CADTH

CADTH REIMBURSEMENT REVIEW

CADTH Reimbursement Recommendation

(Final)

EMICIZUMAB (HEMLIBRA — HOFFMANN-LA ROCHE LTD.)
Indication: Bleeding prevention, hemophilia A (congenital factor VIII deficiency)

RECOMMENDATION
The CADTH Canadian Plasma Protein Product Expert Committee (CPEC) recommends that emicizumab be reimbursed for the treatment of patients with hemophilia A (congenital factor VIII deficiency) without factor VIII (FVIII) inhibitors only if the following conditions are met.

Conditions for Reimbursement

Initiation criteria
1. Patients with severe hemophilia A (intrinsic FVIII level < 1%) who are candidates for routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes.

Prescribing conditions
1. The patients must be under the care of a hematologist with experience in the diagnosis and management of hemophilia A.

Pricing conditions
1. The public payer cost of emicizumab should not exceed the public payer cost of treatment with the least costly FVIII replacement that is being reimbursed for the prophylactic treatment of patients with hemophilia A without FVIII inhibitors.

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Reasons for the Recommendation

1. In one 24-week randomized controlled trial (HAVEN 3), emicizumab regimens of 1.5 mg/kg weekly and 3 mg/kg every two weeks showed a statistically significant and clinically meaningful reduction in bleeding outcomes (annualized bleeding rate [ABR] for treated bleeds, all bleeds, treated joint bleeds, and treated spontaneous bleeds) compared with no prophylaxis (episodic FVIII treatment). This reduction in bleeding outcomes was shown in patients with severe hemophilia A without FVIII inhibitors who were previously treated with episodic FVIII replacements. In HAVEN 4, a non-randomized, single-arm trial, results of descriptive analyses showed that patients treated with 6 mg/kg emicizumab every four weeks had ABRs that were generally aligned with those observed in patients in the HAVEN 3 trial.
2. The evidence comparing emicizumab to prophylactic FVIII replacement (the current standard of care) is limited. The only available direct comparative evidence was from an intra-patient analysis in a small sample of patients in the HAVEN 3 study who were previously treated with FVIII prophylaxis. This analysis showed that emicizumab at 1.5 mg/kg weekly led to a statistically significant and clinically meaningful reduction in the ABR ratio for treated bleeds and all bleeds compared with the patient's previous prophylactic treatment. However, the magnitude of the comparative clinical benefit was uncertain due to limitations of the study design.
3. CADTH re-analysis of the sponsor's submitted economic evaluation found that emicizumab was not cost-effective at the submitted price, with an incremental cost-effectiveness ratio (ICER) of $5.53 million per quality-adjusted life-year (QALY) compared with prophylactic FVIII in the population studied in the HAVEN-3 clinical trial. Given the uncertainty regarding the comparative effectiveness of emicizumab compared to prophylactic FVIII replacement and other model limitations that could not be adequately addressed in the submitted cost-utility analysis, there is insufficient evidence to justify a price premium over the least expensive FVIII replacement reimbursement for the treatment of patients with hemophilia A without FVIII inhibitors.

Implementation Considerations

- If the pricing condition above cannot be achieved, reimbursement of emicizumab will likely be associated with a high budget impact due to the size of the population that would be expected to be eligible for life-long treatment. To manage this potential impact on public payer budgets, public payers should consider establishing an agreement that would mitigate the budget impact of emicizumab.

Discussion Points

- The majority of patients (> 97%) enrolled in the HAVEN 3 and HAVEN 4 studies had severe congenital hemophilia A (intrinsic FVIII level < 1%). No evidence was available to support the effectiveness of emicizumab in patients with mild or moderate hemophilia A without FVIII inhibitors.
- Canadian patients with hemophilia A currently have access to several recombinant and plasma-derived FVIII replacement therapies, all of which are for IV administration and must be administered two to three times per week. Patients expressed a desire for a treatment with an easier route and less frequent administration. CPEC acknowledged that emicizumab has the potential to meet these needs given its subcutaneous route of administration and that the recommended dosing ranges from once weekly to once monthly.
- One network meta-analysis (NMA) was submitted by the sponsor, which suggested that both emicizumab prophylaxis regimens (1.5 mg/kg weekly and 3.0 mg/kg every two weeks) were associated with a reduction in total treated bleeds compared with recombinant FVIII (rFVIII) prophylaxis in patients with severe hemophilia A without inhibitors. However, this analysis is limited by the small number of trials, a high degree of clinical and statistical heterogeneity across the included studies, and inconsistent or unclear definitions of the bleeding outcomes.

Background

Emicizumab is indicated for hemophilia A (congenital factor VIII deficiency) patients with or without factor VIII inhibitors as routine prophylaxis to prevent bleeding or reduce the frequency of bleeding episodes. At the sponsor's request, the focus of the current review is in patients without factor VIII inhibitors only. Emicizumab has not been previously reviewed by CADTH but has been available for use in Canada since August 2018 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.

Emicizumab is an engineered humanized monoclonal modified immunoglobulin G4 bispecific antibody. It is available as a solution for subcutaneous injection. The Health Canada–approved dose includes a loading dose of 3 mg/kg emicizumab once weekly for the first four weeks, which is followed by a maintenance dose administered one week after the last loading dose. The maintenance dose should be selected based on physician and patient and/or caregiver dosing regimen preference to support adherence taking into account the age and weight of the patient:

- The recommended maintenance dose for adolescents (12 to 17 years of age) and adults (≥ 18 years of age) who weigh 40 kg or more is 1.5 mg/kg once weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks, administered as a subcutaneous injection.
- The recommended maintenance dose for pediatric patients (< 12 years of age) of any weight or patients of any age who weigh less than 40 kg is 1.5 mg/kg once weekly or 3 mg/kg every two weeks, administered as a subcutaneous injection.

Summary of Evidence Considered by CPEC

The committee considered the following information prepared by CADTH: a systematic review of one randomized controlled clinical trial and one non-controlled clinical trial of emicizumab, a sponsor-submitted indirect treatment comparison, and a critique of the sponsor's pharmacoeconomic evaluation. The committee also considered input from clinical experts with experience treating patients with hemophilia A and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Canadian Hemophilia Society (CHS), provided input for this submission. Patient perspectives were obtained from personal meetings, conferences, and an online survey conducted between May 31, 2019, and June 15, 2019, for patients with hemophilia A and their caregivers. The following is a summary of key input from the perspective of the CHS:

- Patient input from the CHS highlighted that hemophilia A negatively affects the lives of patients on a physical, psychological, and financial level. The key concerns raised by patients are breakthrough bleeds despite FVIII prophylaxis, damage to joints, venous access challenges, time lost from school and work, and adherence difficulties due to the complex treatment regimen.

- According to the patient input from the CHS, although most patients recognized current treatments as quite effective, most patients and caregivers expressed a clear desire for longer-lasting treatment, more reliable efficacy (i.e., lower risk of breakthrough bleeds), and an easier mode of administration, such as subcutaneous injections instead of IV infusions.
- The CHS suggested that patients with severe hemophilia and those with mild and moderate disease who have a severe phenotype would benefit most from treatment with emicizumab. As well, the CHS believes that the new treatment would greatly benefit infants and children for whom venous access is most difficult, patients who suffer from frequent breakthrough bleeds and joint disease despite FVIII prophylaxis, and patients who have difficulties adhering to the current treatment regimen, which requires frequent IV infusions.

Clinical Trials

The CADTH systematic review included two phase III trials (HAVEN 3, N = 152; HAVEN 4, N = 41).

HAVEN 3 was a 24-week open-label, multi-centre, randomized controlled clinical trial that aimed to evaluate the efficacy of prophylactic emicizumab compared with no prophylaxis in patients with severe hemophilia A without FVIII inhibitors who received prior treatment with episodic or prophylactic factor VIII. Patients who received episodic treatment with FVIII before study entry were randomized in a 2:2:1 ratio to the following emicizumab maintenance dose groups: emicizumab prophylaxis at 1.5 mg/kg weekly, emicizumab prophylaxis at 3 mg/kg every two weeks, and no prophylaxis (control arm). All patients randomized to either of the emicizumab prophylaxis arms received a 3 mg/kg weekly loading dose for four weeks. Patients who received FVIII prophylaxis before study entry (derived from a previous study: the Non-Interventional Study) were enrolled in a separate, non-randomized arm in which they received treatment with emicizumab prophylaxis at 3 mg/kg every week for four weeks, followed by the maintenance dose of 1.5 mg/kg weekly. In HAVEN 3, the primary outcome was the annual bleeding rate ratio for treated bleeds. Secondary outcomes pre-specified in the statistical testing hierarchy included additional bleeding outcomes (annual bleeding rate ratio for all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds) and health-related quality of life (HRQoL) measured with the Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL) Physical Health.

HAVEN 4 was 24-week open-label, non-randomized, single-arm trial that aimed to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab prophylaxis in patients with severe congenital hemophilia A without inhibitors or congenital hemophilia A with FVIII inhibitors. Patients in HAVEN 4 received treatment with emicizumab prophylaxis at 3 mg/kg weekly for four weeks, followed by 6 mg/kg every four weeks. No formal hypothesis testing was performed, and no primary efficacy end point was identified. Analyses for all outcomes (e.g., bleeding outcomes, productivity, and HRQoL) were descriptive.

The key limitations of the body of evidence related to the open-label study design; absence of randomized, direct comparative evidence between emicizumab and FVIII prophylaxis; and generalizability to the Canadian patient population.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol.

Outcomes of HAVEN 3 and HAVEN 4 discussed by the committee included bleeding events, productivity, HRQoL, and patient satisfaction.

<u>Bleeding:</u>

Definitions for bleeds were consistent in HAVEN 3 and HAVEN 4. The annual bleeding rate for each outcome was calculated using the following formula: ABR = (Number of Bleeds ÷ Total Number of Days During the Efficacy Period) × 365.25.

- An event was considered a treated bleed if coagulation factors were administered for the treatment signs or symptoms of bleeding (e.g., pain, swelling) irrespective of the time between the treatment and the preceding bleed.
- All bleeds included both treated and non-treated bleeds. Bleeds due to surgery or procedures were excluded.
- Treated joint bleeds were defined as bleeds occurring in a joint with at least one of the following symptoms: increasing swelling or warmth of the skin over the joint and/or increasing pain, decreased range of motion, or difficulty in using the joint compared with baseline.

- Treated spontaneous bleeds were defined as a treated bleed with no known contributing factor, such as trauma, surgery, or procedure.
- Treated target joint bleeds where target joints were defined as a major joint (e.g., hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of three or more bleeds into the same joint over the last 24 weeks prior to study entry).

HRQoL

The Haem-A-QoL Physical Health was the only HRQoL outcome included in the statistical testing hierarchy for HAVEN 3. The Haem-A-QoL is a disease-specific self-reported questionnaire used to measure HRQoL in adult patients (18 years or older) with hemophilia. It measures the following 10 domains: physical health, feelings, view of yourself, sports and leisure, work and school, dealing with hemophilia, treatment, future, family planning, and partnership and sexuality. Scores range from zero to 100, with higher scores indicating worse health status. Construct validity was adequate for eight of 10 domains and the total score, and convergent validity was determined to be acceptable in patients with hemophilia. Internal consistency was determined to be acceptable in patients with hemophilia, and the questionnaire was sensitive to detect change over time in patients with hemophilia. No generally accepted minimally important difference (MID) was identified; however, one study in patients with hemophilia used half a standard deviation of the mean baseline score as the MID. Responder definitions were estimated to be a 7-point reduction for the total score.

Patient Satisfaction

Patient preference and satisfaction with treatment were assessed through the Emicizumab Preference Survey (EmiPref) and the Satisfaction Questionnaire - Intravenous Subcutaneous Hemophilia Injection (SQ-ISHI).

- The EmiPref is a non-validated, disease-specific, fit-for-purpose questionnaire developed by the sponsor that measures patient preference for emicizumab treatment. No literature was identified that tested the EmiPref for reliability, validity, or responsiveness in patients with hemophilia. No MID information was identified in patients with hemophilia.
- The SQ-ISHI is a non-validated, disease-specific, fit-for-purpose questionnaire that measures patient satisfaction with hemophilia treatments. No literature was identified that tested the SQ-ISHI for reliability, validity, or responsiveness in patients with hemophilia. No MID information was identified in patients with hemophilia.

Efficacy

Bleeding

Treated Bleeds

In HAVEN 3, the primary outcome related to the ABR ratio for treated bleeds demonstrated a statistically significant reduction in bleeding for both emicizumab at 1.5 mg/kg weekly and 3 mg/kg every two weeks compared with no prophylaxis (i.e., episodic FVIII) for patients previously treated with episodic FVIII. The ABR ratio between emicizumab at 1.5 mg/kg weekly (ABR = 1.5) and no prophylaxis (ABR = 38.2) was 0.04 (95% confidence interval [CI], 0.020 to 0.075; P < 0.0001), in favour of emicizumab at 1.5 mg/kg weekly. The ABR ratio between emicizumab at 3 mg/kg every two weeks (ABR = 1.3) and no prophylaxis (ABR = 38.2) was 0.03 (95% CI, 0.017 to 0.066; P < 0.0001), in favour of emicizumab at 3 mg/kg every two weeks.

For treated bleeds, an ABR ratio of 0.32 (95% CI, 0.195 to 0.514; P < 0.0001) in favour of emicizumab at 1.5 mg/kg weekly was reported for the intra-patient comparison of patients treated with FVIII prophylaxis in the Non-Interventional Study (NIS; ABR = 4.8) compared to treatment with emicizumab at 1.5 mg/kg weekly in HAVEN 3 (ABR = 1.5).

In HAVEN 4, the ABR was 2.4 (95% CI, 1.38 to 4.28).

All Bleeds

In HAVEN 3, the secondary outcome related to ABR ratio for all bleeds demonstrated a statistically significant reduction in bleeding for emicizumab at both 1.5 mg/kg weekly and 3 mg/kg every two weeks compared with no prophylaxis for patients previously treated with episodic FVIII. The ABR ratio between emicizumab at 1.5 mg/kg weekly (ABR = 2.5) and no prophylaxis (ABR = 47.6) was 0.05

(95% CI, 0.028 to 0.099; P < 0.0001), in favour of emicizumab at 1.5 mg/kg weekly. The ABR ratio between emicizumab at 3 mg/kg every two weeks (ABR = 2.6) and no prophylaxis (ABR = 47.6) was 0.06 (95% CI, 0.030 to 0.103; P < 0.0001) in favour of emicizumab at 3 mg/kg every two weeks.

For all bleeds, an ABR ratio of 0.37 (95% CI, 0.220 to 0.626; P < 0.0001) in favour of emicizumab at 1.5 mg/kg weekly was reported for the intra-patient comparison of patients treated with FVIII prophylaxis in the NIS (ABR = 8.9) compared with treatment with emicizumab at 1.5 mg/kg weekly in HAVEN 3 (ABR = 3.3). The reduction in bleeding was clinically relevant according to clinical experts consulted for this review.

In HAVEN 4, the ABR was 4.5 (95% CI, 3.10 to 6.60).

Treated Joint Bleeds

In HAVEN 3, the secondary outcome related to ABR ratio for treated joint bleeds demonstrated a statistically significant reduction in bleeding for emicizumab at both 1.5 mg/kg weekly and 3 mg/kg every two weeks compared with no prophylaxis for patients previously treated with episodic FVIII. The ABR ratio between emicizumab at 1.5 mg/kg weekly (ABR = 1.1) and no prophylaxis (ABR = 26.5) was 0.04 (95% CI, 0.019 to 0.085; P < 0.0001), in favour of emicizumab at 1.5 mg/kg weekly. The ABR ratio between emicizumab at 3 mg/kg every two weeks (ABR = 0.9) and no prophylaxis (ABR = 26.5) was 0.03 (95% CI, 0.015 to 0.070; P < 0.0001), in favour of emicizumab at 3 mg/kg every two weeks.

In HAVEN 4, ABR was 1.7 (95% CI, 0.82 to 3.68).

Treated Spontaneous Bleeds

In HAVEN 3, the secondary outcome related to ABR ratio for treated spontaneous bleeds demonstrated a statistically significant reduction in bleeding for emicizumab at both 1.5 mg/kg weekly and 3 mg/kg every two weeks compared with no prophylaxis for patients previously treated with episodic FVIII. The ABR ratio between emicizumab at 1.5 mg/kg weekly (ABR = 1.0) and no prophylaxis (ABR = 15.6) was 0.06 (95% CI, 0.025 to 0.151; P < 0.0001), in favour of emicizumab at 1.5 mg/kg weekly. The ABR ratio between emicizumab at 3 mg/kg every two weeks (ABR = 0.3) and no prophylaxis (ABR = 15.6) was 0.02 (95% CI, 0.006 to 0.056; P < 0.0001), in favour of emicizumab at 3 mg/kg every two weeks.

In HAVEN 4, the ABR was 0.6 (95% CI, 0.27 to 1.53).

Treated Target Joint Bleeds

In HAVEN 3, the ABR ratio for treated target joint bleeds between emicizumab at 1.5 mg/kg weekly (ABR = 0.6) and no prophylaxis (ABR = 13.0) was 0.05 (95% CI, 0.016 to 0.143; P < 0.0001), in favour of emicizumab at 1.5 mg/kg weekly. The ABR ratio between emicizumab at 3 mg/kg every two weeks (ABR = 0.7) and no prophylaxis (ABR = 13.0) was 0.05 (95% CI, 0.018 to 0.147; P < 0.0001), in favour of emicizumab at 3 mg/kg every two weeks .

In HAVEN 4, the ABR was 1.0 (95% CI, 0.31 to 3.26).

The ABR ratios for treated bleeds and all other bleeding outcomes (i.e., all bleeds, treated joint bleeds, treated spontaneous bleeds, treated target joint bleeds) in both the HAVEN 3 and HAVEN 4 studies were considered to be clinically relevant according to clinical experts consulted for this review (although no statistical hypothesis testing was performed in HAVEN 4).

HRQoL

The Haem-A-QoL Physical Health subscore was a secondary outcome in HAVEN 3. The difference in adjusted mean Haem-A-QoL Physical Health subscore at week 25 between the emicizumab at 1.5 mg/kg weekly and no prophylaxis groups was 12.51 (95% CI, –1.96 to 26.98; P = 0.891). Given that statistical significance was not achieved, statistical testing according to the pre-specified hierarchy was stopped before the assessment of emicizumab at 3 mg/kg every two weeks. Therefore, the potential effect of emicizumab on improved quality of life in patients without FVIII inhibitors remains unknown.

Patient Preference:

HAVEN 3 and HAVEN 4 provided descriptive results of patient preference assessed via the EmiPref and SQ-ISHI. Results showed a consistent patient preference for treatment with emicizumab compared with patients' previous hemophilia treatment (FVIII). Although this finding is consistent with expectations of patients and clinicians consulted for this review, it should be noted that the EmiPref was a scale developed by the sponsor, and both scales were not validated and had no recognized MID.

Harms (Safety)

In HAVEN 3, adverse events (AEs) occurred in 94.4% of patients in the emicizumab at 1.5 mg/kg weekly group, 85.7% in the emicizumab at 3 mg/kg every two weeks group, 50.0% in the no prophylaxis arm, and 87.3% in the previous FVIII prophylaxis (emicizumab at 1.5 mg/kg weekly) arm. In HAVEN 4, 73.2% of patients treated with emicizumab at 6 mg/kg every four weeks experienced an AE. In both studies, the most common AEs were attributed to injection site reactions. Notable harms identified in the protocol for this review included thrombotic events, injection site reaction, hypersensitivity reactions, inhibitor development, and blood-borne infections. The only notable harms reported in HAVEN 3 and HAVEN 4 were injection site reactions, which occurred in 25.0% of patients in the emicizumab at 1.5 mg/kg weekly group, emicizumab at 20.0% in the 3 mg/kg every two weeks group, 12.5% in the no prophylaxis arm, and 31.7% in the previous FVIII prophylaxis (emicizumab at 1.5 mg/kg weekly) arm. In HAVEN 4, 22.0% of patients treated with emicizumab at 6 mg/kg every four weeks experienced an injection site reaction.

Throughout HAVEN 3 and HAVEN 4, there were no instances of de novo inhibitor development detected in patients who tested negative for inhibitors (titer < 0.6 chromogenic Bethesda unit/mL) at baseline.

In HAVEN 3, serious AEs (SAEs) occurred in 2.8% of patients in the emicizumab at 1.5 mg/kg weekly group, 8.6% in the emicizumab at 3 mg/kg every two weeks group, 0% in the no prophylaxis arm, and 12.7% in the previous FVIII prophylaxis (emicizumab at 1.5 mg/kg weekly) arm. In HAVEN 4, 2.4% of patients treated with emicizumab at 6 mg/kg every four weeks experienced an SAE. No SAEs occurred in more than one patient per arm. No patients died in the studies.

Indirect Treatment Comparisons

In the absence of direct evidence comparing emicizumab and rFVIII prophylaxis, the sponsor conducted an NMA in patients with severe hemophilia A without inhibitors. The NMA compared the efficacy of emicizumab (1.5 mg/kg weekly and 3.0 mg/kg every two weeks) with rFVIIIFc (Elocta/Eloctate), rFVIII (Kovaltry), rFVIII-FS (Kogenate), and rFVIII (Advate) for prophylactic treatment of patients with hemophilia A without inhibitors. The only outcome analyzed was total treated bleeds. The NMA was conducted using a Bayesian framework. Random effects models were chosen as the base case for the total treated bleed outcomes because of various heterogeneity across the five included trials. The between-study variance could not be accurately estimated due to the small number of studies available; therefore, informative priors were used. Total treated bleeds were modelled as a bleed rate and fitted using a generalized linear model with a log link Poisson likelihood. Model inputs included total treatment exposure in person-years and number of bleeding events.

In terms of total treated bleeds, results of the NMA suggest that both emicizumab prophylaxis regimens (1.5 mg/kg weekly and 3.0 mg/kg every two weeks) were associated with a reduction (64% and 69% reduction, respectively) compared with rFVIII prophylaxis in patients with severe hemophilia A without inhibitors.

The NMA was limited by the small number of trials included in the analysis (N= 4 for the base-case analysis). There was a high degree of heterogeneity across the included studies, including the variable severity of hemophilia A, different comparator FVIII products (e.g., long-acting vs. short-acting FVIII) used in different trials. inconsistent or unclear definitions of the bleed outcomes (i.e., the treated bleed), variable outcome estimation time points across trials, and differences in the study design (e.g., randomization vs. partial randomization, blind vs. open label, parallel vs. crossover). In addition, no NMA was performed for safety outcomes, and no evidence for children younger than 7 years old was included in the NMA.

In conclusion, the sponsor-submitted NMA suggested that emicizumab prophylaxis was associated with a reduction of bleed rates compared with FVIII products prophylaxis in the treatment of patients with severe hemophilia A without inhibitors. These results were aligned with those observed in patients previously treated with FVIII prophylaxis (Arm D) in the HAVEN 3 trial. However, due to

various methodological limitations, no robust conclusions on the comparative clinical efficacy and safety profile of emicizumab prophylaxis regimens versus rFVIII prophylaxis in patients with hemophilia without inhibitors can be drawn.

Cost and Cost-Effectiveness

The sponsor's submitted price for emicizumab is $3,661.52 per 30 mg/mL vial, $7,323.04 per 60 mg/0.4 mL vial, $12,815.31 per 105 mg/0.7 mL vial, and, $18,307.59 per 150 mg/mL vial. The recommended regimen is a loading dose of 3 mg/kg for the first four weeks, followed by maintenance treatment with dosage based on the patient's weight and age. Adolescent and adult patients 40 kg or more can receive 1.5 mg/kg weekly, 3 mg/kg every two weeks, or 6 mg/kg every four weeks; pediatric patients can receive 1.5 mg/kg once weekly or 3 mg/kg every two weeks. At the sponsor's submitted price, for patients weighing 80 kg, the annual cost of emicizumab is $822,272 in the first year and $763,688 thereafter.

The sponsor submitted a cost-utility analysis comparing emicizumab with FVIII prophylaxis and on-demand use of FVIII prophylaxis in patients with severe hemophilia A without inhibitors. The analysis was conducted from the perspective of the Canadian publicly funded health care system over a lifetime time horizon (98 years; starting age two years). A Markov state-transition model was submitted based on two health states (alive with hemophilia A and death), with a one-year model cycle length. Patients had the risk of dying during each model cycle, dependent on their treatment and their age. Patients alive could experience zero, one, two, or three or more bleeds per year. Annualized bleed rates were sourced from the HAVEN 3 trial. Health state utilities were derived from a de novo time trade-off vignette study conducted on the Canadian general public. Drug acquisition costs for the comparators were sourced from the Patented Medicine Prices Review Board (PMPRB). Other costs (i.e., hospitalization, AEs) were taken from a variety of sources. In the sponsor's base case, emicizumab was more costly and more effective than FVIII prophylaxis and on-demand FVIII therapy; the ICER of emicizumab was $1.66 million per QALY gained compared to on-demand therapy.

CADTH identified several key limitations with the submitted analysis:

- The model structure does not accurately capture the clinical disease pathway and the effects of treatments appropriately. For instance, rather than employing transition probabilities to describe how patients move between different bleeding strata over time, a fixed proportion was assumed to apply across all time periods.
- The target population of the model (patients with severe hemophilia A without inhibitors) does not reflect the Health Canada indication (i.e., hemophilia A patients of all disease severities) nor the sponsor's reimbursement requested population (i.e., severe patients, and mild or moderate patients who meet specific eligibility criteria). Furthermore, although HAVEN 3 did not recruit patients younger than 12 years, the sponsor's base case assumed patients entered the model at the age of two years.
- Comparative treatment efficacy for FVIII prophylaxis was sourced from a non-randomized arm of the NIS trial and, therefore, reflects a naïve clinical comparison.
- Dispensing of treatment was assumed to be at the closest milligram. This does not reflect clinical practice in which treatment is dispensed to the nearest vial size to minimize wastage.
- Treatment-specific utility estimates were applied, which double-counted the utility decrement associated with FVIII prophylaxis.
- The sponsor included the disutility associated with arthroplasty.
- Average patient weight in the model was underestimated, resulting in lower costs of treatment.

CADTH attempted to address some of the identified limitations: changing the patient starting age in the model to reflect HAVEN 3, adjusting dispensing to the nearest vial size, setting the baseline patient utility equal across treatments, attaching a disutility to arthroplasties, and revising patients' weight to reflect what was observed in HAVEN 3. In the CADTH base case, emicizumab was found to have an ICER of $5.53 million per QALY gained compared to FVIII prophylaxis. A price reduction of at least 89% is required for emicizumab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. However, a greater price reduction may be required if the price of FVIII products are lower than the PMPRB published values. CADTH was unable to address several of the limitations, including that the evidence directly comparing emicizumab to prophylactic FVIII was limited due to the absence of clinical evidence, and the limitations associated with the model structure. Because the Health Canada indication for emicizumab and the sponsor's reimbursement request do not align with the modelled population, uncertainty remains to the cost-effectiveness of emicizumab in either population.

CPEC Members

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Irene Sadek, Dr. Yvonne Shevchuk, Dr. Andrew Shih, and Dr. Adil Virani.

November 18, 2020 Meeting

Regrets

None

Conflicts of Interest

None