we know to be the list price for emicizumab in the U.S., known to be over $500,000 U.S. per adult patient per year.

This is CHS' estimate of anticipated drug therapy costs:

	Emicizumab				Factor VIII	
	Total number of patients	High est.	Switches	Total cost	Cost per patient per year	Total cost
Moderate	225*	10%	22	$8,800,000	$100,000**	$2,200,000
Severe	700*	25%	175	$70,000,000	$100,000**	$17,500,000
				$88,800,000		**$19,700,000**
Difference				+$69,100,000		

* Based on the CHS/AHCDC data reported to 2016 World Federation of Hemophilia Global Survey

** Based on 2,000 IUs per dose X 3 times per week X 52 weeks X $0.32

This is the worst-case scenario in terms of increased costs with emicizumab for non-inhibitor patients. It …

- uses the highest estimate for the anticipated number of switches (25% in Year 1);
- uses an average weight and dose. We believe the majority of early adopters will be children, even very small children, and their weight and dose will be lower, and therefore cheaper;
- uses the international list price for emicizumab; the negotiated price is very likely to be substantially lower;
- uses the lowest price FVIIIs in the Canadian market to calculate FVIII costs (as does CADTH). The average price, when all FVIII products are considered, is considerably higher;
- considers only savings directly related to drug costs. Additional savings related to avoided hospitalizations and arthroplasty care are excluded.

This scenario is quite similar to the manufacturer's scenario in Table 4 (line 511).

CADTH scenarios, however, are wildly different. Table 7 (line 624) quotes costs in Year 1 as $410,152,600 (five times those calculated by CHS) and incremental costs as $238,690,523 (four times higher). While the large number of redactions makes analysis difficult, CHS observed the following:

In the CADTH base case analysis for the non-inhibitor population on page 20 at lines 585 to 589, it is stated: *The number of patients with hemophilia A and the proportion with inhibitors was based on the most recent 2017 estimates provided by CBS. Based on this, 91%, 7%, and 2% of the pediatric population have severe, moderate, and mild hemophilia, respectively. Whereas, 84%, 15%, and 1% of the adult population have severe, moderate, and mild hemophilia respectively.* The actual proportions of patients with severe, moderate and mild hemophilia A are 30%, 10% and 60% (latest World Federation of Hemophilia Global Survey, based on data from the Canadian Bleeding Disorders Registry [CBDR] and iCHIP). Does CADTH mistakenly base their calculations on a percentage (20%? 30%? 40%?) uptake of emicizumab in 91% and 84% of the entire population of 2,798 patients (line 555), including mild and moderate patients, rather than the 30% of patients, 700 in all, with severe disease? That would seem to be the case and would account for the over-estimate of costs by a factor of 4 or 5.

Table 34 assumes 100% uptake of emicizumab in all patients, costs of $1,519,198,953 (17 times higher than the CHS estimate and incremental costs of $1,324,722,853 (19 times higher than the CHS estimate)! It is difficult to understand why this would even be considered by CADTH as there is no suggestion in any research that emicizumab would be indicated for the 60% of patients with mild hemophilia. In fact, given their background level of endogenous FVIII, emicizumab would be ineffective. This reflects the lack of serious consultation undertaken in this review.

Why are the CADTH scenarios so wildly unrealistic? One can only conclude that the assumptions as to the numbers of patients switching to emicizumab are erroneous and the prices chosen for purposes of comparison unfairly selective.

The CHS has focused its analyses to date on the inhibitor population and is awaiting more real-world experience with emicizumab before submitting its views to health authorities on the non-inhibitor population.

We sincerely hope the consultation process with patient and physician groups will be more inclusive and undertaken early in the process. In the meantime, this CADTH economic review with regard to patients with hemophilia A without inhibitors should be entirely discounted.