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CADTH Reimbursement Recommendation

Etranacogene Dezaparvovec (Hemgenix)

Indication: For treatment of adults (aged 18 years of age or older) with Hemophilia B (congenital factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Sponsor: CSL Behring Canada Inc.

Recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Hemgenix?

CADTH recommends that public drug plans reimburse Hemgenix for the treatment of hemophilia B if certain conditions are met.

Which Patients Are Eligible for Coverage?

Hemgenix should only be covered to treat patients (≥ 18 years of age) with moderately severe to severe hemophilia B (circulating coagulation factor IX [FIX] ≤ 2%) if their bleeding requires ongoing prophylactic treatment, their titre of the neutralizing antibody to variant adeno-associated virus 5 (AAV5) is below 1:900, they do not have FIX inhibitors, and if they have not previously received gene therapy to treat hemophilia B.

What Are the Conditions for Reimbursement?

Hemgenix should only be reimbursed if it is prescribed by specialists who are experts in treating hemophilia B and the cost of Hemgenix is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Hemgenix decreased annualized bleeding rates and reduced FIX use compared to routine FIX prophylaxis in adult male patients with moderately severe to severe hemophilia B.
- Hemgenix meets additional needs important to patients because it is a 1-time gene therapy that can restore coagulation factors to clinically effective levels.
- Based on CADTH's assessment of the health economic evidence, Hemgenix does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Hemgenix is estimated to cost the public drug plans approximately $140 million over the next 3 years. The estimated budget impact is highly sensitive to the number of patients eligible for Hemgenix.
- The implementation of Hemgenix may raise ethical and equity considerations related to access because of the resource-intensive nature of gene therapy and the currently limited number of infusion centres across Canada.

Additional Information

What Is Hemophilia B?

Hemophilia B is a lifelong genetic bleeding disorder resulting from a deficiency in FIX that leaves patients at risk for excessive blood loss

Summary

and organ damage. As of 2021, there were more than 700 patients with hemophilia B in Canada.

Unmet Needs in Hemophilia B

Treatments for hemophilia B that improve bleeding outcomes, lead to fewer FIX infusions, minimal needle injections, less stress, less bleeding, and fewer restrictions on activities are needed.

How Much Does Hemgenix Cost?

Treatment with Hemgenix is expected to cost $4,690,000 per patient.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that etranacogene dezaparvovec be reimbursed for the treatment of adults (aged 18 years of age or older) with Hemophilia B (congenital factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

CDEC recognized the rarity of hemophilia B and the unmet needs of patients with this disease who require coagulation factor IX (FIX) prophylaxis. Evidence from a phase III, single-arm, open-label clinical trial (HOPE-B) demonstrated that treatment with etranacogene dezaparvovec decreased annualized bleeding rates (ABR) and reduced the use of FIX infusions in adult male patients with moderately severe to severe hemophilia B (circulating coagulation factor IX [FIX: C] ≤ 2%) compared to the same patients treated with routine FIX prophylaxis during a lead-in period. At the 36-month postdose analysis, the adjusted mean difference (95% CI) in ABR for all bleeding events from month 7 to month 36 was −2.65 (95% confidence interval [CI], −3.83 to −1.47), in favour of etranacogene dezaparvovec compared to FIX prophylaxis. Results for other bleeding outcomes (ABR for spontaneous bleeds, ABR for joint bleeds) and the use of FIX (annualized infusion rate [AIR] and annualized FIX consumption postinfusion of the gene therapy) also showed a benefit with etranacogene dezaparvovec compared to FIX prophylaxis during the follow-up period.

Patients identified a need for effective treatments that improve bleeding outcomes as well as lead to fewer FIX infusions, minimal needle injections, less stress, less bleeding, and fewer restrictions on activities. CDEC concluded that etranacogene dezaparvovec may meet some of these needs since it is a one-time gene therapy designed to provide an alternative active source of endogenous FIX that improves bleeding outcomes and reduces FIX use after treatment. However, the evidence from the HOPE-B trial is associated with uncertainty, as the comparative evidence is nonrandomized and multiple potential sources of bias were identified (e.g., open-label design, self-reported bleeding events, multiplicity not controlled for in later analyses, assumptions of the statistical models used for intrapatient comparisons). Furthermore, while patients expect gene therapy to be effective for at least 10 years, the long-term efficacy of etranacogene dezaparvovec is unknown due to the limited duration of follow-up in the available evidence.

Based on CADTH's base-case analysis, etranacogene dezaparvovec may improve health outcomes and reduce overall health care costs relative to coagulation FIX (recombinant) fc fusion protein and coagulation FIX (recombinant) pegylated nonacog beta pegol. However, at the submitted price, it will take at least 10 years for the acquisition cost of etranacogene dezaparvovec to be offset by cost savings to the health care system, and therefore, be considered cost-neutral. There is limited data to support the long-term efficacy of etranacogene dezaparvovec, a high degree of clinical uncertainty, and the potential for the scope of clinical practice to change during this period. Jurisdictions may wish to consider price reductions and/or other product listing mechanisms to mitigate the long-term financial risk to public payers.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Adults (≥ 18 years of age) who meet all of the following criteria: 1.1. Documented moderately severe to severe hemophilia B based on FIX:C ≤ 2% and bleeding requiring ongoing. prophylactic treatment. 1.2. AAV5 neutralizing antibodies below a threshold of 1:900 titre.	The HOPE-B trial demonstrated that treatment with etranacogene dezaparvovec had a clinical benefit in adult patients who had moderately severe to severe hemophilia B, which was defined as circulating FIX: C ≤ 2% and had been on stable prophylaxis for at least 2 months before screening. Clinical experts indicate that disease severity should be based on FIX:C level as well as the patient's clinical phenotype and clinician judgment regarding their need for treatment to prevent bleeds. The neutralizing antibody threshold (1:900) was determined based on the highest titre recorded in the subgroup of patients in the HOPE-B trial with preexisting AAV5 neutralizing antibodies that showed clinically meaningful increases in FIX activity and the updated analytical validation assay.	Testing for anti-AAV5 neutralizing antibodies will be required before infusion of etranacogene dezaparvovec.
2. Etranacogene dezaparvovec should not be reimbursed in patients who meet any of the following criteria: 2.1. Presence of FIX inhibitors. 2.2. Previous receipt of gene therapy for the treatment of hemophilia B.	Patients were excluded from the HOPE-B trial if they had a prior history of FIX inhibitors or a positive FIX inhibitor test. Patients previously dosed with a gene therapy were excluded from the HOPE-B trial. Clinical experts noted that if a gene therapy uses an AAV vector, then the patients will develop neutralizing antibodies against the AAV vector post-treatment.	In case of a positive test for alloantibodies against FIX, a re-test within 2 weeks should be performed. If both tests are positive, the patient should not receive etranacogene dezaparvovec.
Renewal		
3. Treatment with etranacogene dezaparvovec is a one-time therapy.	Etranacogene dezaparvovec is administered as a single-dose, and gene therapy re-treatment has not been established as an efficacious strategy at this time.	—
Prescribing		
4. Etranacogene dezaparvovec must be prescribed by specialists who have expertise in treating hemophilia B.	This is to ensure that etranacogene dezaparvovec is prescribed for the most appropriate patients and that adverse effects are managed appropriately.	Etranacogene dezaparvovec should be prescribed based on the judgment of a multidisciplinary team, which is organized by a hemophilia comprehensive treatment centre and may consist of specialists such as a hematologist with experience in treating hemophilia patients, a physiotherapist to assess joint function, a hepatologist for liver related issues, pharmacy support, and an HIV specialist if the patient is HIV positive.

Reimbursement condition	Reason	Implementation guidance
Pricing		
5. A reduction in price	The committee noted that due to the high degree of uncertainty regarding long-term efficacy, a price reduction is required. Although CADTH's base-case analysis suggests etranacogene dezaparvovec may improve health and reduce overall health care costs relative to coagulation FIX (recombinant) fc fusion protein and coagulation FIX (recombinant) pegylated nonacog beta pegol, this result was based on uncertain assumptions concerning long-term efficacy and assumed prices for rFIX. Based on CADTH's analysis, it will take at least 10 years for the cost of etranacogene dezaparvovec to be offset by cost savings to the health care system sufficiently enough to be considered cost-effective at a $50,000 per QALY gained threshold. Price reductions of approximately 49% and 5% would require etranacogene dezaparvovec to be considered cost-neutral after 5 and 10 years, respectively, using assumed prices for rFIX prophylaxis. Further price reductions would be required if the treatment efficacy of etranacogene dezaparvovec was not sustained indefinitely or if the prices paid for FIX prophylaxis were lower than assumed.	—
Feasibility of adoption		
6. The feasibility of adoption of etranacogene dezaparvovec must be addressed	At the submitted price, the incremental budget impact of etranacogene dezaparvovec is expected to be greater than $40 million in year 2 and 3. Further, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's and CADTH's estimates.	—
7. The organizational feasibility of conducting anti-AAV neutralizing antibody testing must be covered by the sponsor.	Neutralizing antibody testing is required to determine eligibility for etranacogene dezaparvovec.	—

AAV = adeno-associated virus; AAV5 = adeno-associated virus of serotype 5; FIX = coagulation factor IX; rFIX = recombinant coagulation factor IX; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet needs:** Due to the uncertainty associated with the submitted evidence, CDEC deliberated on etranacogene dezaparvovec considering the criteria for significant unmet needs described in section 9.3.1 of the *Procedures for CADTH Reimbursement Reviews*. CDEC noted that hemophilia B is a rare and severe disease, and the committee concluded that the limitations and uncertainty of the evidence

were balanced with the significant unmet need and the condition's rarity. Overall, CDEC concluded that the available evidence reasonably suggests that etranacogene dezaparvovec has the potential to reduce bleeding rates and the use of FIX prophylaxis. The GRADE assessment of selected outcomes from the HOPE-B trial's evidence concluded with low certainty that etranacogene dezaparvovec may decrease ABRs and reduce the use of FIX infusions; the evidence is uncertain about the effect of etranacogene dezaparvovec on harms, joint health, and patient-reported outcomes.

- **Need for new treatments:** CDEC discussed which patients with hemophilia B have the greatest need for gene therapy to treat their disease. In consultation with clinical experts, CDEC considered that patients with FIX: C ≤ 2% and bleeding history should be prioritized, followed by those with FIX: C ≤ 2% and receiving FIX prophylaxis that controls their bleeding, then FIX: C > 2% with bleeding history, then FIX: C > 2% and receiving FIX prophylaxis, then FIX: C > 2% and no bleeding history or receiving FIX prophylaxis, then patients without bleeding or treatment experience.
- **Long-term efficacy and safety:** According to the patient group input, most patients indicated that they would expect a gene therapy to be effective in preventing bleeding for at least 10 years. Similarly, clinical experts noted that a longer follow-up of 20 years is warranted to determine the long-term efficacy of etranacogene dezaparvovec. Therefore, an important limitation in the results in the pivotal HOPE-B trial is the relatively short duration of follow-up. CDEC determined that the long-term efficacy and safety of etranacogene dezaparvovec remains inconclusive.
- **Indirect evidence:** One indirect treatment comparison (ITC) provided efficacy data on the estimated effect of etranacogene dezaparvovec relative to the following rFIX products used for FIX prophylactic therapy using inverse probability of treatment weighting (IPTW) and unanchored matching-adjusted indirect comparisons (MAIC): recombinant FIX albumin fusion protein (rIX-FP), recombinant factor IX Fc fusion protein (rFIXFc), and pegylated nonacog beta pegol. No conclusions could be drawn on the relative efficacy of the ITC. Interpretation of the effect magnitude is uncertain and hindered by the lack of connected evidence available and potential confounding due to the lack of reporting of potentially influential prognostic and predictive factors. No safety data were reported in the sponsor-submitted ITC, and therefore, no conclusions could be drawn on the comparative safety of etranacogene dezaparvovec to other products based on this evidence.
- **Additional patient needs:** Patients indicated that they hope gene therapy would lead to less stress, fewer restrictions on activities, and make it easier to travel, but CDEC could not definitively conclude that etranacogene dezaparvovec would meet these needs based on the submitted evidence. In addition, patients reported that joint damage caused by repeated internal hemarthroses is the primary physical health impact of hemophilia B. Although health-related quality of life (HRQoL) was assessed in the HOPE-B trial using the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire and joint health was assessed using the Hemophilia Joint Health Score (HJHS), this evidence was noncomparative and therefore no conclusions could be drawn by CDEC regarding the effects of etranacogene dezaparvovec on this outcome.
- **Uncertainty in the economic evaluation:** CDEC discussed the uncertainty in the economic analysis, specifically the absence of robust comparative evidence and limitations associated with the model

structure. Most benefits associated with etranacogene dezaparvovec (90% of incremental QALYs) were accrued after the duration of the HOPE-B trial and rely on assumptions about the sustained long-term benefit relative to rFIX prophylaxis. Further, the sponsor's submitted model structure and related assumptions precluded the ability to account for long-term changes in quality of life related to the number of bleeds (i.e., account for a lower quality of life for patients who have experienced multiple bleed events). These limitations contributed to the uncertainty in the predicted QALYs for etranacogene dezaparvovec.

- **Number of eligible patients**: CDEC discussed the uncertainty in the number of patients with moderately severe to severe hemophilia B in Canada eligible for etranacogene dezaparvovec. Clinical experts consulted by CADTH indicated that some patients who are classified as having mild or moderate disease may have a severe bleeding phenotype, which would require routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Experts noted that the number of patients expected to receive etranacogene dezaparvovec in the next 3 years is uncertain and may be higher than estimated by the sponsor. Should the total number of patients with moderately severe to severe hemophilia B be larger or uptake of etranacogene dezaparvovec be higher than estimated by the sponsor, the budget impact of reimbursing etranacogene dezaparvovec will be greater.
- **Testing requirements:** CDEC noted that testing for anti-AAV5 neutralizing antibodies and the presence of FIX inhibitors will be required to determine whether patients are eligible for treatment with etranacogene dezaparvovec. Regarding the presence of FIX inhibitors, the product monograph states that in case of a positive test for alloantibodies against factor IX, a retest within approximately 2 weeks should be performed. If both the initial test and re-test results are positive for alloantibodies against factor IX, the patient should not receive etranacogene dezaparvovec.
- **Ethical and equity considerations related to hemophilia B and the use of etranacogene dezaparvovec:** CDEC discussed ethical and equity considerations for etranacogene dezaparvovec, including the high burden of care posed by FIX prophylaxis, which may leave patients susceptible to breakthrough bleeds and require restricting daily activities. The committee noted that although very rare, females may experience disparities in access to care, including for gene therapy, as they may be under-recognized or under-diagnosed as living with hemophilia. The committee discussed that despite uncertain long-term safety and efficacy, health equity considerations support accommodating higher uncertainty when determining reimbursement for hemophilia B, which is severe and rare and where there is an unmet need. The committee discussed that a strictly FIX-based eligibility criterion was inconsistent with clinical practice, potentially limiting equitable access for some patients who could benefit from etranacogene dezaparvovec. As a one-time therapy that cannot be terminated or reversed once infused, the committee highlighted the importance of robust informed consent and establishing reasonable expectations regarding long-term effectiveness and potential ineligibility for future gene therapies.
- **Ethical and equity considerations for health systems and implementation:** The committee discussed the importance of addressing potential geographic barriers to equitable access given the limited number of infusion centres in Canada. The committee also discussed that resource constraints,

including personnel shortages, at hemophilia treatment centres in Canada, might limit the capacity to deliver therapy and collect robust registry data on long-term safety and efficacy. CDEC also discussed how the high cost of the therapy challenges health care system sustainability given finite resources, and noted the possible role that alternative funding models may play in the fair distribution of risks and benefits associated with reimbursing a high-cost therapy with uncertain long-term effectiveness. Given the high costs, uncertainty about which patients are most likely to benefit and capacity challenges, the committee discussed the potential need to develop clear, fair criteria to prioritize patients for access to etranacogene dezaparvovec.

Background

Hemophilia is a serious X-chromosome-linked, lifelong genetic disorder that leaves patients vulnerable to blood loss and organ damage due to impaired functioning of the coagulation cascade. Hemophilia B is the second most common type of hemophilia (after hemophilia A) and is characterized by an absence or shortage of coagulation factor IX (FIX) resulting from a mutation in the F9 gene. A FIX deficiency in hemophilia B prevents or reduces the ability of the coagulation cascade to produce fibrin. The severity of hemophilia B generally correlates with the degree of clotting factor deficiency. Moderate and severe hemophilia B cases are defined by the World Federation of Hemophilia as having 1% to 5% and lower than 1% of normal enzymatic FIX activity, respectively. However, according to the clinical experts consulted by CADTH, severity in clinical practice is defined by the patients' phenotype (i.e., tendency to bleed) and not simply their factor activity levels; the decision to initiate prophylaxis with clotting factor concentrates takes into the account their clinical phenotype, factor activity levels, as well as lifestyle and professional activities. As of 2021, there were 704 patients with hemophilia B (with recorded severity) in Canada, 535 of which were adult male patients. Of the adult male patients, 218 had moderate, and 145 had severe hemophilia B. The estimated prevalence at birth per 100,000 males in Canada from 1991 to 2015 was 3.9 for all severities of hemophilia B and 1.3 for severe disease only.

Current treatment strategies for hemophilia B are based on replacing the missing factor and can be done either as needed when bleeding episodes occur (on-demand therapy) or in a preventive manner (prophylaxis). FIX prophylaxis can be administered regularly, to keep the plasmatic FIX levels above a certain threshold (regular prophylaxis) or occasionally, to increase the plasmatic FIX levels in high-risk situations, like physical activity (situational prophylaxis). The goal of prophylaxis is to prevent bleeding in patients with hemophilia while allowing them to live an active life and achieve a quality of life comparable to people without hemophilia.10 According to the clinical experts consulted by CADTH, FIX prophylaxis therapy is the preferred management approach for patients with moderately severe or severe hemophilia.

Etranacogene dezaparvovec has been approved by Health Canada for treating adults (18 years of age or older) with Hemophilia B (congenital factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes. Etranacogene dezaparvovec is an adeno-associated virus (AAV) vector-based gene therapy. It is available as 1×10^{13} genome copies per millilitre (gc/mL), and the dosage

recommended in the product monograph is 2×10^{13} genome copies per kilogram (gc/kg) of body weight after dilution with 0.9% sodium chloride solution (normal saline), administered as a single-dose IV infusion.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III, single-arm, open-label clinical trial (HOPE-B) in adult male patients who had moderately severe to severe hemophilia B (defined as normal circulation FIX ≤ 2%) and 1 ITC
- patient perspectives gathered by 1 patient group, the Canadian Hemophilia Society (CHS)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- a panel of 3 of clinical specialists with expertise in diagnosing and treating patients with hemophilia B
- input from 1 clinician group, the Association of Hemophilia Clinic Directors of Canada (AHCDC)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of relevant ethical issues related to etranacogene dezaparvovec from published literature.

Stakeholder Perspectives

Patient Input

Patient input was gathered by the CHS from an online survey, conducted between July 10 and July 31, 2023. In total, 17 responses were gathered by the CHS. All respondents were affected by severe or moderately severe hemophilia B without inhibitors. In addition, in September 2022, the CHS conducted an online survey of Canadians with severe hemophilia A and B and received 39 responses, among them 31 were with hemophilia A, 7 with hemophilia B and 1 not specified.

Joint damage, primarily to knees, ankles and elbows, caused by repeated internal hemarthroses, was reported to be the primary physical health impact of hemophilia B. Regarding the currently available treatments, 4 patients reported being very satisfied, 7 satisfied, 5 neither satisfied nor dissatisfied, and 1 very dissatisfied in the 2023 CHS survey. Patients from this survey noted that treatments greatly complicate their everyday life, travel, and leisure activities. They also mentioned the difficulty in infusion due to vein visibility, poor vein issues, and side effects. Patients also reported socioeconomic problems they face due to regular visits, such as missing work due to visits, travel and insurance issues, and access issues.

Patients hope gene therapy will lead to fewer FIX infusions, minimal needle injections, less stress, less bleeding, fewer restrictions on activities, and make it easier to travel. In addition, about 63% of the respondents from the 2022 survey indicated they expected gene therapy to be effective in preventing bleeding for at least 10 years. The 2022 survey asked if people would receive gene therapy knowing that there would be frequent blood draws in the weeks and months following administration and they would need

to be followed up in a registry for 10 to 20 years. In response, 66% answered yes, 10% answered no and 24% indicated they did not know.

The CHS mentioned that a small number (likely close to 5) of individuals living in Canada have undergone gene therapy for hemophilia B, but the CHS knows nothing about their experience outside preliminary data from the trials.

Clinician Input

Input From Clinical Experts Consulted by CADTH

According to the clinical experts consulted by CADTH, there are several unmet needs for hemophilia B. First, people with hemophilia B have a life disadvantage and quality of life disadvantage compared to the general population as no treatment is available to reverse the course of the disease. In addition, a therapy that reduces treatment burden (e.g., recurrent IV injections, delayed/missed doses and overall suboptimal treatment due to poor venous access and difficulties in preparing FIX regimen) and improves adherence is needed.

The clinical experts consulted by CADTH noted that the current standard of care (SOC) in Canada for hemophilia B is the IV replacement therapy with the missing clotting factor (i.e., FIX), and unlike hemophilia A there are currently no approved subcutaneous nonfactor therapies for patients with hemophilia B. The clinical experts noted that etranacogene dezaparvovec is a gene therapy for hemophilia B that would provide to be a potential curative option (i.e., a long-term phenotypic cure) by addressing the underlying disease process, which may represent a shift in the current treatment paradigm.

The clinical experts consulted by CADTH noted that it is conceivable to give priority to those patients who have a severe bleeding phenotype, difficult venous access/high treatment burden from FIX prophylaxis, those who have recurrent bleeds despite prophylaxis/challenges in being adherent to prophylaxis regimen, need to have sustained FIX levels because of comorbidities (e.g., joint disease, cardiovascular issues that require antiplatelets/anticoagulants). Eligible patients should meet the criteria for neutralizing antibodies (nAbs) against FIX and AAV. The clinician would also complete an assessment of patient eligibility based on clinical judgment and lab tests (e.g., complete blood count and differential, liver/kidney function, FIX activity and FIX inhibitor); other tests required are for infectious diseases, including HIV, hepatitis B virus, and hepatitis C virus. According to the clinical experts consulted by CADTH, etranacogene dezaparvovec should not be given to pediatric patients with hemophilia B (< 18 years), while there is no concern using etranacogene dezaparvovec in hemophilia B patients aged 65 years and older.

The clinical experts consulted by CADTH noted that the most important assessment for treatment response is to monitor patients' bleeding to observe whether etranacogene dezaparvovec prevents bleeding events and allows patients to live the lifestyle they want without concern for the risk of bleeding. The clinical experts consulted by CADTH noted that FIX activity level may also be monitored for assessing response to treatment, allowing clinicians to determine the degree to which the deficiency in FIX has been corrected by etranacogene dezaparvovec. The clinical experts consulted by CADTH noted that follow-up should focus on both efficacy and safety through clinical follow-ups (e.g., checking patients' bleeding events and joint status

via phone or virtual check-up) and lab tests (e.g., liver enzymes, FIX activity levels, liver ultrasound to detect hepato-carcinomas). The length of follow-up for hepatic function and FIX activity levels postinfusion of etranacogene dezaparvovec should be lifelong.

To define treatment failure of etranacogene dezaparvovec, the clinical experts consulted by CADTH noted that the composite of FIX level (e.g., patient's baseline FIX level before receiving etranacogene dezaparvovec) and return to prophylaxis with hemostatic therapy (e.g., return to the regular administration of prohemostatic products to prevent any bleeding episode for at least 6 months per year) could be used to determine whether there is a treatment failure occurred in patients treated with etranacogene dezaparvovec. According to the clinical experts consulted by CADTH, etranacogene dezaparvovec should be prescribed based on the judgment of a multidisciplinary team (e.g., consisting of specialists such as a hematologist with experience in treating hemophilia patients, a physiotherapist to assess joint function, a hepatologist for liver related issues, pharmacy support, and an HIV specialist if the patient is HIV positive), and can be administered in a specialty clinic in the outpatient setting, with longitudinal follow-up.

Clinician Group Input

A total of 8 clinicians from the AHCDC provided input for the CADTH review of etranacogene dezaparvovec. AHCDC highlighted some unmet needs for persons with hemophilia with the severe bleeding phenotype, specifically hemophilia B. AHCDC mentioned that with currently available treatments in Canada, persons with hemophilia B are dependent on regular IV infusions of FIX to prevent and treat bleeding for their whole life. In addition, AHCDC noted there could be a major challenge with frequent venipuncture to routine prophylaxis for patients with poor venous access, as well as long-term complications with the placement of a central venous catheter, including risks of infection, bleeding, thromboembolism, and loss of function requiring removal.

AHCDC noted that gene therapy provides a possible long-term phenotypic cure for persons with hemophilia B. If effective, the new treatment option could provide a one-time treatment leading to sustained FIX production. This may represent a paradigm shift in the treatment of hemophilia B. AHCDC also mentioned that in contrast to patients with hemophilia A, who have the option of emicizumab, patients with hemophilia B have no current alternatives to coagulation factor concentrates outside of clinical trials, making the need for gene therapy greater for hemophilia B patients.

AHCDC indicated that eligible candidates for the gene therapy under review include those with clinically severe bleeding phenotype requiring prophylaxis, no history of inhibitory antibodies, no significant comorbidities, and anti-AAV nAb titre less than 1:900. The group also added that patients with hemophilia who are not currently receiving prophylactic therapy (e.g., due to poor venous access, or adherence issues with routine prophylaxis), but who experience repeated, serious spontaneous bleeding episodes, or have a history of life-threatening hemorrhage, are also candidates for gene therapy.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Public drug plans do not fund the proposed comparators, which are FIX replacement products provided via Canadian Blood Services. Funding for these agents ultimately flows from separate provincial/territorial mechanisms/programs.	This is a comment from the drug plans to inform expert committee deliberations.
Considerations for initiation of therapy	
The indication includes patients "who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes." In the pivotal trial (HOPE-B), patients had to have > 150 previous exposure days of treatment with FIX and had been on stable prophylaxis for at least 2 months before screening. Questions for clinical experts/CDEC: • Is there any minimum duration of time patients should be on FIX therapy before being eligible for reimbursement with etranacogene dezaparvovec? • If the concept of "stable prophylaxis" is introduced into any reimbursement criteria, how should this be defined?	According to the clinical experts consulted by CADTH, the rationale for setting a minimum duration of treatment with FIX in the HOPE-B trial was mostly due to safety concerns regarding developing inhibitors against FIX. The clinical experts noted that patients having > 150 previous exposure days of treatment lifetime with FIX is a reasonable duration, and the likelihood of excluding patients who do not meet this criterion but would have benefited from etranacogene dezaparvovec is very low. The clinical experts consulted by CADTH noted that patients who require prophylaxis do not necessarily mean patients have to be on 'stable prophylaxis' to be eligible for etranacogene dezaparvovec, and thus the concept of 'stable prophylaxis' should not be introduced into the reimbursement criteria. The clinical experts noted that requiring patients to be on 'stable prophylaxis' was reasonable for selecting participants in the clinical trial setting but not in the real-world setting because using "stable prophylaxis" as a reimbursement criterion in the real world would prevent some patients from benefiting from etranacogene dezaparvovec. For instance, although all patients with severe hemophilia B should be on prophylaxis, some of these patients may have difficulties complying with stable or routine FIX prophylaxis prescribed (e.g., difficult veins, having trouble getting access to FIX) but may benefit more from etranacogene dezaparvovec because they are not able to do stable/routine prophylaxis.
In the pivotal trial (HOPE-B), patients had to have severe or moderately severe FIX deficiency (defined as ≤ 2% of normal circulating FIX) and the indication notes there is no clinical experience in patients with FIX activity > 2%. Question for clinical experts/CDEC: • Are there any instances where treatment of individuals with mild or moderate disease (and levels > 2% of normal circulating FIX) would be considered appropriate?	According to the clinical experts consulted by CADTH, the severity of hemophilia B in clinical practice is defined by the patients' phenotype (i.e., tendency to bleed) and not only their factor activity levels; the decision to initiate prophylaxis with clotting factor concentrates takes into the account patients' clinical phenotype, factor activity levels, as well as lifestyle and professional activities. In this context, there will be a small number of patients who may have a FIX level > 2% but would

Implementation issues	Response
	benefit from etranacogene dezaparvovec because of severe bleeding phenotype and/or lifestyle.
It is expected a CADTH recommendation will be issued for another gene therapy for hemophilia B (fidanacogene elaparvovec) before etranacogene dezaparvovec is reviewed by CDEC. The drug plans request that CDEC considers alignment with the initiation criteria for fidanacogene elaparvovec, if applicable and appropriate.	This is a comment from the drug plans to inform expert committee deliberations.
Considerations for continuation or renewal of therapy	
The product is proposed as "a single-administration gene therapy that provides long-term prevention of hemophilia-related bleeds and eliminates the need for FIX prophylaxis therapy in most adult patients with hemophilia B." Question for clinical experts/CDEC: Are there any instances where a second dose would be considered appropriate? If so, what would be an appropriate interval before administering the second dose?	The clinical experts consulted by CADTH noted that nAbs against AAV5 will be developed from the first dose of etranacogene dezaparvovec, and it is not possible under current technology to give a second dose to a patient. The clinical experts consulted by CADTH further noted that if in the future technology could offer solutions to the antibody response issue, a second dose may be useful for patients whose FIX expression has been declining years after receiving the first dose of etranacogene dezaparvovec.
Therapy will not be continued, per se, as it is a single-administration drug. However, there may be a need to confirm a long-term response to therapy. Questions for clinical experts/CDEC: • How should the clinically meaningful response be defined using objective parameters (including the need for FIX)? • How long should follow-up last to confirm a clinically meaningful response is maintained?	The clinical experts consulted by CADTH noted that objective parameters to assess treatment response included number of bleeds, FIX level (surrogate outcome), return to FIX prophylaxis and FIX consumption. The clinical experts consulted by CADTH further noted that the composite of FIX level (e.g., patient's baseline FIX level before receiving etranacogene dezaparvovec) and return to prophylaxis with hemostatic therapy (e.g., the definition provided by the HOPE-B trial) could be used to determine whether there is a treatment failure occurred in patients treated with etranacogene dezaparvovec. According to the clinical experts consulted by CADTH, ideally, follow-up should last a lifetime. The experts further noted that 20 years may be a reasonable duration for confirming a clinically meaningful response is maintained.
Considerations for prescribing therapy	
The sponsor notes: • Etranacogene dezaparvovec must be prescribed and administered in a clinical treatment centre (a hemophilia treatment centre) by a health care professional with experience in treating hemophilia B. • They are convening national advisory boards with key hemophilia treatment centres and health care personnel (clinicians, nurses and pharmacists) to assess training needs for gene therapy infusions. • They will be utilizing the national network of hemophilia treatment centres managed by the Association of Hemophilia Clinic Directors of Canada (https://www.ahcdc.ca/) and that these centres of excellence (https://www.hemophilia.ca/-	This is a comment from the drug plans to inform expert committee deliberations.

Implementation issues	Response
treatment-centres-by-province/) will be screened and offered the opportunity to receive gene therapy infusion training and product support for nursing and pharmacy. ◦ The submission indicates that in the first year, there will only be 4 treatment centres (1 each in Alberta, British Columbia, Ontario, Quebec) and this number will expand in years 2 (14 centres) and 3 (16 centres).	
Another gene therapy for hemophilia B (fidanacogene elaparvovec) is in the pipeline. Question for clinical experts/CDEC: • Are there any instances where a dose of etranacogene dezaparvovec would be considered appropriate after a patient receives fidanacogene elaparvovec (or vice versa)?	The clinical experts consulted by CADTH noted that, under current technology, it is impossible to give etranacogene dezaparvovec to a patient who has received fidanacogene elaparvovec or vice versa. Both etranacogene dezaparvovec and fidanacogene elaparvovec were developed using an AAV vector, which will cause patients to develop nAbs against the AAV vector post-treatment. According to the clinical experts consulted by CADTH, although the AAV vectors used by etranacogene dezaparvovec and fidanacogene elaparvovec are not exactly the same, there still will be a very high proportion of cross reactivity between AAV vectors.
It is expected a CADTH recommendation will be issued for another gene therapy for hemophilia B (fidanacogene elaparvovec) before etranacogene dezaparvovec is reviewed by CDEC. The drug plans request that CDEC considers alignment with the prescribing criteria for fidanacogene elaparvovec, if applicable and appropriate.	This is a comment from the drug plans to inform expert committee deliberations.
Generalizability	
The pivotal trial (HOPE-B) listed numerous exclusion criteria, but the product monograph does not list any related contraindications to therapy. The pivotal trial only included male patients, and the product monograph notes, "Etranacogene dezaparvovec is not intended for administration in women." Question for clinical experts/CDEC: • Which, if any, of the pivotal trial exclusion criteria should be used for determining eligibility for treatment? • If a female patient otherwise met the characteristics of the approved indication/reimbursement request, would treatment be considered appropriate?	According to the clinical experts consulted by CADTH, many factors need to be considered before initiation of etranacogene dezaparvovec to identify patients who are likely to benefit from etranacogene dezaparvovec. In general, the decision should be based on the judgment the treating clinician via discussion with patients and their referring centres. The clinical experts consulted by CADTH highlighted several criteria that must be evaluated when determining a patient's eligibility, such as anti-AAV5 nAb status, status of nAbs against FIX (FIX inhibitors), poor liver function, and allergy to corticosteroids. The clinical experts consulted by CADTH noted that some exclusion criteria used by the pivotal HOPE-B trial, which were reasonable in the clinical trial setting, may not be applicable in real-world clinical practice. For instance, HOPE-B excluded patients who had a history of an allergic reaction to FIX products. However, in the real world, these patients may be eligible for etranacogene dezaparvovec if they are only allergic to the components in the FIX products other than FIX protein. Otherwise, according to the clinical experts consulted by CADTH, if patients are allergic to all available FIX products and, in the meantime, ineligible for gene therapy, then there

Implementation issues	Response
	will be no treatment options to offer these patients. According to the clinical experts consulted by CADTH, another exclusion criterion of HOPE-B — having a history of nAbs against FIX – may alone-not serve as the basis of excluding patients from receiving etranacogene dezaparvovec in the real world. In general, the clinical experts consulted by CADTH noted that treatment effects are not expected to be different between males and females due to the same underlying mechanism of disease, and female patients who would need etranacogene dezaparvovec are very rare. However, the clinical experts consulted by CADTH also noted that unless the safety risk of etranacogene dezaparvovec on female reproduction becomes clearer, it may not be appropriate for female patients at childbearing ages to receive etranacogene dezaparvovec.
The approved indication is specific to adults. The originally proposed indication, but not the approved indication, specified that patients have preexisting neutralizing AAV5 antibody titre below 1:900. The product monograph notes, "Based on information obtained from the phase III CT-AMT-061-02 clinical study *(HOPE-B)*, a threshold for an acceptable AAV5 neutralizing titre has been established to screen patients for eligibility to receive etranacogene dezaparvovec"; however, the product monograph does not appear to include a specific threshold. Questions for clinical experts/CDEC: • Should pediatric patients be considered for reimbursement? • What neutralizing AAV5 antibody titre threshold should be used for determining treatment eligibility and when should it be measured in relation to drug administration?	The clinical experts consulted by CADTH noted that etranacogene dezaparvovec should not be given to pediatric patients given the lack of evidence. The clinical experts consulted by CADTH were aware of the sponsor's clarification on the titre threshold of anti-AAV5 nAbs, which is < 1:900. The clinical experts consulted by CADTH agreed that selection of eligible patients, if etranacogene dezaparvovec were to be publicly reimbursed, should follow the threshold 1:900. The clinical experts consulted by CADTH noted that the anti-AAV5 titre should be measured as close as possible before infusion of etranacogene dezaparvovec.
Care provision issues	
The submission notes that continued hemostatic support with exogenous human FIX may be required during the first weeks after etranacogene dezaparvovec administration to provide sufficient FIX coverage for the initial days post-treatment. Corticosteroid treatment is recommended for those who experience transaminitis after receiving etranacogene dezaparvovec.	This is a comment from the drug plans to inform expert committee deliberations.
Neutralizing AAV5 antibody testing is required for eligibility (the submission notes, "A validated assay for neutralizing AAV5 antibodies approved for etranacogene dezaparvovec should be used"). However, it is unclear how widely such testing will be available or who will cover the associated costs.	This is a comment from the drug plans to inform expert committee deliberations.
System and economic issues	
The submission indicates reimbursement would result in an incremental pan-Canadian cost of $15.44 million in Year 1, $24.70 million in Year 2, and $22.62 million in year 3, for a 3-year total incremental cost of $62.72 million. The sensitivity analyses	This is a comment from the drug plans to inform expert committee deliberations.

Implementation issues	Response
estimated the 3-year total incremental costs could range from $31.36 million to $94.08 million.	
Costs related to required laboratory testing should be considered. The submission notes that several tests are required for patient selection purposes, including neutralizing AAV5 antibody titre (as noted above), assay for FIX inhibitor presence, liver enzymes, and hepatic ultrasound and elastography. In addition, regular monitoring is required after administration of etranacogene dezaparvovec, including liver enzymes, FIX activity, assay for FIX inhibitor presence. Any related travel costs should also be considered.	This is a comment from the drug plans to inform expert committee deliberations.
The sponsor notes: • They are in preliminary discussions with its current patient support provider ([redacted] | [redacted] patient support program) to examine the feasibility of the PSP playing a role in pre and post-treatment screening and follow-up for gene therapy patients. • They are currently evaluating [redacted] support for hemophilia patients who meet screening requirements and who have expressed an interest in undergoing gene therapy infusion [redacted] | [redacted].	This is a comment from the drug plans to inform expert committee deliberations.

AAV5 = adeno-associated virus of serotype 5; FIX = coagulation factor IX; nAb = neutralizing antibody.

Clinical Evidence

One phase III, single-arm, open-label clinical trial (HOPE-B, N = 54) was included in the systematic literature review (SLR) conducted by the sponsor. HOPE-B consisted of a screening phase, lead-in phase, etranacogene dezaparvovec infusion phase, and post-treatment follow-up phase. In HOPE-B, 67 patients of adult male patients, who had moderately severe to severe hemophilia B (defined as normal circulation FIX ≤ 2%) and had been on stable prophylaxis for at least 2 months before screening were enrolled into the lead-in phase, during which patients were receiving continuous FIX prophylaxis and followed up for at least 6 months (i.e., 26 weeks). Those with a history of FIX inhibitors or who tested positive for FIX inhibitors at the last visit of the lead-in period and during the screening period of HOPE-B were excluded. Pre-existing nAbs against adeno-associated virus of serotype 5 (AAV5) was not used as an exclusion criterion in HOPE-B. Thirteen patients discontinued or were excluded during the lead-in phase, and 54 patients from 33 study sites globally received etranacogene dezaparvovec and were followed for efficacy and safety.

The primary objective of HOPE-B was to demonstrate the noninferiority of etranacogene dezaparvovec to reduce ABR for all bleeding events between month 7 and month 18 postinfusion, compared to continuous routine FIX prophylaxis. Other efficacy end points included the proportion of patients with no bleeds, ABR for spontaneous bleeds, ABR for joint bleeds, AIR of FIX replacement therapy, annualized consumption of FIX replacement therapy, HJHS, and PROBE. Safety outcomes such as treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), withdrawal due to adverse events (WDAEs),

mortality, and notable harms (e.g., alanine transaminase [ALT] increased, aspartate aminotransferase [AST] increased) were also reported. Data collected during the lead-in phase served as a comparison against etranacogene dezaparvovec for some efficacy (e.g., ABR for all bleeding events, ABR for spontaneous bleeds, ABR for joint bleeds, AIR, and annualized FIX consumption) and safety outcomes.

Of the 54 patients who received etranacogene dezaparvovec, the majority of patients were white (74.1%) with a mean (standard deviation [SD]) age of 41.5 (15.8) years; 21 (38.9%) had pre-existing nAbs against AAV5 before infusion of etranacogene dezaparvovec. The last testing before infusion of etranacogene dezaparvovec showed that 21 (38.9%) of the 54 patients had a titre between 1:9 and 1:3212 (median: 56.9). Excluding 1 patient with an anti-AAV5 titre greater than 1:3000 (i.e., 1:3212), the remaining 20 patients had a titre between 1:9 and 1:678 (median: 49.1). There were 33 (62.3%) patients with an anti-AAV5 nAb titre below the lower limit of detection (i.e., 1:7).

HOPE-B is ongoing and expected to be completed in 2025. Up to 36-month postdose analysis (data cut-off date: June 6, 2023) were used to support the sponsor's present submission to CADTH.

Efficacy Results

Bleeding Outcomes

From month 7 to month 18 postetranacogene dezaparvovec infusion, 34 of the 54 patients (63.0%) treated with etranacogene dezaparvovec had no bleeds, compared to 14 (25.9%) in the same patients who received FIX prophylaxis during the lead-in phase. The adjusted mean difference (95% confidence interval [CI]) in ABR for all bleeding events between etranacogene dezaparvovec and routine FIX prophylaxis was −2.68 (−3.81 to −1.55) from month 7 to month 18 postetranacogene dezaparvovec infusion, favouring etranacogene dezaparvovec. From month 7 to month 36 postinfusion of etranacogene dezaparvovec, 23 of the 54 patients (42.6%) treated with etranacogene dezaparvovec had no bleeds, compared to 14 (25.9%) in the same patients who received FIX prophylaxis during the lead-in phase. The adjusted mean difference (95% CI) in ABR for all bleeding events from month 7 to month 36 was −2.65 (−3.83 to −1.47), favouring etranacogene dezaparvovec.

The adjusted mean difference (95% CI) in ABR for spontaneous bleeds between etranacogene dezaparvovec and routine FIX prophylaxis was −1.08 (−1.72 to −0.44) from month 7 to month 18 postetranacogene dezaparvovec infusion in favour of etranacogene dezaparvovec. The adjusted mean difference (95% CI) in ABR for spontaneous bleeds from month 7 to month 36 was −0.93 (−1.62 to −0.25), favouring etranacogene dezaparvovec.

The adjusted mean difference (95% CI) in ABR for joint bleeds between etranacogene dezaparvovec and routine FIX prophylaxis was −1.84 (−2.54 to −1.13) from month 7 to month 18 postetranacogene dezaparvovec infusion in favour of etranacogene dezaparvovec. The adjusted mean difference (95% CI) in ABR for joint bleeds from month 7 to month 36 was −1.87 (−2.54 to −1.20), favouring etranacogene dezaparvovec.

Use of FIX Postinfusion of Etranacogene Dezaparvovec

From month 7 to month 18 postetranacogene dezaparvovec infusion, the adjusted mean difference (95% CI) in AIR between etranacogene dezaparvovec and routine FIX prophylaxis was −69.96 (−79.77 to −60.16) which favoured etranacogene dezaparvovec. Similarly, the adjusted mean difference (−69.89; 95% CI, −79.70 to −60.08) in AIR favoured etranacogene dezaparvovec from month 7 to month 36 postetranacogene dezaparvovec infusion. From month 7 to month 36 postetranacogene dezaparvovec infusion, the adjusted mean difference (95% CI) in annualized consumption of FIX replacement therapy between etranacogene dezaparvovec and routine FIX prophylaxis was −3,037.6 (−3,617.4 to −2,457.9) international units per kilogram (IU/kg), in favour of etranacogene dezaparvovec.

Hemophilia Joint Health Score

Change from baseline at month 12 (mean: −1.6; SD: 5.1), month 24 (mean: −2.6; SD: 5.0), and month 36 (mean: −3.0; SD: 7.4) postinfusion of etranacogene dezaparvovec all showed improvements in the HJHS total score in patients treated with etranacogene dezaparvovec.

Patient Reported Outcomes, Burdens and Experiences

Change from baseline at month 12 (mean: 0.040; SD: 0.097) and month 24 (mean: 0.034; SD: 0.113) postinfusion of etranacogene dezaparvovec both showed improvements in the PROBE summary score in patients treated with etranacogene dezaparvovec. Data from month 36 were not available.

Harms Results

The data cut-off date for harm results was June 6, 2023 (i.e., a 36-month data cut-off). Harms results at the 24-month data cut-off were generally consistent.

At 36 months postinfusion of etranacogene dezaparvovec, all patients had at least 1 TEAEs. The system organ classes with the highest incidence of reported TEAEs were infections and infestations (87.0%), followed by musculoskeletal and connective tissue disorders (72.2%) and general disorders and administration site conditions (59.3%). The TEAEs reported in more than 20% of the safety population of HOPE-B were arthralgia (44.4%), headache (33.3%), nasopharyngitis (27.8%), fatigue (27.8%), ALT increased (24.1%), and back pain (22.2%). During the lead-in period (excluding discontinuers), 68.5% patients experienced at least 1 TEAEs. The system organ classes with the highest incidence of reported TEAEs were infections and infestations (35.2%), followed by musculoskeletal and connective tissue disorders (22.2%) and gastrointestinal disorders (13.0%). The only adverse event (AE) reported in more than 10% of the patients was nasopharyngitis (14.8%).

At 36 months postinfusion of etranacogene dezaparvovec, 27.8% of the safety population had at least 1 serious adv TESAEs. The TESAEs most frequently reported in the system organ classes were infections and infestations (7.4%, consisting of 5 events: biloma infection, COVID-19, cellulitis, device-related infection, diverticulitis intestinal hemorrhagic) and musculoskeletal and connective tissue disorders (5.6%, consisting of 3 events: hemarthrosis, musculoskeletal chest pain, osteoarthritis). During the lead-in period (excluding

discontinuers), 7.4% of the patients experienced TESAEs, of which 5.6% were reported in the system organ classes of musculoskeletal and connective tissue disorders.

One patient discontinued the study drug infusion due to an event of hypersensitivity after approximately 10% of the full dose of the study drug was administered; this patient did not have FIX expression. One patient died due to a fatal event of cardiogenic shock 464 days (approximately 15 months) postinfusion of etranacogene dezaparvovec. According to the product monograph,[2] the patient, with numerous cardiovascular and urologic risk factors, aged 75 at screening, died of urosepsis and cardiogenic shock at month 15 postdose (at age 77 years), an event determined not treatment-related.

Postinfusion of etranacogene dezaparvovec, the ALT increase occurred in 24.1% (13/54) of the patients, followed by AST increased (16.7%, 9/54), anemia (9.3%, 5/54), and infusion related reaction (5.6%, 3/54). Only 1 patient had anemia during the lead-in period when receiving FIX prophylaxis.

Critical Appraisal

Overall, the trial design of the pivotal HOPE-B trial (e.g., nonrandomized, open-label, single-arm design) was considered appropriate and acceptable in the field of hemophilia B, although the interpretation of the study findings could be challenging. According to the clinical experts consulted by CADTH, the inclusion and exclusion criteria of HOPE-B were appropriate and reflective of patients they would have expected in clinical practice. It was noted that 67 patients were enrolled in the lead-in phase and only 54 patients were treated with etranacogene dezaparvovec and assessed for efficacy and safety, although it was determined by CADTH that the potential selection bias due to a considerable number of patients being excluded was low. Due to the single-arm, open-label design, reliable assessments of patient-reported outcomes (e.g., HRQoL end points) could not be made. In the primary analyses, the documentation of bleeding events in HOPE-B relied on the use of an electronic diary (e-diary) by patients, which was also reviewed and assessed by the investigator. Based on details provided by the sponsor upon request, CADTH determined that the potential risk of bias that may lead to exaggeration of treatment effects of etranacogene dezaparvovec (i.e., ABR outcomes) was likely low. According to the clinical experts consulted by CADTH, there were no serious concerns with the use of corticosteroids postinfusion of etranacogene dezaparvovec, the conditions for the use of FIX postinfusion of etranacogene dezaparvovec were generally considered appropriate, and the definition of "return to routine FIX prophylaxis" in the context of the HOPE-B trial was acceptable. In HOPE-B, multiple statistical testing was conducted for several end points in a fixed sequential test. However, multiplicity was controlled only for analyses using data from the month 18 data cut-off, not for analyses with data from the month 24 or month 36 data cut-offs, which might have resulted in potential inflation of the type I error rates. There were some concerns about the statistical models/assumptions adopted for bleeding outcomes in HOPE-B, which may pose challenges in interpreting the magnitude of the effect estimates of etranacogene dezaparvovec compared to FIX prophylaxis.

There are several considerations related to the generalizability of the HOPE-B trial. First, evidence from the currently available follow-up period (i.e., 36 months) in HOPE-B may not be adequate to inform long-term efficacy and safety given the expectation of long-lasting effects of etranacogene dezaparvovec. In addition, HOPE-B included patients who had congenital hemophilia B with known severe or moderately severe FIX

deficiency (≤ 2% of normal circulating FIX) and had been on stable prophylaxis for at least 2 months before screening. However, the indication does not restrict on patients with severe or moderately severe hemophilia B (≤ 2% of normal circulating FIX) or require eligible patients to have been on stable FIX prophylaxis for 2 months. According to the clinical experts consulted by CADTH, the eligibility criteria of patients in HOPE-B were generally aligned with the indication. However, the clinical experts consulted by CADTH noted that some patients, including those who have a FIX level greater than 2% and present severe clinical symptoms and those who require but not receiving stable FIX prophylaxis, may also benefit from etranacogene dezaparvovec.

Of note, according to the product monograph of etranacogene dezaparvovec, to be eligible to receive etranacogene dezaparvovec the titre of pre-existing nAbs against AAV5 should be tested. However, patients enrolled in the pivotal HOPE-B trial were not selected based on the titre of pre-existing nAbs against AAV5. Via correspondence with CADTH, the sponsor claimed that a threshold for an acceptable AAV5 nAb, which is below 1:900, is expected to screen patients for eligibility to receive etranacogene dezaparvovec. According to the sponsor, there was no exclusion criterion in HOPE-B regarding the eligibility of patients with anti-AAV5 nAbs. In other words, all patients with detectable pre-existing AAV5 nAbs were enrolled. Regarding how the threshold (1:900) was determined, according to the sponsor, a cut-off at an AAV5 nAb titre of greater than 1:678 was selected based on the highest titre recorded in the subgroup of patients in HOPE-B with pre-existing AAV5 nAbs who showed clinically meaningful increases in FIX activity. The titre 1:678 was obtained from an in vitro cell-based assay custom-developed by the sponsor. The sponsor confirmed with Health Canada that the assay method was later validated to extend the linear measuring range with additional dilutions of the samples to be analyzed, with an improved test accuracy especially at higher titres. The nAb titre value of 678 (rounding off to 1:700), is equivalent to 9-point nAb titre value of 898 (rounding off to 1:900). The new 1:900 titre value is based on the updated nAb analytical validation assay with an extended linear measuring range (9-point dilution curve assay), versus the investigational clinical study assay at 7-point dilution. This does not represent a change in the concentration of the AAV5 nAb in the serum sample, but rather that the improved assay response curve of the validated method yields a comparatively higher titre.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for the Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members: ABR for all bleeding events (including percentage of patients without any bleeds), ABR for spontaneous bleeds, ABR for joint bleeds, AIR, annualized FIX consumption, HJHS, PROBE, and harms. According to the GRADE guidance, nonrandomized comparative evidence starts at low certainty and noncomparative evidence starts at very low certainty. The GRADE summary of findings is presented in

Table 3: Summary of Findings for Etranacogene Dezaparvovec for Patients With Hemophilia B (outcomes with comparative data)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Bleeding outcomes				
ABR for all bleeding events Follow-up: • Months 7 to 18 postinfusion of etranacogene dezaparvovec • Months 7 to 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	**Months 7 to 18 postinfusion of etranacogene dezaparvovec** Number (%) of patients without any bleeds: • Etranacogene dezaparvovec: 34 (63.0) • FIX prophylaxis: 14 (25.9) Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 1.51 (0.81 to 2.82) • FIX prophylaxis: 4.17 (3.20 to 5.44) Adjusted mean difference in ABR (95% CI) • −2.68 (−3.81 to −1.55) **Months 7 to 36 postinfusion of etranacogene dezaparvovec** Number (%) of patients without any bleeds: • Etranacogene dezaparvovec: 23 (42.6) • FIX prophylaxis: 14 (25.9) Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 1.52 (0.81 to 2.85) • FIX prophylaxis: 4.17 (3.20 to 5.44) Adjusted mean difference in ABR (95% CI) • −2.65 (−3.83 to −1.47)	Low[a]	Etranacogene dezaparvovec may result in a decrease in annualized bleeding rate for all bleeding events when compared with FIX prophylaxis.
ABR for spontaneous bleeds Follow-up: • Months 7 to 18 postinfusion of etranacogene dezaparvovec • Months 7 to 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	**Months 7 to 18 postinfusion of etranacogene dezaparvovec** Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 0.44 (0.17 to 1.12) • FIX prophylaxis: 1.52 (1.01 to 2.30) Adjusted mean difference in ABR (95% CI) • −1.08 (−1.72 to −0.44)	Low[a]	Etranacogene dezaparvovec may result in a decrease in annualized bleeding rate for spontaneous bleeds when compared with FIX prophylaxis.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		Months 7 to 36 postinfusion of etranacogene dezaparvovec Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 0.59 (0.25 to 1.40) • FIX prophylaxis: 1.52 (1.01 to 2.30) Adjusted mean difference in ABR (95% CI) • −0.93 (−1.62 to −0.25)		
ABR for joint bleeds Follow-up: • Months 7 to 18 postinfusion of etranacogene dezaparvovec • Months 7 to 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	**Months 7 to 18 postinfusion of etranacogene dezaparvovec** Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 0.51 (0.23 to 1.11) • FIX prophylaxis: 2.34 (1.74 to 3.16) Adjusted mean difference in ABR (95% CI) • −1.84 (−2.54 to −1.13) **Months 7 to 36 postinfusion of etranacogene dezaparvovec** Adjusted ABR (95% CI) • Etranacogene dezaparvovec: 0.47 (0.24 to 0.95) • FIX prophylaxis: 2.34 (1.74 to 3.16) Adjusted mean difference in ABR (95% CI) • −1.87 (−2.54 to −1.20)	Low[a]	Etranacogene dezaparvovec may result in a decrease in annualized bleeding rate for joint bleeds when compared with FIX prophylaxis.
Use of FIX postinfusion of Etranacogene Dezaparvovec				
AIR Follow-up: • Months 7 to 18 postinfusion of etranacogene dezaparvovec • Months 7 to 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	**Months 7 to 18 postinfusion of etranacogene dezaparvovec** Adjusted AIR (95% CI) • Etranacogene dezaparvovec: 2.52 (0.91 to 6.95) • FIX prophylaxis: 72.48 (63.51 to 82.70) Adjusted mean difference in AIR (95% CI) • −69.96 (−79.77 to −60.16) **Months 7 to 36 postinfusion of etranacogene dezaparvovec** Adjusted AIR (95% CI)	Low[a]	Etranacogene dezaparvovec may result in a decrease in annualized infusion rate when compared with FIX prophylaxis.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Etranacogene dezaparvovec: 2.59 (1.04 to 6.43) • FIX prophylaxis: 72.48 (63.51 to 82.70) Adjusted mean difference in AIR (95% CI) • −69.89 (−79.70 to −60.08)		
Annualized FIX consumption (IU/kg) Follow-up: • Months 7 to 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	**Months 7 to 36 postinfusion of etranacogene dezaparvovec** Adjusted mean difference in annualized FIX consumption (95% CI) • −3037.6 (−3617.4 to −2457.9)	Low[a]	Etranacogene dezaparvovec may result in a decrease in total FIX consumption when compared with FIX prophylaxis.
Harms				
TESAEs Mortality ALT increased AST increased Anemia Infusion related reaction Follow-up: • Month 36 postinfusion of etranacogene dezaparvovec	N = 54 (1 single-arm study, with intrapatient comparison)	TESAEs: • Etranacogene dezaparvovec: 278 per 1,000 • FIX prophylaxis: 74 per 1,000 Mortality, n (%): • Etranacogene dezaparvovec: 19 per 1,000 • FIX prophylaxis: 0 ALT increased: • Etranacogene dezaparvovec: 241 per 1,000 • FIX prophylaxis: 0 AST increased: • Etranacogene dezaparvovec: 167 per 1,000 • FIX prophylaxis: 0 Anemia: • Etranacogene dezaparvovec: 93 per 1,000 • FIX prophylaxis: 19 per 1,000 Infusion related reaction increased: • Etranacogene dezaparvovec: 56 per 1,000 • FIX prophylaxis: 0	Very Low[b]	The evidence is uncertain about the effect of etranacogene dezaparvovec on harms outcomes.[c]

ABR = annualized bleeding rate; AIR = annualized infusion rate; ALT = alanine transaminase; AST = aspartate aminotransferase; FIX = coagulation factor IX; CI = confidence interval; IU/kg = international units per kilogram; max = maximum; min = minimum; SD = standard deviation; TESAE = treatment-emergent serious adverse event.

[a]The start point for the study design (single-arm with comparative data) was low certainty. Risk of bias was not rated down. Although not optimal, the study design adopted by HOPE-B was considered to be of sufficiently low risk of confounding and sampling bias. The differences between patients in the proposed indication and patients in pivotal trial were not considered sufficient by the clinical experts consulted by CADTH to result in important differences in the observed effect. Imprecision was not rated down as the improvement was considered clinically meaningful by the clinical experts consulted by CADTH.

[b]The start point for the study design (single-arm with comparative data) was low certainty. Rated down 1 level for imprecision due to the small sample size, although the safety profile was considered acceptable by clinical experts consulted by CADTH.

[c]Based on a comparison between harms data from the lead-in period and harms data from postinfusion of etranacogene dezaparvovec. The median duration of the lead-in phase was 7.129 months (min: 6.05, max: 10.61), The data cut-off date for harm results postinfusion of etranacogene dezaparvovec was June 6, 2023 (i.e., 36-month data cut-off).

Table 4: Summary of Findings for Etranacogene Dezaparvovec for Patients With Hemophilia B (outcomes without comparative data)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Bleeding Outcomes				
HJHS (0 [best] to 124 [worst]) Follow-up: • Month 12 postinfusion of etranacogene dezaparvovec • Month 24 postinfusion of etranacogene dezaparvovec • Month 36 postinfusion of etranacogene dezaparvovec	N = 50 (month 12) N = 45 (month 24) N = 42 (month 36) (1 single-arm study)	**Month 12 postinfusion of etranacogene dezaparvovec** Mean HJHS score (SD) • etranacogene dezaparvovec: 19.5 (16.8) Change from baseline (SD) • −1.6 (5.1) **Month 24 postinfusion of etranacogene dezaparvovec** Mean HJHS score (SD) • etranacogene dezaparvovec: 18.8 (16.3) Change from baseline (SD) • −2.6 (5.0) **Month 36 postinfusion of etranacogene dezaparvovec** Mean HJHS score (SD) • etranacogene dezaparvovec: 16.7 (14.1) Change from baseline (SD) • −3.0 (7.4)	Very Low[a]	The evidence is uncertain about the effect of etranacogene dezaparvovec on HJHS.
PROBE summary score (0 [worst] to 1 [best]) Follow-up: • Month 12 postinfusion of etranacogene dezaparvovec • Month 24 postinfusion of etranacogene dezaparvovec	N = 43 (month 12) N = 41 (month 24) (1 single-arm study)	**Month 12 postinfusion of etranacogene dezaparvovec** Mean PROBE summary score (SD) • etranacogene dezaparvovec: 0.803 (0.158) Change from baseline (SD) • 0.040 (0.097) **Month 24 postinfusion of etranacogene dezaparvovec** Mean PROBE summary score (SD) • etranacogene dezaparvovec: 0.801 (0.140)	Very Low[b]	The evidence is uncertain about the effect of etranacogene dezaparvovec on HJHS.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		Change from baseline (SD) • 0.034 (0.113)		

CI = confidence interval; HJHS = Hemophilia Joint Health Score; MID = minimal important difference; PROBE = Patient Reported Outcomes Burdens and Experience; SD = standard deviation.

[a]In the absence of a comparator arm, certainty of evidence started at very low. The differences between patients in the proposed indication and patients in the pivotal trial were not considered sufficient by the clinical experts consulted by CADTH to result in important differences in the observed effect. There was no MID identified. Imprecision was not rated down as the improvement was considered clinically meaningful by the clinical experts consulted by CADTH.

[b]In the absence of a comparator arm, the certainty of evidence started at very low. Rated down 1 level for risk of bias due to the potential for bias arising from the open-label nature of the study and the subjective nature of the outcome. Indirectness was not rated down as PROBE is commonly used in Canada. Imprecision was rated down 2 levels because change from baseline was not considered clinically relevant by the clinical experts consulted by CADTH.

Indirect Comparisons

Description of Studies

The sponsor submitted an ITC report, containing a feasibility assessment and analysis of etranacogene dezaparvovec relative to 4 comparator therapies: recombinant FIX albumin fusion protein (rIX-FP, Idelvion), recombinant FIX Fc fusion protein (rFIXFc, Alprolix), pegylated nonacog beta pegol (Rebinyn), and nonacog alfa (BeneFIX), using a previously published SLR to identify studies. No information was provided with respect to the search strategy, data extraction process, or quality assessment of included studies. The sponsor concluded that no connected evidence network could be established and assessed the feasibility of unanchored comparisons. For the comparison against rIX-FP, the sponsor had patient-level data and adopted an IPTW approach. For comparisons against rFIXFc and pegylated nonacog beta pegol, only aggregate-level data were available, and the sponsor opted for an unanchored MAIC approach. Further, for rFIXFc and pegylated nonacog beta pegol the primary analysis population of interest, patients receiving prophylaxis, limited information was available with respect to clinical outcomes of interest and clinically relevant covariates. Owing to challenges in reporting data for nonacog alfa, the sponsor noted that significant limitations may confound any conclusions drawn. Accordingly, the sponsor indicated these results as a sensitivity analysis, and comparisons of nonacog alfa are not summarized in this report.

Efficacy Results

For the comparison against rFIXFc, ABR among the unadjusted etranacogene dezaparvovec population (ABR: 0.38; N = 51) was lower than patients receiving rFIXFc (ABR: 2.99; N = 32), corresponding to a relative risk (RR) of 0.13 (95% CI, 0.07 to 0.25). When adjusted for ABR, the sponsor reported a similar trend, with the ABR-adjusted MAIC population of etranacogene dezaparvovec receiving patients (ABR: 0.43; effective sample size [ESS] = 28.2) being lower than among patients receiving rFIXFc (ABR: 2.99; N = 32), corresponding to an RR of 0.14 (95% CI, 0.08 to 0.25). Other efficacy end points were not available in the primary analysis population.

For the comparison against pegylated nonacog beta pegol, unadjusted ABR (0.36; N = 51) was lower for etranacogene dezaparvovec than for pegylated nonacog beta pegol (ABR: 3.33; N = 17) (RR: 0.11; 95% CI, 0.06 to 0.22). A similar trend was seen following univariable adjustment for prior ABR (RR for etranacogene dezaparvovec [ESS = 8.5] relative to pegylated nonacog beta pegol [N = 17]: 0.24; 95% CI, 0.07 to 0.82) and following univariable adjustment for prior FIX product class (RR for etranacogene dezaparvovec [ESS = 21] relative to pegylated nonacog beta pegol [N = 17]: 0.10; 95% CI, 0.03 to 0.27). Other efficacy end points were not available in the primary analysis population.

Comparisons against rIX-FP demonstrated a consistent trend in favour of etranacogene dezaparvovec with respect to ABR, ABR for spontaneous bleeds, ABR for joint bleeds, the proportion of patients with no bleeds, and FIX utilization.

Harms Results

Harms were not assessed in the ITC.

Critical Appraisal

With respect to indirect treatment efficacy, the sponsor-provided ITC reported favourable comparative efficacy for the available outcomes relative to rIX-FP, pegylated nonacog beta pegol, and rFIXFc. These comparisons should be considered uncertain owing to methodological limitations owing to the lack of a common comparator, which necessitated unanchored comparisons. These comparisons rely on strong assumptions of complete reporting and statistical adjustment for all plausible characteristics, which may be effect modifiers or prognostic factors. This assumption cannot be tested, and for the comparison relative to pegylated nonacog beta pegol and rFIXFc, there was a substantial proportion of missing data on key covariates. Accordingly, the results of this ITC are subject to significant uncertainty.

Ethical Considerations

CADTH reviewed patient group, clinician group, clinical expert, and drug program input gathered during this review, as well as relevant literatures, to identify ethical considerations related to the use of etranacogene dezaparvovec for the treatment of adults (aged 18 years of age or older) with hemophilia B (congenital factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

Ethical considerations identified in this review included those related to:

- **Treatment and experiences of hemophilia B:** SOC FIX prophylaxis is physically and psychosocially burdensome for individuals with moderate to severe hemophilia B. This therapy requires frequent IV infusions, which impact quality of life and lead to varying FIX activity levels despite adherence. Additionally, the therapeutic effect of FIX prophylaxis wanes between infusions which leaves individuals vulnerable to bleeds and associated joint damage. This can impact peoples' sense of freedom to fully engage in daily activities. There is an unmet need for a therapeutic option that can reduce the burden of treatment associated with FIX prophylaxis and provide a sustained therapeutic effect that limits the long-term risk of experiencing a bleed.
- **Clinical and economic evidence used in evaluating etranacogene dezaparvovec**: Clinical trial evidence indicated treatment with etranacogene dezaparvovec may result in a clinically relevant reduction in the ABR for all bleeds. Similarly, as of the 36-month data cut provided by the sponsor, 51 of 54 HOPE-B trial participants remained free of FIX prophylaxis. However, there is uncertainty regarding interpretations of the magnitude of benefits and long-term safety and efficacy. This uncertainty challenges clinical and shared decision-making and will require rigorous informed consent. Uncertainty is further exacerbated for females and people with FIX activity greater than 2% as they were excluded from the HOPE-B trial. Similarly, clinical experts indicated that people identified as "Black/African American" were underrepresented in the trial. Though clinical experts assumed trial outcomes would be generalizable to all people with hemophilia B, there is uncertainty about who may benefit beyond the population reflected in the trial. Finally, uncertainty around long-term safety, efficacy and comparative effectiveness limits the ability to accurately model cost-effectiveness and understand opportunity costs associated with reimbursement.

- **Clinical use and implementation of etranacogene dezaparvovec as a gene therapy:** As with other gene therapies, the use of etranacogene dezaparvovec poses potential risks, including transaminitis (9 of 54 HOPE-B trial participants experienced elevated transaminase levels), and theoretical concerns of long-term genotoxicity resulting in cancer. As a one-time infusion that cannot be reversed, clinicians must facilitate a thorough consent process that supports shared decision-making and helps patients weigh potential benefits and harms. These conversations will need to include the consideration of the uncertainty regarding long-term safety and efficacy, the possibility of waning treatment effect resulting in a return to FIX prophylaxis, the ambiguity surrounding determinations of treatment failure, and the development of cross-reactive anti-AAV neutralizing antibodies that may render individuals ineligible for future gene therapies. As it is presently unclear who will benefit from treatment, determining who should receive etranacogene dezaparvovec may be ethically challenging for providers. In particular, the absence of some populations from the HOPE-B trial (e.g., those with FIX activity greater than 2% and females) may incidentally lead to disparities in access if treatment is prioritized for populations for whom some safety and efficacy data are available. Ensuring equitable access to etranacogene dezaparvovec will also require addressing geographic barriers to accessing specialist care and monitoring.
- **Health systems:** Ethical considerations related to the implementation of etranacogene dezaparvovec highlight challenges in fairly allocating limited resources for expensive therapies for rare diseases. Uncertainty around the long-term efficacy and safety of etranacogene dezaparvovec may prompt consideration of alternative payment models (APMs) to manage and redistribute the risks and benefits associated with reimbursing a highly expensive therapy of uncertain benefit for payers and manufacturers. The design of an APM has ethical implications as it impacts the distribution of risks and benefits among parties. It is also necessary to consider the availability and costs of data and clinical infrastructure required to effectively implement an APM. In particular, clinical experts flagged that personnel shortages at HTCs across Canada may impact the capacity to deliver therapy and to collect robust registry data. Uncertainty regarding who will most likely benefit from therapy, potential shortages of the AAV vector used in etranacogene dezaparvovec, or limited delivery capacity at some HTCs may necessitate clear prioritization criteria to facilitate fair and equitable access. Moreover, geographic challenges may require some patients to cross jurisdictions for access, leading to complexities in determining responsible reimbursement jurisdictions for the therapy and associated costs.

Economic Evidence

Table 5: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Adults (aged 18 years or older) with hemophilia B (congenital factor IX deficiency) who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
Treatment	Etranacogene dezaparvovec
Dose regimen	Single IV infusion of 2×10^{13} genome copies per kg of body weight
Submitted price	1×10^{13} vector genomes in 10 mL vials: $4,690,000.00 per administration
Treatment cost	$4,690,000.00 per administration per patient
Comparators	• Coagulation FIX (recombinant) fc fusion protein (Alprolix) • Coagulation FIX (recombinant) nonacog alfa (BeneFIX) • Coagulation FIX (recombinant) pegylated nonacog beta pegol (Rebinyn)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (59 years)
Key data sources	Effectiveness of etranacogene dezaparvovec informed by the HOPE-B trial; effectiveness of rFIX prophylaxis treatments informed by sponsor conducted ITCs.
Key limitations	• The comparative efficacy of etranacogene dezaparvovec is uncertain due to limitations of the evidence comparing etranacogene dezaparvovec to rFIX prophylaxis treatments, including limitations associated with the sponsor-submitted ITC and the pivotal HOPE-B trial (e.g., the nonrandomized comparative design, potential risk of bias in self-recording bleeding events caused by the open-label design, multiplicity was not controlled for in the analyses using the Month 24 and 36 data cut-offs). Additionally, the sponsor's ITC feasibility assessment described several key limitations in reporting in the key coagulation FIX (recombinant) nonacog alfa trial and provided this comparison only as an addendum. • The duration of benefit with etranacogene dezaparvovec, in terms of both bleed rates and the duration that patients would remain FIX prophylaxis-free, is highly uncertain owing to a lack of long-term follow-up data (HOPE-B trial duration was 36 months). Bleed rates for those who received etranacogene dezaparvovec and remained prophylaxis-free were assumed to be consistent with those observed in the HOPE-B trial applied over a lifetime. The sponsor based the duration of benefit for etranacogene dezaparvovec, in terms of time spent rFIX prophylaxis free, on a statistical model that assumed patients would return to rFIX prophylaxis when their FIX activity was ≤ 2%. However, clinical feedback received by CADTH indicated that FIX activity levels are not the primary driver of return to prophylaxis; instead, this will likely be determined by bleed rates and patients' physical activities, and they may return to prophylaxis when their FIX activity levels are greater than 2%. • The HOPE-B trial was restricted to a narrower population than the indicated population. As a result, there is no direct comparative evidence for using etranacogene dezaparvovec in patients with FIX levels greater than 2% but with a severe bleeding phenotype or patients requiring, but not receiving, stable rFIX prophylaxis. • The sponsor inappropriately applied treatment-specific utilities for etranacogene dezaparvovec and rFIX prophylaxis treatments rather than health state utilities in the submitted model.

Component	Description
	• The model structure did not appropriately capture potential long-term changes in well-being associated with bleed events or costs and consequences related to joint-related surgeries. • The sponsor failed to accurately reflect uncertainty around the ICER by using the wrong standard deviation for key efficacy parameters and an arbitrary standard deviation of 20% of the mean for most model parameters in the probabilistic analysis. • The submitted model did not account for the costs and consequences associated with nAb testing.
CADTH reanalysis results	• CADTH could not address uncertainty related to comparative clinical data, long-term comparative efficacy assumptions, the model structure, the price of rFIX prophylaxis, and the costs and consequences of nAb testing. CADTH conducted a reanalysis addressing limitations associated with implementing utilities and assumptions about return to FIX prophylaxis after treatment with etranacogene dezaparvovec. • Based on the CADTH reanalysis, treatment with etranacogene dezaparvovec is associated with less total cost and is more effective (i.e., dominant) vs. coagulation FIX (recombinant) fc fusion protein and coagulation FIX (recombinant) pegylated nonacog beta pegol. The one-time treatment cost of etranacogene dezaparvovec ($4,690,000) is offset by the costs of coagulation FIX (recombinant) fc fusion protein and coagulation FIX (recombinant) pegylated nonacog beta pegol for 10.6 and 10.8 years, respectively. • As the confidentially negotiated price of comparator rFIX prophylaxis are unknown, CADTH conducted threshold analyses to determine the price of comparators where etranacogene dezaparvovec would no longer be considered cost-effective. If the prices of coagulation FIX (recombinant) fc fusion protein and coagulation FIX (recombinant) pegylated nonacog beta pegol is approximately 48% and 61% less, respectively than those used in the model, etranacogene dezaparvovec will no longer be cost-effective at a WTP threshold of $50,000 per QALY gained.

FIX = factor IX; ICER = incremental cost-effectiveness ratio; ITC = indirect treatment comparison; nAB = neutralizing antibody; QALY = quality-adjusted life-year; rFIX = recombinant factor IX; vs. = versus; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the eligible patient population did not align with the Health Canada limitation; the uptake of etranacogene dezaparvovec is uncertain and may be underestimated; market share estimates for FIX prophylaxis therapies did not align with clinical expectations; the analyses were not conducted from a drug plan payer perspective as blood products are not funded by drug plan programs; the cost of FIX treatments paid by Canadian Blood Services (CBS) is confidential and uncertain; neutralizing antibody testing coverage status is uncertain. CADTH reanalysis was conducted from the perspective of the CADTH participating drug plans and updated the eligible patient population to align with the Health Canada indication. Under this change, CADTH reanalysis reported that the reimbursement of etranacogene dezaparvovec for the treatment of adults with hemophilia B who require routine prophylaxis to prevent or reduce the frequency of bleeding episodes would be associated with a budgetary increase of $31,520,232 in year 1, $53,523,195 in year 2, $54,760,039 in year 3, with a 3-year total incremental cost of $139,803,466.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Ms. Sally Bean, Mr. Dan Dunsky, Dr. Edward Xie, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Peter Jamieson, Mr. Morris Joseph, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Trudy Huyghebaert, Dr. Danyaal Raza, and Dr. Peter Zed.

Meeting date: February 28, 2024

Regrets: Two expert committee members did not attend.

Conflicts of interest: None

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