CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

danicopan (Voydeya)

(Alexion Pharma GmbH)

Indication: As an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have residual hemolytic anemia due to extravascular hemolysis (EVH).

October 4, 2024

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	**SR0815-000**
Brand name (generic)	Voydeya (danicopan)
Indication(s)	PNH with continued anemia from extravascular hemolysis
Organization	Canadian PNH Network
Contact information[a]	Name: C. Patriquin MD MSc FRCPC, [redacted]

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

- Recognition that PNH patients with clinically significant EVH may require additional therapy, and some require ongoing C5 inhibition as a backbone therapeutic strategy
- Overall, the Canadian PNH Network and the contributing reviewers list below agree with this; however, we do wish to point out that an international consensus definition of "csEVH" has not been established and it is our experience that patients with either higher hemoglobin values (i.e. >95 g/L) and/or lower reticulocytes (due to concomitant marrow failure but still clear EVH) can still suffer from the same issues and those patients too could benefit from this approach. As safety/efficacy data become available for patients with higher hemoglobins, we would hope that this information could be incorporated and permit clinical decision making in these situations based on case review by PNH experts. Essentially, we would hope to have approval criteria aligned essentially with other proximal inhibitors (e.g. pegcetacoplan).

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	☐

- As above, overall we would agree that the input has been carefully considered and accepted, but would again just highlight that ideally we would hope for a situation where the diagnosis of csEVH would not be strictly bound to a hemoglobin cut-off as this can range patient to patient, and it would be helpful to allow the treating PNH expert the opportunity to review the situation in its entirety instead of being beholden to the Hb cut-off employed by different trials. This may not be many patients, ultimately, but there will indeed be some.

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	☐
If not, please provide details regarding the information that requires clarification.		
	Yes	☒

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	No	☐
If not, please provide details regarding the information that requires clarification.		

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

Appendix 2. Conflict of Interest Declarations for Clinician 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.
- For conflict of interest declarations:
  - Please 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.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
2. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
3. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
If yes, please detail the help and who provided it.		
B. Previously Disclosed Conflict of Interest		
4. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☐
	Yes	☒
Clinicians 1-9 in the initial submission: C. Patriquin, M. Oliver, B. Leber, D. Marceau, T. Nevill, C. Sperlich, M. Bienz, K. Grewal, J. Grossman		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	
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	☐	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Please state full name*
Position	*Please state currently held position*
Date	*Please add the date form was completed (DD-MM-YYYY)*
☐	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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	SR0815
Name of the drug and Indication(s)	Danicopan As an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have residual hemolytic anemia due to extravascular hemolysis (EVH)
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
Original bullet under Discussion Points on page 6: *"CDEC acknowledged that the recommended criteria for starting danicopan could potentially overlap with the criteria currently implemented in some jurisdictions for discontinuing C5*

inhibitors (ravulizumab and eculizumab) for treating PNH. CDEC discussed the need to potentially modify the criteria for discontinuing C5 inhibitors in those jurisdictions to allow patients with PNH who have residual hemolytic anemia due to EVH to continue receiving C5 inhibitors, even if they meet the discontinuation criteria. This adjustment would enable these patients to benefit from the treatment combination of danicopan with C5 inhibitors (ravulizumab or eculizumab). If after adding danicopan to C5 inhibitors (ravulizumab or eculizumab), response to treatment as defined in condition 4 of Table 1 is not achieved, treatment with danicopan should be discontinued."

This may be better explained as follows:

"CDEC acknowledged that the recommended criteria for starting danicopan could potentially overlap with the criteria currently implemented in some jurisdictions for discontinuing C5 inhibitors (ravulizumab and eculizumab) for treating PNH. However, because danicopan is indicated as add-on therapy to a C5 inhibitor (ravulizumab or eculizumab), the criteria discussed within this document apply to concomitant C5 inhibitor (ravulizumab or eculizumab) and danicopan use. The previously published recommendations regarding ravulizumab and eculizumab apply to their use as monotherapy and not in combination with danicopan. With the introduction of danicopan, reaching the failure criteria for ravulizumab or eculizumab monotherapy could result in:

1. addition of danicopan to the current C5 inhibitor therapy, or

2. discontinuation of the C5 inhibitor without initiation of danicopan, or

3. prompt a switch from current C5 inhibitor therapy to pegcetacoplan, without initiation of danicopan.

In other words, "failure" on a C5 inhibitor alone (ravulizumab or eculizumab) does not necessarily preclude further use with danicopan as this combination is considered a unique therapeutic option.

In practice, jurisdictions may benefit from concurrently reviewing concomitant C5 inhibitor (ravulizumab or eculizumab) and danicopan use. For example, jurisdictions may wish to synchronize the special authority approval dates for both drugs so that they are reviewed concurrently. If after adding danicopan to a C5 inhibitor (ravulizumab or eculizumab), response to treatment as defined in condition 4 of Table 1 is not achieved, treatment with danicopan should be discontinued. Continuation of the C5 inhibitor (ravulizumab or eculizumab) despite failure from combination C5 inhibitor (ravulizumab or eculizumab) and danicopan use is out of scope of this review."

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.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0815
Brand name (generic)	VOYDEYA™ (danicopan)
Indication(s)	As an add-on to ravulizumab or eculizumab for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH) who have residual hemolytic anemia due to extravascular hemolysis (EVH)
Organization	Alexion Pharma GmbH
Contact information[a]	[redacted]

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

Alexion Pharma GmbH (Alexion) agrees with the draft recommendation issued by CEDAC to reimburse VOYDEYA (danicopan) with conditions as an add-on to C5 inhibitors (ravulizumab or eculizumab) for the treatment of adult patients with PNH who are experiencing EVH. Alexion appreciates the committee recognizing the unmet need in managing EVH for the patients with PNH along with the benefits of danicopan as an add-on proximal therapy in improving EVH signs and symptoms as well as alleviating the need for transfusions, while allowing patients to remain on standard-of-care C5 inhibitors to maintain critical IVH control.

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	☐

Alexion believes the committee has appropriately considered patient and clinician input during deliberations in the review of VOYDEYA.

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☒
	No	☐

The reasons for the committee's decision are clearly stated in the draft recommendation. Based on the results of the pivotal ALPHA randomized-controlled trial, danicopan, when added to C5 inhibitors, provide a meaningful increase in hemoglobin (Hb) levels from baseline, significantly reduces the need for transfusions and improves symptoms of fatigue, thus maintaining IVH control and addressing residual anemia due to EVH. In addition, Alexion appreciates the committee for noting the importance of reducing the patient's treatment burden based on a convenient every-8-week maintenance administration schedule (corresponding to only 6 or 7 maintenance administrations per year), "*Ravulizumab is the suggested C5i therapy*" (VOYDEYA Draft Recommendation, page 23).

4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐

In general, the implementation issues are clearly outlined and adequately addressed in the draft recommendation (e.g. the Initiation criteria are reflective of the patient population studied in the ALPHA trial.)

Renewal criterion #4 outline that "*the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as either of the following:*

4.1. Reduction in transfusion needs from baseline before initiating danicopan.

4.2. Normalization of Hb levels to above the lower limit of the normal reference range."

Alexion would like to highlight the implementation guidance provided by clinical experts for reimbursement criteria #4 "*that any improvement from a patient's baseline in Hb levels or transfusion needs could be considered a response to therapy*." (VOYDEYA Draft Recommendation, page 4). Since clinical experts have indicated that any improvement from baseline Hb levels is considered a response, requiring complete normalization of Hb levels for reimbursement renewal may lead to treatment discontinuation in patients who have responded to therapy and deprive them of continuing to benefit from danicopan add-on treatment, leading to re-emergence of EVH signs and symptoms of anemia and fatigue.

Furthermore, the CDA-AMC recommendation for pegcetacoplan note that "*Pegcetacoplan should be renewed in a similar manner to other complement inhibitors currently reimbursed for the treatment of patients with PNH.*" Implementation guidance for the renewal of pegcetacoplan does not specify normalization of Hb values as a requirement. Instead, determination of "…*clinical improvement and/or stabilization of the patient's condition*..." was recommended to evaluate response to therapy (Pegcetacoplan Final Recommendation, page 6).[1] Considering that danicopan add-on to C5 inhibitor has the same place in therapy as pegcetacoplan since "*The experts noted that danicopan would be an alternative to pegcetacoplan, as a second-line agent*" (VOYDEYA Draft Recommendation, page 8), the reimbursement criteria including renewal criteria for VOYDEYA should be aligned with those recommended for pegcetacoplan. Moreover, as noted by clinicians when comparing danicopan add-on to pegcetacoplan in the treatment of patients with PNH, "*Dual complement blockade (i.e., C5i plus danicopan) would provide these patients with the same benefits of improved Hb but with a lower risk of complications*." (VOYDEYA Draft Recommendation, page 9).

Alexion looks forward to collaborating with public drug plans in providing access to danicopan add-on therapy for patients with PNH. Alexion would like to propose that renewal criterion #4.2 be revised at the time of drug plan reimbursement criteria development to be consistent with the implementation guidance provided by clinical experts:
Renewal criterion #4: "*the physician must provide proof of beneficial clinical effect when requesting continuation of reimbursement, defined as either of the following:*

4.1. Reduction in transfusion needs from baseline before initiating danicopan.
4.2. ***Improvement in hemoglobin levels from baseline before initiating danicopan****."*

5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

Overall, the reimbursement conditions are clearly stated and the rationale for the conditions are clearly outlined in the draft recommendation.

Alexion appreciates CDEC for noting "*the need to potentially modify the criteria for discontinuing C5 inhibitors in those jurisdictions to allow patients with PNH who have residual hemolytic anemia due to EVH to continue receiving C5 inhibitors, even if they meet the discontinuation criteria. This adjustment would enable these patients to benefit from the treatment combination of danicopan with C5 inhibitors (ravulizumab or eculizumab)*." (VOYDEYA draft recommendation, page 6). A common renewal criterion listed on the formularies of participating drug formularies for continued reimbursement of ravulizumab and eculizumab is the requirement for there to be "*demonstrated clinical improvement in the patient*".[2-6]

Alexion proposes that this criterion be revised to "*demonstrated clinical improvement in the patient. Persistent anemia and continued transfusion need as a result of extravascular hemolysis (EVH)*

alone does not indicate a lack of clinical improvement in response to C5 inhibitors and patients may continue on their C5 inhibitor therapy."

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

References

1. CADTH. *CADTH Reimbursement Recommendation pegcetacoplan (EMPAVELI)*. 2023. Accessed September 26, 2024. https://www.cda-amc.ca/sites/default/files/DRR/2023/SR0748REC-Empaveli_KT-meta.pdf
2. Ontario Drug Benefit Program. *Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs*. Ontario Ministry of Health; 2023. Accessed September 23, 2024. https://health.gov.on.ca/en/pro/programs/drugs/docs/frequently_requested_drugs.pdf
3. Alberta Drug Benefit List. 2024. Accessed March 29, 2024. https://www.ab.bluecross.ca/dbl/publications.php
4. Non-Insured Health Benefits Program. *NIHB Drug Benefit List*. Accessed June 30, 2023. https://nihb-ssna.express-scripts.ca/en/0205140506092019/16/160407
5. Plan SD. *Saskatchewan Online Formulary Database*. 2024. Accessed 2024-09-25. https://formulary.drugplan.ehealthsask.ca/SearchFormulary
6. Formulary NS. *Nova Scotia Formulary*. 2024. https://novascotia.ca/dhw/pharmacare/documents/formulary.pdf