CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

etranacogene dezaparvovec (Hemgenix)

(CSL Behring Canada Inc.)

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.

April 8, 2024

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SG0805
Brand name (generic)	HEMGENIX
Indication(s)	Hemophilia B
Organization	Canadian Hemophilia Society
Contact information[a]	Name: David Page

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐

Yes, the Canadian Hemophilia Society (CHS) agrees with the recommendation that etranacogene dezaparvovec be reimbursed for the treatment of adults (aged 18 years or older) who require routine prophylaxis. Eligibility should be based not only on baseline factor IX level but also on clinical bleeding phenotype. The CHS agrees with a threshold of AAV5 neutralizing antibodies of 1:900 until such time that further research establishes a more accurate upper limit. The CHS agrees that a reduction in price is warranted but urges cost-effectiveness analyses to fully take into account likely savings to the health system and to the broader socio-economic context (i.e. individual savings and productivity gain).

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☒

Yes, the recommendation demonstrates consideration of CHS input. However, paragraph 2 of the rationale states, *Patients identified a need for effective treatments that improve bleeding outcome 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 <u>some</u> of these needs since it is a one-time gene therapy designed to provide an alternative active source of endogenous FIX that improved bleeding outcomes and reduced FIX use after treatment.* The CHS strongly believes that, based on the clinical trial results, and first-hand knowledge of the capacity of FIX replacement therapy to historically prevent bleeding when FIX levels reach the 12-50% range, etranacogene dezaparvovec will meet <u>all</u> of these needs in the vast majority of patients. 52/54 patients in the trial stopped FIX prophylaxis. 80% maintained FIX levels above 12%, shown by research to be critical in preventing non-traumatic bleeding. The Phase 2 etranacogene dezaparvovec trial now shows stable FIX expression beyond 6 years and counting.

Discussion Point 5 states that *"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."* While CHS could not submit hard evidence of these benefits from Canadian patients before the therapy was even introduced, it is self-evident to patients, as demonstrated by the comments submitted, that a one-time therapy that provides constant factor IX expression in the upper range of mild to the lower range of normal (20-50%) for a period likely to last many years, obviating the need for weekly IV infusions, would inevitably lead to less worry about bleeding and greater ability to engage in activities of daily living, and therefore improved physical and mental fitness, without the risk of spontaneous bleeding. These expectations are supported by the etranacogene dezaparvovec clinical trial results.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
If not, please provide details regarding the information that requires clarification.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☒
The second-to-last Discussion Point states that, *"As a one-time therapy that cannot be terminated once infused, the committee highlighted the importance of robust informed consent and establishing reasonable expectations regarding long-term effectiveness."* The CHS is in full agreement with this point and has created a robust gene therapy education program (www.hemophilia.ca/gene-therapy) to promote shared decision-making. The final Discussion Point states,*"The committee discussed the importance of addressing potential geographic barriers to equitable access given the limited number of infusion centers in Canada."* The CHS would see like to see in the final report a recommendation that, with the goal of equity, provinces and territories provide financial support for individuals to travel to the infusion centres. This would reduce the geographic and financial barriers to treatment. Ideally, all provinces and territories will add etranacogene dezaparvovec to their formularies.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☒
The Canadian Hemophilia Society is generally in agreement with the Reimbursement Conditions. Notably, we fully support the clinician view that that disease severity should be based on FIX:C level as well as the patient's clinical bleeding phenotype (Reimbursement Condition 1). Therefore, Reimbursement Condition 1.1 should be modified to read: *"Documented moderately severe to severe hemophilia B based on FIX:C ≤ 2% **and/or** clinical bleeding phenotype requiring prophylactic treatment."* With regard to conditions 5 and 6, we have these comments. Yes, the price must be reduced to be cost-effective. However, the CHS urges that cost-effectiveness analyses fully take into account likely downstream savings to the health system and to the broader socio-economic context (i.e. individual savings and productivity). Regarding the feasibility of adoption of etranacogene dezaparvovec, the CHS urges CADTH to recommend in its final report consideration by pCPA of alternate reimbursement mechanisms, such as annual payments spread over 5 to 7 years. This would reduce the budget impact in the initial years and allow more patients to access the therapy after introduction. We also urge consideration of pay-for-performance mechanisms, including stopping or reducing payments if the therapy is ineffective or loses efficacy in certain patients. At an appropriate negotiated price, CHS is convinced that etranacogene dezaparvovec gene therapy will result in long-term savings for the health system in addition to significant health and quality-of-life benefits.		

[a] CADTH may contact this person if comments require clarification.

Appendix 1. Conflict of Interest Declarations for Patient Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.

A. Patient Group Information	
Name	*David Page*
Position	*CHS consultant, safety and supply of coagulation products*
Date	*(03-04-2024)*
☒	I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

B. Assistance with Providing Feedback		
1. Did you receive help from outside your patient group to complete your feedback?	No	☒
	Yes	☐
2. Did you receive help from outside your patient group to collect or analyze any information used in your feedback?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		

C. Previously Disclosed Conflict of Interest		
1. Were conflict of interest declarations provided in patient group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section D below.	No	☐
	Yes	☒

D. New or Updated Conflict of Interest Declaration

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Add company name	☐	☐	☐	☐
Add company name	☐	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SG0805
Name of the drug and Indication(s)	Etranacogene Dezaparvovec (Hemgenix) 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
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	X
	No requested revisions	☐

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance
Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.

(1) Seeking clarification surrounding AAV5 neutralizing antibodies. Reimbursement condition #1 states "AAV5 neutralizing antibodies" and the Implementation guidance states anti-AAV. Are there different classes of AAV5 antibodies (or are we specifically looking for 5).
(2) Adding a discussion point in regard to implementation guidance #2. Often criteria in the implementation guidance does not makes its way into the LOI. Having an additional discussion point about having this as a reimbursement condition will be helpful.
(3) To confirm is FIX:C ≤ 2% and AAV5 antibody threshold levels of 1:900 are the common metric/units that are resulted by labs.

Outstanding Implementation Issues

In the event of a positive draft recommendation, drug programs can request further implementation support from CADTH on topics that cannot be addressed in the reimbursement review (e.g., concerning other drugs, without sufficient evidence to support a recommendation, etc.). Note that outstanding implementation questions can also be posed to the expert committee in Feedback section 4c.

Algorithm and implementation questions
1. Please specify sequencing questions or issues that should be addressed by CADTH (oncology only)
1. 2.
2. Please specify other implementation questions or issues that should be addressed by CADTH
1. 2.
Support strategy
3. Do you have any preferences or suggestions on how CADTH should address these issues?
May include implementation advice panel, evidence review, provisional algorithm (oncology), etc.

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SG0805-000
Brand name (generic)	HEMGENIX (etranacogene dezaparvovec)
Indication(s)	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. There is no clinical experience of HEMGENIX use in patients with mild or moderate Hemophilia B (FIX activity 2%).
Organization	CSL Behring Canada Inc.
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☒
	No	☐
CSL Behring Canada agrees with the committee's recommendation based on the strength of the evidence coupled with the clinician and patient input stating the high unmet need for "effective treatments that improve bleeding outcome as well as lead to fewer FIX infusions, minimal needle injections, less stress, less bleeding, and fewer restrictions on activities" (page 3).		

Expert committee consideration of the stakeholder input		
2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☒
	No	☐
CSL Behring Canada believes that the recommendation demonstrates that the committee has considered the stakeholder input provided to CADTH.		

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐
CSL Behring Canada believes the reasons for the recommendation are clearly stated.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
CSL Behring Canada believes the implementation issues have clearly been articulated and adequately addressed in the recommendation.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☒

In the Discussion Points section, under unmet needs, there is contrasting language between fidanacogene elaparvovec and etranacogene dezaparvovec (HEMGENIX®) which appears to favour fidanacogene elaparvovec.

The statement in the fidanacogene elaparvovec recommendation says, *"Overall, CDEC concluded that the available evidence reasonably suggests that fidanacogene elaparvovec has the potential to reduce bleeding rates and use of FIX prophylaxis"*, while the verbiage used for etranacogene dezaparvovec: *"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" (page 6)*.

Based on CADTH's language, it appears as though fidanacogene elaparvovec may have more certainty around its effectiveness at reducing bleeding rates and the use of FIX infusions. Based on the submitted evidence, it should be noted that, using a naïve comparison approach, etranacogene dezaparvovec demonstrated similar results in these two endpoints compared to fidanacogene elaparvovec which studied a similar population of adult patients with hemophilia B using similar trial designs.

The adjusted mean difference in ABR for all bleeding events between etranacogene dezaparvovec and routine FIX prophylaxis was **-2.68 (95% CI, -3.81 to -1.55) at year 1 after etranacogene dezaparvovec** infusion, favouring etranacogene dezaparvovec. Whereas the estimated mean difference in ABR between patients treated with fidanacogene elaparvovec during the BeneGene-2 trial and the same patients treated with routine FIX prophylaxis during the lead-in BeneGene-1 study was **−2.62 (95% CI, −4.27 to −0.96) at year 1 after fidanacogene elaparvovec infusion.** Regarding the use of FIX after infusion with gene therapy, the adjusted mean difference in AIR between etranacogene dezaparvovec and routine FIX prophylaxis was -**69.96 (95% CI, -79.77 to -60.16) at year 1 after etranacogene dezaparvovec** which favoured etranacogene dezaparvovec. The difference in AIR between patients treated with fidanacogene elaparvovec during the BeneGene-2 trial and the same patients treated with routine FIX prophylaxis during the lead-in BeneGene-1 study was **−54.37 (95% CI, −63.64 to −45.10) at year 1 after fidanacogene elaparvovec infusion.**

CSL Behring Canada believes the contrasting language and inconsistent use of GRADE assessment to two similarly designed trials could have negative downstream impacts on the perceived effectiveness of etranacogene dezaparvovec versus fidanacogene elaparvovec, which may impair clinical decision-making and patient access to etranacogene dezaparvovec. Therefore, CSL Behring Canada requests the following editorial revision to page 6 of the etranacogene dezaparvovec draft recommendation in the Discussion Points section: "HOPE-B trial's evidence concluded <u>that</u> ~~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~~".

Further support of the above point is that the etranacogene dezaparvovec data has been supported by publication and peer-review in the New England Journal of Medicine[1] while fidanacogene elaparvovec has yet to be published.

References

1. Pipe SW, Leebeek FWG, Recht M, et al. Gene Therapy with Etranacogene Dezaparvovec for Hemophilia B. *N Engl J Med.* 2023;388(8):706-718.

[a] CADTH may contact this person if comments require clarification.