CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

Isatuximab (Sarclisa)

(Sanofi Genzyme, a division of sanofi-aventis Canada Inc.)

Indication: Multiple myeloma

January 14, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0256-000
Brand name (generic)	Sarclisa (isatuximab)
Indication(s)	In combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Organization	Ontario Health (CCO) Hematology Drug Advisory Committee
Contact information[a]	Name: Dr. Tom Kouroukis Title: Provincial Head – Complex Malignant Hematology (OH-CCO) [redacted]

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

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	☐

Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
The reasons for the budgetary portion of the recommendation are not clearly stated. The budget impact estimate of effectiveness seem unreasonable and quite generous. The efficacy estimates seem unreasonable (ex. median survival of 10 years).		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☒
There may be greater resource utilization than the recommendation clearly articulated, particularly around chemotherapy chair time.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
The reimbursement conditions are clearly stated but the Hematology DAC would add patients with non-measurable/non-secretory disease to the inclusion criteria.		

[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		
1. Did you receive help from outside your clinician group to complete this submission?	No	☐
	Yes	☒
OH-CCO provided secretariat support to the DAC in completing this input.		
2. Did you receive help from outside your clincian group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
No.		
B. Previously Disclosed Conflict of Interest		
3. 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	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Dr. Tom Kouroukis • Dr. Lee Mozessohn		

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.	

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PCO256
Brand name (generic)	Sarclisa (Isatuximab)
Indication(s)	In combination with carfilzomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior lines of therapy
Organization	Canadian Myeloma Research Group (CMRG)
Contact information[a]	Name: Donna E Reece,MD

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

Please explain why the stakeholder agrees or disagrees with the draft recommendation. Whenever possible, please identify the specific text from the recommendation and rationale.

The optimal treatment of myeloma patients progressing after initial therapy has been uncertain, particularly in the high proportion of Canadian patients who now progress on lenalidomide as part of first-line therapy. The use of an anti-CD38 monoclonal antibody (MoAb)-containing regimen as early as possible in treatment sequencing has become the standard of care in Canada and elsewhere for many reasons, including rendering patients eligible for innovative new immunotherapeutic trials early in the disease when results are likely to be better. To date, DaraVd, which contains bortezomib as the proteasome inhibitor (PI) for a fixed-duration of 8 cycles has been the only available MoAb-based second-line regimen in patients progressing on lenalidomide, based on results from the CASTOR trial.[1] However, recent real-world data from CMRG confirms that younger and generally healthier individuals who progress on relatively low doses of lenalidomide as maintenance post-ASCT experience a PFS of less than 1 year when treated with DVd at first relapse[2]—an outcome that is disappointing and is in keeping with the suboptimal outcome of this regimen in more heavily treated patients progressing on a range of lenalidomide doses in the phase 3 CASTOR study of DVd versus Vd.[1] Therefore, identification of more effective MoAb-containing regimens for relapsed/refractory myeloma has been highly desirable, particularly since MoAbs are not yet integrated into first-line therapy in Canada.

The Discussion Points of the Draft Recommendation on page 6, paragraph 5 appropriately note that direct evidence comparing the options for second-line therapy is lacking and that indirect treatment comparisons have limitations. Nevertheless, Canadian hematologist generally accept a combination of a MoAb, carfilzomib and dex, such as IKEMA, provides better anti-myeloma efficacy than DVd for second-line therapy, particularly for those progressing on lenalidomide patients, with less peripheral neuropathy as an additional benefit. This decision is based on the better efficacy outcomes seen with IsaKd in IKEMA (CR rate, VGPR rate and PFS as outlined in the Discussion Points on page 3, paragraph 2) as well as on the higher rate of MRD negativity with IsaKd (clinicians are increasingly accepting this parameter as a useful surrogate marker in myeloma trials expected to have a long read-out time for overall survival) compared to Kd as well as the results from previous ENDEAVOR trial which documented the superiority of the carfilzomib doublet (Kd) over the Vd doublet. In addition, the strong hazard ratio for IsaKd over Kd for PFS in patients progressing on lenalidomide (HR=0.34) in IKEMA is reassuring for this challenging subgroup. (0f note, in CASTOR, the hazard ratio in patients progressing on lenalidomide as the last line was 0.36 in favor of DVd over the less

potent PI Vd). Finally, the clinicians agree with the points on page 6, paragraph 4 that the toxicity profile of IsaKd was manageable.

Therefore, the CMRG consensus is that IsaKd is a more effective regimen than DVd and its availability will offer many patients the opportunity for a longer PFS when the combination of an anti-CD38 MoAb and PI combination is desirable.

However, there are several points under Implementation Guidance that need clarification or re-consideration, as described below.

Reference:
[1]Palumbo A, et al. *N Engl J Med* (2012) 375: 754-766.
[2]Mian H, et al. *Blood* (2020) 136 (Supplement 1): 26–27; https://doi.org/10.1182/blood-2020-133372.

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	☐
If not, what aspects are missing from the draft recommendation?		

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.

Comment regarding Table 2, item "Condition #1 in Table 1": There is a need to expand/clarify the list of myeloma patients who will be eligible for IsaKd. Specifically, a small proportion of myeloma patients have disease that: 1) is completely "non-secretory" even with the use of the serum free light chain assay; 2) is "oligosecretory" with measurements of M-spike or/or serum free light chains below the threshold levels cited; or 3) is characterized by multiple bony or soft tissue plasmacytomas with a normal posterior iliac crest biopsy with/without oligosecretory/non-secretory features. These patients are often excluded from registry trials only to meet the strict response/relapse criteria based on quantification of monoclonal antibody "tumor markers" by electrophoresis (which is relatively insensitive and requires an M-spike concentration of ≥ 0.5-1 g/L). However, myeloma patients vary considerably in their capacity to secrete these "tumor markers" and those who do not meet such limited definitions of "measureable disease" have a natural history—and treatment outcomes —that are comparable to more restricted study populations. As such, they deserve access to the same effective regimen as their study counterparts.

Comment regarding Table 2, item "Condition #1 in Table 1": Previous correspondence from CADTH has indicated that myeloma patients can receive either a funded carfilzomib- or funded pomalidomide-containing regimen in different relapses of myeloma, but not both agents during the entire course of a patient's disease. However, there is still an important (albeit decreasing) population of myeloma patients who have missed the opportunity to access a CD38 MoAb as they are no longer eligible for combinations with either lenalidomide or bortezomib. These patients are now excluded from virtually all clinical trials involving newer immunotherapy platforms, such as CAR-T cells or bispecific antibody therapy, even if they are young, otherwise fit, and likely to survive several more years with such therapy. It is highly desirable that patients who have already progressed on pomalidomide and have not yet received a MoAb have access to IsaKd. (In addition, although not

directly part of this IKEMA recommendation, CMRG members feel strongly that patients who may not be able to tolerate carfilzomib due to cardiac or logistic issues and/or have progressed through carfilzomib, have not yet been exposed to a MoAb and have progressed after ≥ 2 prior treatment lines have access to the ICARIA regimen as their eligibility ensures fair access to the new standard—i.e., anti-CD38 MoAbs-- that has revolutionized myeloma care). It is important to note that the IKEMA eligibility did not exclude patients with prior pomalidomide, which now represents is an important component of modern myeloma therapy .

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

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

However, some CMRG members have respectfully requested information regarding the establishment of cost-effectiveness at a threshold of $50,000 per QALY. In the past, the impression among members has been that a higher threshold was acceptable. Can CADTH provide clarity around the rationale and timing of this policy?

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

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  - 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 clincian 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	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	*Dr. Donna Reece*
Position	*Chief Medical Officer, CMRG*
Date	*14-01-2022*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
BMS/Celgene	☐	☐	☒	☐
Janssen	☐	☐	☒	☐
Amgen	☐	☐	☒	☐
Sanofi	☒	☐	☐	☐
GSK	☒	☐	☐	☐
Takeda	☒	☐	☐	☐

New or Updated Declaration for Clinician 2	
Name	*Dr. Debra Bergstrom*
Position	*Associate Professor*
Date	*14-01-2022*
☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Nothing to declare	☐	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	*Mohammed Aljama*
Position	*Hematologist, JCC. Assistant Professor, Department of Oncology*
Date	*14-01-2022*
☒	**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
Jansen	☐	☒	☐	☐

New or Updated Declaration for Clinician 4	
Name	*Rodger Tiedemann*
Position	*Consultant Hematologist, Senior Scientist, Princess Margaret Cancer Centre, UHN, Toronto*
Date	*14-01-2022*
☒	**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
No COI	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	*Anette Hay*
Position	*Associate Professor, Queens University*
Date	*14-01-2022*
☒	**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 6	
Name	*Irwindeep Sandhu*
Position	*MD, Associate Professor Dept of Oncology University of Alberta*

Date	*14-01-2022*
☒	**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
Celgene/BMS	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Takeda	☒			
Sanofi	☒			
Kite/Gilead	☒			

New or Updated Declaration for Clinician 7

Name	*Heather Sutherland*
Position	*Hematologist, Vancouver General Hospital*
Date	*01-14-2022*
☒	**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
Sanofi	☒	☐	☐	☐
Amgen	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 8

Name	*Dr. Vishal Kukreti*
Position	*Hematologist/ Oncologist*
Date	*14-01-2022*

☒	**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

Company	Check Appropriate Dollar Range			
	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Amgen	☒	☐	☐	☐
Kirin Kyoto	☒	☐	☐	☐

New or Updated Declaration for Clinician 9	
Name	*Christine Chen*
Position	*Hematologist, Princess Margaret Cancer Centre*
Date	*14-01-2022*
☒	**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
BMS	☒	☐	☐	☐
Janssen	☒	☐	☐	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 10	
Name	*Chloe Yang*
Position	*Staff Hematologist*
Date	*14-01-2022*
☒	**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

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 11	
Name	*Kevin Song MD*
Position	*Hematologist, Vancouver General Hospital*
Date	*14-01-2022*
☒	**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**
Bristol Myers Squibb	☐	☒	☐	☐
Janssen	☐	☒	☐	☐
Amgen	☐	☒	☐	☐

New or Updated Declaration for Clinician 12	
Name	*Dr. Christopher Venner*
Position	*Hematologist Lymphoma and Myeloma Program, BC Cancer Vancouver Centre*
Date	*14-01-2022*
☒	**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

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Celgene/BMS	☒	☐	☐	☐
Takeda	☒	☐	☐	☐

Janssen	☒	☐	☐	☐
Amgen	☒			
Sanofi	☒			
GSK	☒			

New or Updated Declaration for Clinician 13	
Name	Suzanne Trudel
Position	Oncologist
Date	14-01-2022
☒	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**
Sanofi	☒	☐	☐	☐
BMS	☐	☐	☒	☐
Add or remove rows as required	☐	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	*Michael Pavic*
Position	*Hematologist*
Date	*14-01-2022*
☒	**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

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	☐	☐	☐	☐

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0256
Name of the drug and Indication(s)	Isatuximab for RRMM
Organization Providing Feedback	PAG

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
None.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
None.
b) Reimbursement conditions and related reasons
In Table 1. Reimbursement Reasons and Conditions, the performance status in the clinical trial eligibility was ECOG 0, 1 or 2. PAG is requesting the following revision ">2" for physician discretion. In Table 3. Responses to Questions from the Drug Programs, under the "generalizability" heading, the response column noted the following, "pERC agreed with the clinical experts that patients currently receiving Kd whose disease has not progressed should be allowed to have isatuximab added to their regimen." PAG is requesting the following text be added "*provided all other eligibility criteria are met*."
c) Implementation guidance
None.

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0256-000
Brand name (generic)	isatuximab
Indication(s)	In combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.
Organization	Myeloma Canada
Contact information[a]	Name: Jessy Ranger

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

"MM is an incurable disease and pERC agreed that there is an unmet need for additional effective treatments in the relapsed and refractory setting particularly for patients who are refractory to IMiDs and PIs. Patients identified a need for new effective treatments that control disease, prolong remission, and improve quality of life with less side effects. Given the totality of the evidence, pERC concluded that IsaKd meets some of these needs by improving disease control resulting in longer remission and having manageable side effects." p.3

- There is no such thing as "one-treatment-fits-all" when it comes to treating myeloma. What works for one patient may not work for another, which is why each case must be assessed individually.

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	☐

"Most patients surveyed indicated that having access to an effective treatment was very important, as was controlling symptoms such as infections, kidney problems, mobility, neuropathy, and fatigue. Patients described impacts on their abilities to perform day-to-day activities such as working, travel, and exercise. Patients expect new effective treatment options to improve their quality of life, have maximum benefits with non-debilitating side effects, reduce their hospital visits, and to be able to achieve the longest remission possible in lieu of a cure. The patient group highlighted the importance of receiving information about emerging treatments and having timely access to these treatments."p.7

- Across subsets, when the opportunity was provided for patient comments, their responses frequently echoed similar sentiments. These are: desiring treatments to have maximum effectiveness but with non-debilitating side effects; to be minimally occupying their time with numerous visits to the hospital, and to ultimately achieve the longest remission possible for themselves (in lieu of a cure); all of which contribute to their (the patients') abilities to lead a "normal" life (one of good quality).

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

"The drug programs identified jurisdictional implementation issues related to considerations for initiating and prescribing of therapy, generalizability, considerations for a funding algorithm, care provision issues, and system and economic issues."p.8 "pERC acknowledged the substantial budget impact associated with IsaKd and noted this must be improved as a reimbursement condition as well as substantial price reductions to improve cost-effectiveness. " p.10 "CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for IsaKd is uncertain; not all relevant comparators were included; the market uptake of IsaKd is uncertain; relative dose intensity was inappropriately used to reduce drug costs; the duration of treatment is uncertain; and there was misalignment between the sponsor's submitted pharmacoeconomic model and the BIA for some parameters." p.15		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
"pERC agreed that this is an important consideration as new therapies come into the MM treatment space, and IsaKd may move further down the lines of therapy." "pERC agreed that weekly dosing has the potential to benefit patients and the health care system, as less drug and less chair time would be needed." "pERC agreed with the clinical experts that patients currently receiving Kd whose disease has not progressed should be allowed to have isatuximab added to their regimen." "pERC acknowledged the substantial budget impact associated with IsaKd and noted this must be improved as a reimbursement condition as well as substantial price reductions to improve costeffectiveness."p.8-10 • As more and more treatment becomes available, it is important for patients to be able to chart, with their healthcare provider, the best action plan for them. This cannot be done without understanding their treatment options and their effects on their quality of life.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐
"CADTH conducted an exploratory reanalysis and determined that the incremental cost-effectiveness ratio (ICER) was likely close to $1,588,632 per QALY compared to Kd and therefore IsaKd is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold. CADTH notes this estimate may underestimate the true ICER due to favourable modelling assumptions as well as the absence of lower cost comparators that could not be considered in the analysis. Based on the exploratory analysis, a 100% price reduction for isatuximab is not sufficient to achieve cost-effectiveness at a $50,000 per QALY threshold unless the price paid by public plans for carfilzomib is also 61% lower than its' list price." p.3 • The $50K per QALY as not being aligned with the pCORD recommendations of past myeloma drug being at $100K per QALY. Patients need to understand why the value of a treatment on improving their health outcomes is less valuable now than when the pCODR made recommendations. The recommendation is clear, but we question the ability of provinces to come to a listing agreement giving these QALY conditions that seem unattainable.		

[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	*Martine Elias*
Position	*Executive Director*
Date	*20220114*
☒	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	☐
If yes, please detail the help and who provided it.		
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

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0256-000
Brand name (generic)	SARCLISA® (Isatuximab for injection)
Indication(s)	In combination with carfilzomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received 1 to 3 prior lines of therapy.
Organization	Sanofi Genzyme, a division of sanofi-aventis Canada Inc. (SGZ)
Contact information[a]	[redacted]

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

Clinical Recommendation

Sanofi Genzyme (SGZ) agrees with the committee's recommendation supporting reimbursement of isatuximab combined with carfilzomib and dexamethasone (IsaKd) for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received 1 to 3 prior lines of therapy. SGZ supports the early conversion of the draft to a final recommendation.

SGZ would like to suggest an amendment to Reimbursement Condition 3.3 [Patients must not have any of the following: Prior treatment with an anti-CD38 mAb]. As stated in the recommendation, "the IKEMA trial included patients who had previous treatment with…an anti-CD38 mAb" (pg 4). Importantly, it was patients who were **refractory** to an anti-CD38 who were excluded from the trial (defined as patients with prior anti-CD38 mAb treatment with progression on or within 60 days after end of anti-CD38 mAb treatment or failure to achieve at least minimum response to treatment). SGZ believes that the Reimbursement Condition should be consistent with the trial design and be amended as follows: *'3.3 Patients must not have any of the following: Refractory to an anti-CD38 mAb'*.

Importantly, SGZ agrees with clinician's recognition of the unmet need among eligible patients. As noted by clinicians providing input into the Clinical Review Report, most 2L patients are refractory to lenalidomide. Among currently funded treatments is DVd, which is associated with *"poor outcomes, as seen in the CASTOR trial (median PFS for DVd of 7.8mo at first relapse in lenalidomide refractory patients). Real-world data from Canada show that outcomes for patients who have progressed on lenalidomide and treated with DVd are poor (mPFS: 11.47mo). Neither regimen typically leads to durable remission and more effective treatments are needed."* (CRR, pg 23) Clinicians stated *"IsaKd…would be preferred over DVd or Kd due to superior efficacy and good tolerability."* (CRR, pg 23)

CADTH (pg 6) pERC noted that the early failure of the statistical testing hierarchy of outcomes meant that for some outcomes no inferences could be drawn about the numerical differences observed between the groups. (pg 6)
SGZ acknowledges that difference in ORR (a composite endpoint) between IsaKd and Kd did not reach a level of statistical significance. This is accounted for by the high % of patients achieving a partial response in the Kd arm. It is notable that this lack of difference did not impact the significant difference in the PFS, since PFS is driven more by the depth of response such as MRD negativity than by ORR. SGZ believes that clinical results from these endpoints in favor of IsaKd, (VGPR or better, MRD negativity, % of patients who achieve CR and MRD- status, median duration of response) may be used in support of the clinical recommendation.

CADTH (pg 6) Patients in the IsaKd group showed little change from baseline in HRQoL scores over time suggesting patients' quality of life was maintained; however, due to the limitations of the evidence, pERC was unable to draw definitive conclusions on the effect of IsaKd on patients' QoL.
SGZ: HRQoL was included in the a priori SAP, but only a descriptive analysis (no statistical testing). Change score and comparative analysis of the C30 and MY20 was performed as post-hoc analysis and the full report has been shared with

CADTH. Overall HRQL was maintained for patients throughout the treatment period, with no decrement observed in EORTC QLQ-C30 GHS/QoL for patients treated with IsaKd. No clinically meaningful change (as defined by a 10-point change) was observed on either arm. Similarly, C30 PF, RF, and FA scores were maintained through the study in both arms. Average change from baseline was <10 points with no significant decreases. Furthermore, pain-related (i.e., C30 PA and MY20 MYDS) scores decreased during the first three-four cycles and maintained the achieved level in both arms. Average decrease from baseline was <10 points. Overall, these results showed that HRQoL was preserved among patients treated with IsaKd.

Economic Recommendation

CADTH Limitation 1a. In modelling overall survival for IsaKd, no survival benefit was assumed for IsaKd and a substantial post-progression survival (PPS) benefit was assumed for KD versus IsaKd (pg 13)

SGZ disagrees with the CADTH re-analysis estimates and price reduction recommendations for IsaKd. Specifically, SGZ disagrees with the EGP's overall survival (OS) projection for IsaKd. The selection of the Gompertz OS curve for IsaKd results in a negligible survival advantage of just under 4 months over a lifetime horizon versus Kd. Although the OS data is immature, the choice of using a Gompertz distribution to model IsaKd OS is not clinically plausible and should be removed from consideration for the CADTH base-case.

- The IKEMA trial reports very strong clinical data that has been accepted not only by clinicians but also CADTH, as indicated by the clinical recommendation. Patients treated with IsaKd see a 47% reduction in the risk of progression, resulting in statistically significant and clinically meaningful improvement in PFS, a strong surrogate for survival. Patients also had much deeper responses, as indicated by more than twice as many patients achieving MRD- status (29.6%) in the IsaKd arm versus Kd (13%). HCPs suggest MRD- as a prognostic indicator for prolonged OS benefit.[1] Median duration of response also favored IsaKd (HR = 0.425 [95% CI: 0.269; 0.672]). The strong clinical data support the use of a more plausible OS curves for IsaKd.
- The Gompertz model to predict OS for IsaKd does not meet external validity. The Orlowski 2016 study reported 9 year OS of bortezomib for RRMM patients whose disease had progressed after an initial response to at least 1 prior line of therapy or had been refractory to initial treatment.[2] The OS rate at 7.8 years was approximately 15% (for patients receiving bortezomib alone) (Orlowski, 2016). Compared to IKEMA, patients in this study had worse ECOG performance status scores and experienced more prior therapies. Therefore, we would expect IsaKd and Kd in the IKEMA trial to have better OS rate than bortezomib in the Orlowski 2016 study, which the Gompertz model does not predict as all patients die within 10 years.
- The Gompertz model is inconsistent with feedback from Canadian HCPs, who unanimously agreed that the Gompertz distribution for IsaKd is too pessimistic and not clinically plausible. Using the Gompertz distribution predicts hazard rates that are similar between the two arms, which is highly unlikely given the clinical superiority of the triplet compared to the doublet, especially one that is viewed as a backbone therapy. Clinicians highlighted evidence supporting an "anti-CD38 class effect," whereby treatment with an anti-CD38 result in long-term OS prolongation and a visible 'tail', as noted in long-term OS data for other anti-CD38s, even among patients who have progressed.[3]
- According to CADTH, "Clinical experts consulted by CADTH noted that the maximum length of survival for this patient population is not expected to exceed 15 years"; however, the choice of OS distribution by CADTH results in all patients dying before year 10.
- The log-normal model for isatuximab has been accepted by other HTA bodies, including NICE.[4] Subsequent validation studies demonstrate that OS extrapolations employed by NICE predicted OS reasonably well when compared to more mature data, when it became available.[5]
- Assumptions around long-term survival benefit should align with precedence established by CADTH in previous MM submissions. For example, EGP assumed a treatment effect of up to 48 months for DRd (4x duration of follow-up), thus assuming a treatment effect of 34.7 months beyond median follow-up.[6] SGZ requests that a survival model be selected that confers similar survival advantage for IsaKd.

Furthermore, a substantial improvement during the PPS health state was assumed for Kd relative to IsaKd. An analysis submitted to CADTH was conducted to test the impact of post-progression treatments, specifically daratumumab, in the Kd arm. The Rank-preserving structural failure time (RPSFT) analysis demonstrates that the addition of daratumumab did not impact survival. Therefore, predicting a significant PPS benefit for Kd attributable to post-progression treatment is flawed.

Overall, SGZ would have preferred the use of a clinically plausible model to predict OS for IsaKd and limit the PPS LY gain in the Kd arm, as it contradicts the results of the RPSFT analysis. Given the limitations of the EGP reanalyses as described above, SGZ supports the consideration of several alternative approaches for modeling IsaKd below (with results summarized in Table 1). Although SGZ is not requesting a reanalysis, we would like to highlight that other analysis could have been explored

to further address issues around OS, which were not considered in the CADTH re-analysis. Also, the CADTH or proposed reanalyses do not assume weekly Kd dosing, which may improve CE profile.

-Analysis 1: Assume PFS:OS correlation. Since these outcomes have been demonstrated to be correlated using validation surrogacy studies, a deceleration of factor of 2.9 (calculated in Dimopoulos study) was applied to the Gompertz PFS models to predict the IsaKd and Kd OS curves based.[7]

-Analysis 2: Lower model time horizon from 37 years to 10 years.

-Analysis 3: Piecewise model using log-normal curve for 5-years beyond treatment cessation for IsaKd patients, upon which the same hazard as the Gompertz model was used. This reanalysis would be similar to the assumption used in past RRMM model reanalyses.

-Analysis 4: Uses Weibull model for both IsaKd and Kd OS curves, which would ensure consistency with the ICARIA CADTH reanalysis, and ensure external validation against long-term data for Kd from ENDEAVOR trial[8], while leading to a very conservative ICER. Furthermore, in NICE TA457[9] (Kd appraisal) and NICE TA573[10] (DVd appraisal), the committees preferred Weibull to model OS of Kd, Vd and DVd, in line with data from ENDEAVOR.[8]

Table 1: Alternative pharmacoeconomic reanalysis to ensure clinical plausibility (deterministic outcomes)

Scenario	OS Segment 1		Time Horizon	Difference (Deterministic)					Deterministic ICER (per QALY)
	IsaKd	Kd		Cost	PFS LYs	PPS LYs	Total LYs	QALY	
SGZ base-case	OS: IsaKd Lognormal (U)	OS: Kd Gompertz (U)	37	$565,584	6.35	1.34	7.70	5.54	$102,112
1) PFS to OS correlation*	PFS: IsaKd Gompertz (U)	PFS: Kd Gompertz (U)	37	$563,805	6.35	-0.32	6.03	4.40	$128,229
2) Shorter time horizon	OS: IsaKd Lognormal (U)	OS: Kd Gompertz (U)	10	$524,012	3.23	-0.75	2.48	1.89	$276,742
3) Piece-wise model**	OS: IsaKd Lognormal (U)	OS: Kd Gompertz (U)	37	$545,540	2.72	-1.31	1.41	1.13	$481,748
4) Weibull model	OS: IsaKd Weibull (U)	OS: Kd Weibull (U)	37	$558,933	4.51	-3.40	1.11	0.97	$573,754
CADTH base-case	OS: IsaKd Gompertz (U)	OS: Kd Gompertz (U)	37	$539,293	2.16	-1.83	0.33	0.36	$1,496,087

*w/ 2.9 segment 1 deceleration factor

**Segment 1 used Lognormal model up to 72 months, Segment 2 used Gompertz (U) model for both treatments w/ duration from 72 to 999 months

CADTH Limitation 1b & 8: "Assuming an overall survival benefit in the absence of evidence is challenging due to the potential impact of subsequent therapy" & "The potential impact of subsequent treatment after disease progression was not considered in the sponsor's model." (pg 13)

SGZ: A RPSFT analysis was conducted to estimate the treatment effect in absence of switch to subsequent anti-myeloma therapy with daratumumab in the Kd arm. The stratified HR for OS from the RPSFT analysis was 0.896 (0.524 to 1.532), which is very close to the ITT estimate of 0.882 (0.519 to 1.501), suggesting that administering daratumumab post-progression does not impact OS. This analysis further mitigates uncertainty around the impact of subsequent therapy. It also highlights the issues with assuming a prolonged PPS benefit in the Kd arm, as assumed in the CADTH re-analysis.

CADTH Limitation #2: "Comparative effectiveness of IsaKd to relevant comparators is highly uncertain." (pg 14)

SGZ: The NMA and MAIC conducted by SGZ followed the best-established practice in the absence of head-to-head trials. Despite limitations identified in the ITC against relevant comparators (such as DVd), there is widespread consensus among clinicians that "the current standard of care, DVd, is suboptimal with poor efficacy data in both clinical trial and real-world Canadian settings." (CRR, pg 23) OH-CCO DAC agreed it was not appropriate to recommend patients try other treatments before initiating treatment with IsaKd. (CRR, pg 24).

CADTH Limitation #3: "The model lacked flexibility to assess relevant subgroups" (pg 15)

SGZ: Reimbursement for a specific subgroup is not being sought, and thus submitted a model that covers the full reimbursement population, as per the CADTH guidelines.[11] Further that segmenting the population by transplant-eligible and ineligible patients does not have any material impact since treatment options for all RRMM patients don't differ based on prior transplant status. The IKEMA ITT population was confirmed to be reflective of the relevant Canadian patient population by KOLs and the results were anticipated to be generalizable for the Canadian population. Furthermore, the IKEMA ITT population includes patients with renal impairment, asthma/COPD, and other co-morbidities that capture the heterogeneity of the Canadian patient population.[12] Furthermore, IsaKd efficacy results are strong among all subgroups. SGZ is seeking funding for the ITT population and not a specific subgroup.

CADTH Limitation #4: Extrapolation of time to treatment discontinuation (TTD) lacked face validity (pg 14)

SGZ: CADTH's assumption that PFS can be used as a proxy to guide TTD does not align with evidence generated in the IKEMA trial. Though using PFS as a proxy is not uncommon in HE models, RWE and studies investigating this relationship do not consistently demonstrate strong correlations.[13,14] Furthermore from the IKEMA trial, there existed a period of time when

patients were awaiting confirmatory results after initial results on progression, suggesting that PFS is not a strong proxy for TTD, something that was further confirmed with clinicians.

CADTH Limitation #5: "The impact of different types of disease progression (e.g., serological, clinical) … not considered in the sponsor's model" (pg 14)
SGZ: Types of disease progression are not conventionally modelled in RRMM health economic submissions, nor do they have any material impact on the final results.

CADTH Limitation: "Relative dose intensity (RDI) may not correlate well with drug costs" (pg 14)
SGZ: Dose delays and dose reductions for isatuximab were permitted for frail/renally impaired/older patients. Assuming 100% dose intensity would be inconsistent with RW clinical practice and overestimate costs.

CADTH limitation #7a: Impact of AEs on the ICER is highly uncertain (pg 14)
SGZ: Though the costs of AEs were applied in the first model cycle, the sponsor captured all AEs, per the threshold, that occurred during the IKEMA trial, as is common modelling convention. AEs with lower incidence and minimal impact to costs were not captured in accordance with CADTH's guidelines which state: "where AEs have a negligible impact on health effects, or no impact on costs and resources, it is often appropriate to exclude these events from the model."

CADTH limitation #7b: "the assumption that each AE could occur only once during the 37-year analysis horizon lacks face validity" (pg 14).
SGZ: The mean duration of AEs (in days) was applied in the model to ensure face validity.

CADTH reanalysis:"...using the IKEMA PFS hazard ratio to model the relationship between IsaKd and Kd ..." (pg 14)
SGZ: It is unclear how this analysis was conducted and whether the PH assumption was held. It is also unclear how this provides more certainty around the IsaKd PFS results. SGZ prefers use of the parametric survival curves as per convention.

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

Yes, in part. CADTH did not make any changes to the CADTH reanalysis, despite significant issues that underestimate the survival benefit associated with the treatment. SGZ also conducted an RPSFT analysis which seems to not have been used to address issues around the impact of post-progression treatment in the Kd arm. Lastly, it also appears that post-hoc analysis results shared to provide statistical credibility to the HRQL was not taken into consideration.

Clarity of the draft recommendation

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

N/A

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

N/A

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

Yes, although the reimbursement condition 3.3 does not align with the clinical trial design (please see SGZ's comment on pg 1). SGZ would like to note that economic recommendations for oncology drugs generally report price reduction recommendation to achieve a 100k/QALY threshold. SGZ is concerned about the omission of this threshold to report price reduction recommendation and suggests its inclusion. Also, the sponsor submitted PE results had been omitted from the draft recommendation. SGZ requests that the following information be added to the report: *IsaKd was associated with a longer time in the progression-free state and the post-progression state, providing for greater quality adjusted life years (QALYs) and total modelled life-years (LYs) than Kd (IsaKd: 8.20 QALYs; Kd QALYs: 4.05). Since patients are on therapy longer, IsaKd was also associated with higher costs ($1,170,887 for IsaKd versus $582,079 for Kd). It was determined that treatment with IsaKd has a mean Incremental Cost-Effectiveness Ratio (ICER) relative to Kd of $141,824 per additional QALY gained.*

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

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