CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

selinexor (Xpovio)

(FORUS Therapeutics Inc.)

Indication: In combination with bortezomib (V) and dexamethasone (d) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy.

July 15, 2022

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	Selinexor PC0276
Brand name (generic)	Selinexor (Xpovio)
Indication(s)	With bortezomib and dexamethasone in adult myeloma patients after at least 1 prior therapy
Organization	Canadian Myeloma Research Group (CMRG)
Contact information[a]	Name: [redacted]

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.		

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. ***Implementation Guidance* #3:** Many provinces fund bortezomib or other PIs only for a fixed duration, so that*		
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.		

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

*patients may be compelled to stop this agent while still responding; their myeloma cells are still showing sensitivity to this drug class and they are not "PI refractory." Re-initiation of bortezomib earlier than 6 months may be appropriate since these patients will likely respond to bortezomib again, particularly in combination with selinexor and dexamethasone. In the phase 3 BOSTON trial design, exclusion of patients with less than a 6 month interval off a prior PI was required to try to ensure clinical trial equipoise for the **CONTROL** arm of the study (i.e., Vd = bortezomib and dexamethasone), by providing a more balanced comparator less likely to be resistant to the main anti-myeloma agent--the PI bortezomib-- in this doublet.

Therefore, CMRG recommends changing *Implementation Guidance* point #3 to read: "Must not be refractory to a PI at the time of SVd initiation."

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	☒
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 Donna Reece, MD • Clinician 2 Darrell White, MD • *Add additional (as required)* Chris Venner, MD Hira Mian, MD		

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	☐	☐	☐	☐

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0276-000
Brand name (generic)	Selinexor
Indication(s)	In combination with bortezomib (V) and dexamethasone (d) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy.
Organization	OH-CCO Hematology Cancer Drug Advisory Committee
Contact information[a]	Name: [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	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

[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	☒
Ontario Health provided secretariat functions to the DAC.		
2. 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		
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. Pierre Villeneuve • Dr. Jordan Herst • Dr. Lee Mozessohn • Dr. Mark Brown • Dr. Guillaume Richard-Carpentier		

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0276
Name of the drug and Indication(s)	Selinexor for Multiple Myeloma
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	☐
	No requested revisions	X

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
None.
c) Implementation guidance
None.

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	PC0276-000
Brand name (generic)	Selinexor (Xpovio)
Indication(s)	In combination with bortezomib (V) and dexamethasone (d) for the treatment of adult patients with multiple myeloma (MM) who have received at least one prior therapy.
Organization	Myeloma Canada
Contact information[a]	Name: [redacted]

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

p. 3
Myeloma Canada is pleased to read that *"pERC agreed that there is an unmet need for additional effective treatments beyond first and second line, as treatment options are limited and associated with short remissions."* For patients who have received 3 previous lines of therapy, Selinexor would now be available to them as a 4th line therapy and when available on provincial formularies will represent one of the only funded treatment options they have left.

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	☐

P. 5
Depending on their location and the treatments available in their province or territories, patients don't have access to the same kind of healthcare services and treatment options or treatment sequencing. It is crucial for them to have valid options that would minimize the time they have to spend at the hospital. Our patient survey responses indicated a significant preference for orally administered treatment, and the desire to make fewer trips to the hospital or cancer centres were taken into consideration by the review committee throughout their draft recommendation. They acknowledged that patients would experience fewer hospital visits which will translate to an improvement in quality of life. Even if this benefit is not totally achieved through XVd because bortezomib must be administered by subcutaneous injection, in a hospital, in some jurisdictions "at-home self-administration" medication is possible. This type of administration has been approved in different contexts, such as clinical research, as well as in other countries, and we submit should be extended to more provincial jurisdictions in the future. This needs to be considered as a significant quality of life benefit for patients.

P. 7
All the key elements of our submission were considered and well stated in the draft recommendation, such as the importance to control symptoms related to myeloma for patients, as well as cost related to treatment and method of administration. When patients consider new treatments, they put a lot of importance in the effectiveness of the treatment, the impact on their quality of life, the

accessibility/portability of treatment, the management of side effects, and having a supportive, communicative and accessible health care team.

Clarity of the draft recommendation

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

P. 4
It was recommended that only clinicians with expertise and experience in managing MM patients, and experience with the adverse effects associated with selinexor be the ones to prescribe this medication.

SVd should only be prescribed by clinicians with expertise and experience in all of the following:

4.1 The management of patients with multiple myeloma

4.2 The adverse effects associated with selinexor

It was unclear to us if the experience referred to can be gained through treating similar side effects caused by other drugs or if it must be direct experience with selinexor itself. We are concerned that this could potentially limit access for patients not seeing a specialist/rurally located and/or in centres that did not participate in the BOSTON clinicals trials, and thus lack expertise in selinexor side-effects management.

P. 6 *Treatment choices for patients depend on whether or not they are transplant eligible or ineligible. Most patients in Canadian clinical practice will receive a lenalidomide-based regimen. At relapse, treatment for patients depends on patient factors, including age, comorbidities, and previous treatments. Most patients will receive a daratumumab-containing regimen. Other treatment options as patients continue to progress can include regimens containing carfilzomib, pomalidomide, isatuximab, or belantamab; funding of these regimens is variable across the Canadian jurisdictions and in some cases, treatments may only be available through special access programs.*

Therefore, it is necessary to have a place for new therapies in funding algorithms and give physician flexibility as no patient's myeloma is the same. We need to provide guidance for physicians to use the appropriate drugs to treat patients based on their own genetic makeup, the patient sensitivity (side effect, response rate) and finally the need to address disparities in access to treatment based on geography and diversity of the myeloma population.

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

p. 11 *pERC agreed with the clinical experts that SVd could be administered to patients in the second-line, or later, but that other treatment options may be preferred. pERC highlighted if DRd was funded in frontline transplant-ineligible patients, SVd is a potential second- line option for these patients. Other funded options are: pomalidomide and dexamethasone (Pd), cyclophosphamide, bortezomib and dexamethasone (CyBorD) and carfilzomib and dexamethasone (Kd).*

We were pleased to see that selinexor could be considered as a second-line option as well and believe this will help address certain shortcomings due to the current reimbursement context.

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

P. 3 *The cost-effectiveness of SVd is highly uncertain due to limitations with the chosen modelling approach, the lack of head-to-head comparative clinical information for most comparators, and uncertainty*

associated with the use of subsequent therapy after disease progression. (…) The committee considered exploratory analyses conducted by CADTH, which considered the cost-effectiveness of SVd relative to Vd based on data from the BOSTON trial and determined that the ICER could be as high as $10,884,623 per QALY. As such, a price reduction would be required for SVd to achieve an ICER of $50,000 per QALY compared to Vd. There is not sufficient evidence to suggest that SVd provides additional clinical benefit when compared to funded treatments used to treat multiple myeloma. Therefore, SVd should not be priced more than currently funded alternatives.

We are accepting that a direct comparison between therapies cannot be clearly made, but from a patient perspective, we would assume the QALYs to be closer to the pCODR recommendations of past myeloma drug being at $100K per QALY. Can CADTH provide insights on why that is?

P. 5 This analysis indicated that a 93% reduction in the price of selinexor may achieve an ICER of $50,000 per QALY compared to Vd. If SVd led to a sustained and durable OS benefit, then a price reduction of 81% may be sufficient to achieve cost-effectiveness relative to Vd. There is insufficient evidence to suggest that SVd provides additional benefit above other funded treatments used to treat multiple myeloma. Therefore, SVd should not be priced more than currently funded alternatives.

In a patient perspective, living is an additional benefit that cannot be reduced to cost.

P. 21 *CADTH identified the following key limitations with the sponsor's analysis: The number of patients eligible for SVd is uncertain and may be underestimated; all relevant comparators were not considered. Relevant comparators may depend on the line of therapy and prior treatments received; the uptake of SVd is uncertain and may be underestimated. Uptake may differ among patients with and without prior lenalidomide exposure; the duration of SVd treatment is underestimated; costs associated with subsequent treatment were not considered. Such costs are relevant to the drug plan budget; costs related to selinexor treatment are underestimated, which may increase the cost to the drug plans of reimbursing Selinexor.*

The fact that the pool of eligible patients is uncertain should not justify a delay in the accessibility of the treatment. The nature of the disease means uncertainty for all affected patients. The most important thing for them will be to have access to the right treatment at the right time.

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

Appendix 1. Conflict of Interest Declarations for Patient Groups

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- 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	*Myeloma Canada*
Position	*Jessy Ranger, Director, Patient Programs, Health Policy and Advocacy*
Date	*13072022*
☒	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	PC0276
Brand name (generic)	XPOVIO (Selinexor)
Indication(s)	Selinexor in combination with bortezomib and dexamethasone (SVd) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy
Organization	FORUS Therapeutics Inc
Contact information[a]	[redacted]

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

Recommendation

Overall, FORUS agrees with CADTH's recommendation supporting the reimbursement of selinexor in combination with bortezomib and dexamethasone (SVd) for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. We support the early conversion of the draft recommendation to a final recommendation, with additional comments and considerations provided below.

CADTH Implementation Guidance: "As per BOSTON trial, prior treatment with bortezomib or other proteasome inhibitor (PI) should be permitted, providing all of the following criteria are met:…." (pg 4, Table 1.1)

FORUS wishes to highlight the potential implications of implementation criteria #3 which requires a proteasome inhibitor (PI)-treatment free interval of at least 6 months in the following context:

- On the basis of the clinical study by Petrucci et al. (2013),[1] the indication for bortezomib in the U.S. was expanded in 2014 to include retreatment in patients who have previously responded to bortezomib and who have relapsed at least 6 months after completing prior bortezomib treatment. Notably, patients who were retreated in this study were only allowed retreatment with either single agent bortezomib (V) or bortezomib and dexamethasone (Vd).
- Clinical trials using a doublet Vd control arm after previously responding to prior PI treatment were required to implement the 6-month interval based on the data supporting the US label change. The BOSTON trial design was therefore required to follow the retreatment data supporting the U.S. prescribing information as the control arm of the study was the doublet Vd. The SVd regimen will be administered as a triplet in PI-sensitive patients.
- In relapsed and refractory multiple myeloma, second and later remissions tend to be shorter and may be more aggressive. Relapsing patients who present with symptomatic relapse with prominent new or worsening CRAB symptoms require immediate treatment to prevent further end-organ damage. If SVd is determined to be the most appropriate course of therapy for a patient, requiring a 6-month PI-treatment free interval before commencing SVd could eliminate access to an effective line of therapy for patients.

Economic Evidence – Key Limitations

CADTH limitation: "The comparative impact of SVd on PFS and OS is highly uncertain … and the high degree of uncertainty in the sponsor's network meta-analysis" (pg 20, first bullet)

FORUS agrees that the submitted NMA, like all NMAs, was not intended to replace head-to-head trials. It was a valid approach to comprehensively present the relative efficacy of the treatments following industry standard guidelines. While not free from limitations, it presents a best estimate of relative OS and PFS of the treatments. Therefore, while there could be uncertainty around the absolute values presented in the NMA, the directionality presented by the NMA should not be discounted for decision-making purposes. Clinical experts consulted by CADTH agreed that while the overall magnitude of the treatment effects was uncertain, the general direction of effects could be reliable. The presence of Vd in the BOSTON trial also enabled us to indirectly compare a large number of comparators for SVd. Nevertheless, the data were still a limiting factor to carry out the ITC for all relevant outcomes (i.e., OS, PFS, ORR) for each of the eight comparators presented in the analysis. Assumptions were unavoidable for missing data. This was the best available course of action given the lack of available data. CADTH used an identical assumption in its own reanalysis of IsaKd cost-effectiveness[2] (p 117, Reanalysis 2).

CADTH limitation: "Whether SVd is associated with improved OS, relative to Vd alone is highly uncertain. While the sponsor's model predicts an incremental gain of 0.86 life years with SVd compared to Vd, this is not supported by the results of the BOSTON trial. …" (pg 20, 2nd bullet 2)

FORUS wishes to provide additional context with respect to CADTH's characterization of OS data from the BOSTON trial. First, although median OS was not reached, this does not have practical importance as to whether there will be more individuals surviving on SVd versus the comparator(s). While median OS is a common indicator used by clinicians, the fact that median OS was not reached does not prohibit inferences regarding additional survival effects. Second, the assumption in CADTH's reanalysis of the cost-utility analysis that OS is equal between SVd and Vd (i.e., HR 1.0) is not supported by data as it does not accurately reflect the OS evidence from the BOSTON trial and the clinical efficacy of SVd. Due to crossover in the BOSTON trial, CADTH's interpretation of the survival curves is misleading. As per the BOSTON clinical study report, of the 207 Vd-treated patients in the ITT population, 111 (53.6%) patients had progressive disease (PD).[3] Of those patients who had PD, 74 (66.7%) patients crossed over to SVd or Sd. A switch-adjusted HR based on the two-stage estimation method[4, 5] comparing overall survival on SVd versus Vd at any point in the study was 0.77.[3] This means that, on average, treatment with SVd over the trial was associated with a reduction in the rate of death, indicating an OS improvement among SVd-treated patients versus Vd. The 27-month survival rate based on Kaplan-Meier estimates was 45% and 63% for the Vd arm and SVd arm, respectively, leading to an NNT of 5.56 to save a life. The weighted average (2L and 3L+) base case HR for OS SVd vs. Vd used in the submitted model was 0.86. This estimate is less favorable to SVd compared to 0.77 and therefore resulted in a conservative OS benefit for SVd compared to Vd. Setting the SVd HR to 1 does not accurately reflect the results of the BOSTON trial, nor does it consider that crossover was a feature of the BOSTON trial design.

CADTH limitation: "Relative dose intensity (RDI) was used to reduce drug costs..." (pg 21, 2nd bullet)

FORUS wishes to provide our perspective that the methods applied to generate RDI did not ignore patients who received a higher dose. Of the SVd patients who underwent dose escalation, only a few had their selinexor dose escalated above a weekly dose of 100 mg. The remaining patients in the SVd arm had dose increases that were readjustments after a preceding dose reduction in selinexor. Dose delays and reductions were permitted in the protocol and assuming 100% dose intensity would be inconsistent with clinical trial and overestimate cost. The efficacy inputs included in the model are inherently associated with the actual doses received by patients in the BOSTON trial. For SVd and Vd, the median dosing from the BOSTON trial were used to inform RDI. For selinexor, median dose (80mg/kg) and mean dose were almost identical. RDI was applied to all comparator therapies in the economic model where data were available, and as reported in their respective pivotal trial

publications. In some cases, the comparator's RDI was greater than 100%. Additionally, drug wastage was not included in the base case submitted by FORUS. The exclusion of drug wastage underestimated the costs of the comparators and biased costs against selinexor. Selinexor is subject to very little if any drug wastage because it is supplied in perforated packages of 20 mg tablets, while the IV and SC comparators are subject to drug wastage.

CADTH limitation: "The model lacked flexibility to assess the cost-effectiveness of SVd by type of prior treatment received …." (pg 21, 4th bullet)
FORUS followed CADTH guidelines with respect to submitting a model with the full reimbursement population instead of specific subgroups. The reimbursed population being sought is after one prior treatment, with no distinction between transplant eligible and ineligible populations. It should be noted that BOSTON's inclusion criteria permitted patients with an extensive list of previous novel MM treatments and patients with renal impairment and other comorbidities.

Economic Evidence – Reanalysis results

CADTH re-analysis results: "assumed equivalent OS for SVd and Vd; …; assumed that all patients received a full dose of all drugs." (pg 21, 2nd bullet)
FORUS's opinion is that the sizeable ICER value presented in the re-analysis improperly characterizes the magnitude of the uncertainty in the model. By removing the assumption of equivalent OS from the stepped reanalysis (a reasonable approach, as discussed earlier in the Comments under Economic Evidence – Key Limitations), FORUS has back-calculated an ICER for SVd compared to Vd of approximately $264,000 per QALY. Further, by maintaining RDI from the BOSTON trial report, the ICER drops to approximately $196,000 per QALY, a significant difference from the reported ICER of $10,884,623 per QALY.

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	☐
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☒
	No	☐
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☒
	No	☐

Yes, the reimbursement conditions are clearly stated.
As noted in Comments to Section 1, FORUS has provided comments to highlight and provide context to the Conditions and Guidance. Notably, FORUS highlights the potential implications of implementation criteria #3 which requires a proteasome inhibitor (PI)-treatment free interval of at least 6 months. In addition, FORUS has provided perspective on the output of the exploratory re-analyses conducted by CADTH, which used an alternative set of assumptions around PFS, OS, and health state utility.

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

Sponsor's References

1. Petrucci MT, Giraldo P, Corradini P, et al. A prospective, international phase 2 study of bortezomib retreatment in patients with relapsed multiple myeloma. *Br J Haematol*. 2013;160(5):649-659.

2. CADTH Reimbursement Review: Isatuximab (Sarclisa). Published online April 2022. Accessed April 21, 2022. https://www.cadth.ca/sites/default/files/DRR/2022/PC0256-Sarclisa-CombinedReport.pdf

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