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Reimbursement Recommendation

Isatuximab (Sarclisa)

Indication: In combination with bortezomib, lenalidomide, and dexamethasone for the treatment of patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant

Sponsor: Sanofi-Aventis Canada Inc.

Final recommendation: Reimburse with conditions

Summary

What Is the Reimbursement Recommendation for Sarclisa?

Canada's Drug Agency (CDA-AMC) recommends that Sarclisa be reimbursed by public drug plans for the treatment of patients with newly diagnosed multiple myeloma (MM) who are not eligible for autologous stem cell transplant (ASCT) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Sarclisa should only be covered to treat patients who have newly diagnosed MM and who have not received any treatment for their disease. Patients also have to be unable to receive a stem cell transplant and should have a good performance status.

What Are the Conditions for Reimbursement?

Sarclisa should only be reimbursed in combination with bortezomib-lenalidomide-dexamethasone (VRd) and if it is prescribed by clinicians with expertise in MM. The total cost of Sarclisa in combination with VRd should be negotiated so that it does not exceed the total drug program cost associated with daratumumab-lenalidomide-dexamethasone (DRd).

Why Did CDA-AMC Make This Recommendation?

- Evidence from a clinical trial demonstrated that treatment with Sarclisa in combination with VRd delayed cancer progression, and more patients had a fewer myeloma cells that survived after treatment (i.e., achieved minimal residual disease [MRD] negativity) compared to VRd alone.
- Sarclisa meets some of the needs that were identified by patients as it is an additional treatment option that delays disease progression.
- Based on the CDA-AMC assessment of the health economic evidence, Sarclisa in combination with VRd does not represent good value to the health care system at the public list price. The committee determined that there is not enough evidence to justify a greater cost for Sarclisa in combination with VRd compared with DRd.
- Based on public list prices, Sarclisa in combination with VRd is estimated to result in cumulative cost savings to the public drug plans of approximately $23 million over the next 3 years. However, the actual budget impact is uncertain because Sarclisa is administered intravenously, which requires infusion chair time, patient monitoring at treatment centres, and sterile compounding. These requirements are expected to place greater demands on health system resources compared with DRd.

Summary

Additional Information

What Is Multiple Myeloma?

MM is a cancer of plasma cells (the white blood cells that make antibodies). It is more common in older adults, and accounts for 10% to 15% of all blood cancers. In Canada, it was estimated that 4,100 people would be diagnosed with MM in 2024, and 1,750 would die of the disease.

Unmet Needs in Multiple Myeloma

There is no cure for MM and there is an unmet need for new treatments that are better at controlling the disease by delaying the first relapse and that are less toxic.

How Much Does Sarclisa Cost?

Treatment with Sarclisa is expected to cost approximately $25,643 in cycle 1, $17,559 in cycles 2 to 4, $13,619 in cycles 5 to 17, and $7,555 in cycles 18 and beyond per patient per 28-day treatment cycle.

Recommendation

The pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that isatuximab be reimbursed in combination with VRd (IsaVRd) for the treatment of patients with newly diagnosed MM who are not eligible for ASCT only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing, randomized, open-label, parallel-group, phase III trial (IMROZ; N = 446) demonstrated that treatment with IsaVRd resulted in added clinical benefit compared with VRd in adult patients with newly diagnosed MM who were ineligible for ASCT. At the second planned interim analysis, treatment with IsaVRd resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to VRd (hazard ratio [HR] = 0.596; 95% confidence interval [CI], 0.406 to 0.876) as well as a significant improvement in MRD-negative complete response (CR) rate (55.5% versus 40.9%). Additional analyses of PFS for IsaVRd versus VRd at the landmark time points of 18 months (88.2% [95% CI, 83.5 to 91.6] versus 79.6% [95% CI, 72.6 to 85.0]), 36 months (76.1% [95% CI, 70.2 to 80.9] versus 66.4% [95% CI, 58.3 to 73.2]), and 60 months (63.2% [95% CI, 56.2 to 69.4] versus 45.2% [95% CI, 35.6 to 54.2]) were supportive of the progression-free advantage demonstrated by IsaVRd. pERC could not draw definitive conclusions on the impact of IsaVRd on overall survival (OS) because the data were immature and median OS was not reached at the interim analysis.

Despite the number of publicly funded treatments available for newly diagnosed MM in Canada, there is a lack of direct comparative evidence for IsaVRd and other treatments, particularly DRd, which pERC considered the most relevant comparator. Per the sponsor-submitted indirect evidence, there was no difference detected between IsaVRd and DRd for PFS or OS at 1 year or 5 years. However, pERC noted several limitations of the indirect treatment comparisons (ITCs), including the immaturity of the IMROZ trial data, the inability to adjust for important effect modifiers, and the small sample sizes. Most estimates were also affected by significant imprecision due to wide 95% CIs, reducing the ability to draw firm conclusions on the comparative efficacy of IsaVRd from the ITCs.

MM is an incurable disease, and pERC agreed that there is an unmet need for additional therapies that effectively delay first relapse. Patients identified a need for treatments with manageable side effects that control the disease, prolong remission, and maintain quality of life (QoL) compared with currently available treatments. Given the totality of the evidence, pERC concluded that IsaVRd meets some of these needs by delaying progression and controlling the disease. Although the results suggested no detriment to health-related quality of life (HRQoL) compared to VRd, pERC was unable to draw definitive conclusions on the effect of IsaVRd on patients' QoL due to limitations of the evidence.

Using the sponsor-submitted price for isatuximab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for IsaVRd was $311,681 per quality-adjusted life-year (QALY) compared with DRd. In the absence of direct comparative evidence, and because of the limitations of the indirect clinical data, there is considerable uncertainty regarding the cost-effectiveness of IsaVRd relative

to DRd. As such, the total cost of IsaVRd should not exceed the total cost of treatment with DRd for adult patients with newly diagnosed MM who are not eligible for ASCT.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with IsaVRd should only be initiated in adult patients with previously untreated multiple myeloma who are ineligible for ASCT.	In the IMROZ trial, treatment with IsaVRd demonstrated a clinical benefit in adult (≥ 18 years) patients with symptomatic multiple myeloma, as defined by the IMWG criteria, who were ineligible to undergo ASCT due to their age (65 years or older) or to coexisting conditions.	—
2. Patients must have good performance status.	The IMROZ trial excluded adults with an ECOG performance status greater than 2. Overall, only 48 patients (10.8%) enrolled in the IMROZ trial had an ECOG performance status score of 2, and 1 patient had an ECOG of 3.	Patients with an ECOG performance status greater than 1 may be treated at the discretion of the treating clinician.
3. Patients must not have either of the following: 3.1. received prior systemic therapy or SCT for multiple myeloma 3.2. a left ventricular ejection fraction < 40%.	The IMROZ trial excluded patients with these characteristics. As such, the potential benefit of IsaVRd in these patients has not been demonstrated.	—
Discontinuation		
4. Treatment should be discontinued upon the occurrence of either of the following: 4.1. evidence of disease progression according to IMWG criteria 4.2. unacceptable toxicity.	Patients in the IMROZ trial discontinued treatment upon progression or unacceptable toxicity, which is consistent with clinical practice.	—
Prescribing		
5. IsaVRd should be prescribed by clinicians with expertise in managing transplant-ineligible newly diagnosed multiple myeloma.	This is meant to ensure that IsaVRd is prescribed for appropriate patients and that adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. The total cost of IsaVRd should be negotiated so that it does not exceed the total cost of treatment with DRd for adult patients with newly diagnosed multiple myeloma who are not eligible for ASCT.	Based on public list prices, the ICER for IsaVRd is $311,681 per QALY gained compared with DRd. Given the lack of head-to-head evidence and limitations with the indirect clinical evidence, the cost-effectiveness of IsaVRd relative to DRd remains highly uncertain. Hence, there is insufficient justification for a price premium for IsaVRd over DRd. To align with the available	—

Reimbursement condition	Reason	Implementation guidance
	clinical evidence, the total cost of IsaVRd should not exceed that of DRd.	
Feasibility of adoption		
7. The organizational feasibility of delivering IsaVRd must be addressed.	IsaVRd includes IV administration of isatuximab, which requires infusion chair time, patient monitoring at treatment centres, and sterile compounding. These requirements are expected to place greater demands on health system resources compared with DRd, which includes subcutaneous administration of daratumumab. As such, IsaVRd may impact infusion capacity, staffing, and infrastructure at cancer treatment centres.	—

ASCT = autologous stem cell transplant; DRd = daratumumab-lenalidomide-dexamethasone; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; IMWG = International Myeloma Working Group; IsaVRd = isatuximab-bortezomib-lenalidomide-dexamethasone; QALY = quality-adjusted life-year.

Discussion Points

- **Unmet need:** MM is an incurable cancer that is associated with significant impairment to patients' QoL because of both the disease and the toxicity of treatment. pERC discussed the input from patient and clinician groups as well as clinical experts, all of whom noted that, despite the treatments currently available, most patients progress and continue to experience myeloma symptoms and even death. pERC discussed the need for more effective first-line therapies that delay first relapse and progression. The committee felt that IsaVRd may meet some of these needs, providing an additional treatment with clinically meaningful and durable responses. However, pERC was unable to ascertain whether IsaVRd met the unmet needs identified versus DRd — the most relevant comparator for patients with newly diagnosed MM who are ineligible for or decline to receive ASCT — due to a lack of direct comparative evidence and limitations associated with the submitted indirect evidence.
- **Relevant comparators and place in therapy:** pERC discussed the relevance of the comparator in the IMROZ trial (VRd), noting that daratumumab-based regimens, specifically DRd, are the most relevant and widely used treatments in patients with newly diagnosed MM who are ineligible for or decline to receive ASCT in the Canadian clinical setting. pERC also discussed the place in therapy of IsaVRd given the current treatment landscape and considering the differences between IsaVRd and DRd that are often considered when choosing treatment options (e.g., mode of administration [IV versus subcutaneous], ease of access, chair time, hospital visits). pERC also noted the potential change in therapeutic landscape considering the recently published results of the CEPHEUS trial of daratumumab plus VRd for this indication.
- **Certainty of evidence:** pERC discussed the pivotal evidence submitted for this review which consisted of 1 phase III, open-label randomized controlled trial (IMROZ). pERC noted treatment with IsaVRd resulted in statistically significant and clinically meaningful improvements in PFS compared with VRd; this was associated with a moderate level of certainty per the CDA-AMC Grading of

Recommendations, Assessment, Development and Evaluation (GRADE) assessment. For the outcomes OS and HRQoL, the certainty of evidence was rated as low. For OS, this was primarily due to the immaturity of the results (median OS not reached, and only 26.0% and 32.6% of patients experienced OS events in the IsaVRd and VR groups, respectively). pERC also noted that longer follow-up for OS is likely to be confounded by subsequent treatments. Overall, this precluded the committee from drawing conclusions on the effect of IsaVRd on OS. For HRQoL, pERC noted that, despite the low certainty rating, there did not appear to be detriment to HRQoL, although there was a substantial amount of missing data due to attrition.

- **Indirect evidence:** pERC discussed the sponsor-submitted indirect evidence, which included unanchored matching-adjusted indirect comparisons (MAICs) comparing IsaVRd to daratumumab-bortezomib-melphalan-prednisone (DVMP), DRd, Rd, and daratumumab-cyclophosphamide-bortezomib-dexamethasone (DCyBorD) as well as a nonrandomized comparison using inverse probability treatment weighting methods to compare IsaVRd to cyclophosphamide-bortezomib-dexamethasone (CyBorD) using real-world individual patient data from the Flatiron data. pERC highlighted that for the comparison with DRd in the MAIC, there was no difference detected between IsaVRd and DRd for PFS at 1 year (HR = [redacted]) and 5 years (HR = [redacted]), as well as for OS at 1 year (HR = [redacted]) and 5 years (HR = [redacted]). pERC noted that, compared with other daratumumab-based regimens (DVMP and DCyBorD), results for PFS generally favoured IsaVRd at 1 year, but there was no difference between IsaVRd and DCyBorD at 5 years, while there was no difference for OS at either time point. pERC also highlighted the limitations with the indirect evidence, noting the immaturity of the efficacy data from the IMROZ trial, the inability to adjust for various effect modifiers due to lack of reporting, and the dichotomization of effect-modifying categories, as well as the small effective sample sizes after matching with reductions ranging from [redacted] to [redacted] across analyses, which could render the results unstable and imprecise. Additionally, the ITCs did not assess HRQoL or safety outcomes, precluding pERC from drawing conclusions on these important outcomes.
- **Generalizability:** pERC discussed the eligibility criteria of the IMROZ trial, which excluded patients older than 80 years of age, and patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) greater than 2. No patients older than 80 years were enrolled, and most patients enrolled had an ECOG PS of 0 or 1 (89.0%); 10.8% of patients enrolled had an ECOG PS of 2. pERC noted that patients aged 80 years and older and those with ECOG PS greater than 1 may be treated on a case-by-case basis at the discretion of the treating clinician. This clinical decision may be based on, among other factors, a patient's frailty assessment, and whether frailty is attributed to disease-related symptoms rather than other characteristics such as age, cognitive conditions, or physical conditions. However, pERC and the clinical experts noted the lack of evidence for these patients. The clinical experts also noted that the quadruplet regimen of IsaVRd may be a good option for patients with renal impairment, with the potential to adjust dosing of individual drugs as needed, noting that the VRd backbone, particularly lenalidomide and dexamethasone, is the most toxic component of the regimen.

- **Economic considerations:** pERC identified substantial remaining uncertainty in the economic analysis, particularly with respect to the relative efficacy of IsaVRd versus DRd. This uncertainty stems from the lack of head-to-head comparative evidence and limitations in the sponsor's indirect treatment comparisons. pERC also noted that most of the QALY benefit for IsaVRd was derived from extrapolation in the posttrial period, reflecting model-based outcomes rather than direct trial evidence. pERC highlighted differences in the mode of administration between IsaVRd and DRd. Isatuximab is administered intravenously, which requires chair time, patient time at treatment centres, travel time to treatment centres for both patients and caregivers, and sterile compounding. In contrast, daratumumab is delivered as a subcutaneous injection, which is expected to place less demand on health system resources. The CDA-AMC base case incorporated administration-related costs, including infusion chair time, nursing and pharmacist wages to account for observation and preparation time, respectively, and a physician specialist fee to reflect supervision of the infusion. In this analysis, IsaVRd was associated with $11,712 higher administration costs over the patients' lifetime compared with DRd ($25,886 versus $14,174). pERC noted that administration costs in real-world clinical practice may be higher than those estimated in the model due to more pronounced differences in chair time, administration frequency, and care setting for isatuximab relative to daratumumab. In addition, pERC observed that although the incremental differences in total treatment costs between IsaVRd and DRd are small, the use of weight-based dosing for isatuximab compared with flat dosing for daratumumab could result in higher real-world treatment costs for IsaVRd. These considerations further underscore the need for IsaVRd to be priced such that its total treatment cost does not exceed that of DRd.
- **Budget impact considerations:** pERC noted that the estimated budget impact, which suggests cost savings with the reimbursement of IsaVRd, is subject to uncertainty due to limitations in the sponsor-submitted model, most notably the exclusion of subsequent therapy costs from the analysis. pERC emphasized that the exclusion of subsequent therapy costs prevents a complete estimation of the budgetary impact associated with the adoption of IsaVRd in clinical practice because differences in progression rates and treatment sequences may lead to downstream cost implications. Finally, at pERC's request, an additional analysis was conducted from the broader Canadian health care payer perspective to incorporate administration costs associated with IV and subcutaneous treatments. When administration costs were included, the reimbursement of IsaVRd for this indication was associated with cost savings of $15,216,695 over 3 years. This was a reduction in cumulative cost savings compared with the CDA-AMC base case, in which the reimbursement of IsaVRd was associated with cost savings of $23,184,144 over 3 years.

Background

MM is an incurable, malignant plasma cell disease that originates from multipotent hematopoietic cells in the bone marrow. It is characterized by clonal proliferation of plasma cells in the bone marrow and excess production of a monoclonal immunoglobulin (Ig). As malignant plasma cells or myeloma cells accumulate in

the bone marrow, they may form localized tumours or plasmacytomas. They also may interfere with normal blood cell production. When multiple plasmacytomas form either within or outside the bone, the condition is known as MM. Worldwide, MM is the second most common hematologic cancer and it is the 15th most diagnosed cancer in Canada. There is limited information on the prevalence of MM in Canada; however, in 2024, it was estimated that 4,100 Canadians were diagnosed and 1,750 would die from it. According to GLOBOCAN 2022 data, the 5-year prevalence for both sexes in North America was 117,011 cases, accounting for 21.7% of all prevalent cases worldwide. In Canada, the 1-year prevalence (2022 data for both sexes) was reported to be 4,044 cases or 10.5 per 100,000 population, whereas the 5-year prevalence was 14,553 cases or 37.9 cases per 100,000 population.

In eligible patients who were previously untreated, newly diagnosed MM is usually treated with ASCT following induction therapy (i.e., typically with high-dose chemotherapy). However, the number of patients who may not be eligible for ASCT is estimated to be as high as 81%. Further, not all patients who are eligible for ASCT are willing to undergo therapy. Despite treatment advances over the past 2 decades, MM remains an incurable disease with the treatment options currently available.

Isatuximab is currently under review in combination with VRd for the treatment of adult patients with transplant-ineligible, newly diagnosed MM; Notice of Compliance was received on April 17, 2025. Isatuximab has been approved by Health Canada in combination with pomalidomide and dexamethasone for the treatment of patients with relapsed and refractory MM who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor as well as in combination with carfilzomib and dexamethasone for the treatment of adult patients with relapsed or refractory MM who have received 1 to 3 prior lines of therapy.

Isatuximab is a monoclonal antibody that binds to a specific extracellular epitope of CD38, triggering mechanisms that result in the death of CD38-expressing tumour cells. It is available as an IV infusion and the dosage recommended in the product monograph is 10 mg/kg.

Sources of Information Used by the Committee

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

- a review of 1 ongoing, randomized, open-label, phase III trial in patients with newly diagnosed MM who are not eligible for ASCT and 2 indirect treatment comparisons (1 matching-adjusted indirect treatment comparison and 1 nonrandomized, observational comparison)
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans and cancer agencies that participate in the reimbursement review process
- 2 clinical specialists with expertise diagnosing and treating patients with MM
- input from 2 clinician groups, the Canadian Myeloma Research Group (CMRG) and the Ontario Health (OH) (Cancer Care Ontario [CCO]) Hematology Cancer Drug Advisory Committee
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Myeloma Canada, an advocacy group supporting individuals with MM, provided input for the CDA-AMC review of isatuximab. Information for this submission was gathered through an online survey of patients and caregivers conducted by Myeloma Canada from October 11 to November 10, 2024. The survey was distributed via email and social media by Myeloma Canada and the Leukemia and Lymphoma Society of Canada.

Of 43 survey responses, 24 were complete and eligible and divided into 2 subsets: 22 respondents ineligible for or not receiving ASCT as first-line therapy and 2 patients who received IsaVRd as first-line therapy.

Respondents rated the most important myeloma symptoms to control as bone issues, such as fractures or pain (extremely important), followed by infections, mobility, and neuropathy. Myeloma symptoms were reported to have a significant impact on daily activities and QoL, with respondents indicating an extreme effect on their ability to travel, work, and carry out household chores. The factors that patients considered most important to myeloma treatment consisted of effectiveness and remission, overall QoL, manageable side effects, minimizing hospital visits, and ease of access.

The 2 respondents with IsaVRd experience reported having received the treatment for 1 to 2 years. They found supportive care very effective, with treatment side effects and hospital visits having a slight to moderate negative impact on QoL. Both respondents rated IsaVRd as effective in controlling myeloma and manageable in terms of side effects. Despite side effects such as diarrhea, infections, and neuropathy, they reported overall improved QoL, with 1 respondent noting significant health improvements.

Clinician Input

Input From Clinical Experts Consulted by CDA-AMC

According to the clinical experts consulted by CDA-AMC, newer and more cost-effective treatments are welcomed because the currently available options are limited.

Unmet Needs

In the absence of a cure for MM, the goal is to prevent disease progression and prolong QoL. Even so, a significant number of patients on the current standard of care in Canada (DRd) progress after 8 months of treatment, and therefore never reach the landmark 5-year PFS average. Prognosis is even worse for patients with early relapses because no other therapy offers this duration of response. Because the average age of individuals with MM is within the transplant-ineligible category, there is an unmet need for treatments that effectively delay first relapse, reduce frailty caused by progressive disease, and minimize health care utilization related to symptoms of progressive disease.

Place in Therapy

According to the clinical experts, IsaVRd would be an alternative to the currently funded first-line therapy for patients with transplant-ineligible MM (e.g., DRd). It is expected that combinations using isatuximab would

be equally considered for first-line treatment in this patient population. VRd may be used more frequently because some patients starting on IsaVRd may not tolerate the side effects of isatuximab and remain on VRd only.

Patient Population

All patients requiring first-line therapy for transplant-ineligible MM would be eligible for treatment with IsaVRd.

Assessing the Response Treatment

In addition to traditional measures of response as per IMWG response criteria, reductions in the frequency and/or severity of symptoms, such as bone pain and renal failure, are documented monthly with laboratory investigations. Improvement in QoL and function would be expected with better and faster response to therapy.

Discontinuing Treatment

The clinical experts noted that treatment discontinuation is guided by IMWG response criteria or clinically determined progressive disease and intolerable side effects (e.g., infusion reactions and infection).

Prescribing Considerations

IsaVRd would be considered as a first-line treatment option for individuals with transplant-ineligible MM. The clinical experts noted that a myeloma therapy expert would be needed to facilitate therapy.

Clinician Group Input

Two clinician groups comprising 19 clinicians provided input for this review: the CMRG (13 clinicians contributed to the input) and the OH (CCO) Hematology Cancer Drug Advisory Committee (6 clinicians contributed to the input). Overall, the input was aligned with the input from the clinical experts consulted by CDA-AMC.

The OH (CCO) Hematology Cancer Drug Advisory Committee highlighted the lack of comparative data with DRd and noted that isatuximab's IV administration may be less appealing than daratumumab's subcutaneous option. The clinical experts consulted by CDA-AMC noted that this may be a less-relevant issue once isatuximab subcutaneous administration becomes approved.

The CMRG pointed out that the key shift in treatment would involve adding bortezomib to the anti-CD38 monoclonal antibody lenalidomide and a steroid backbone, which would support IsaVRd as the new first-line standard of care for newly diagnosed, transplant-ineligible MM due to its potential for greater efficacy than VRd alone. They also remarked that although isatuximab requires longer infusion times, shorter durations are feasible. Furthermore, patients who are bortezomib refractory in the frontline setting could still benefit from carfilzomib-based regimens, making IsaVRd unlikely to alter the relapsed treatment landscape significantly.

Drug Program Input

The clinical experts consulted for the review provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
Funded treatment options for patients with newly diagnosed transplant-ineligible myeloma include VRd, DRd, DCyBorD, and DVMP. The trial compared IsaVRd against VRd, with 4 induction cycles of VRd ± isatuximab, followed by continuous Rd ± isatuximab until disease progression or unacceptable toxicity. How does IsaVRd compare to DRd, DCyBorD, or DVMP?	The clinical experts theorized that IsaVRd would have better, if not similar, efficacy to DRd but that head-to-head trials would be needed to confirm this. The experts also noted that DCyBorD and DVMP are not commonly used due to their safety profiles and clinical inferiority compared with DRd. Additionally, the MRD response rates are higher with the combinations containing bortezomib. pERC agreed with the clinical experts but noted that the comparisons between DCyBorD and DVMP relative to DRd were not evaluated.
Considerations for initiation of therapy	
Should patients with the following be considered for IsaVRd: • age > 80 years • ECOG PS > 2 • amyloidosis, monoclonal gammopathy of undetermined significance, or smouldering multiple myeloma • concomitant plasma cell leukemia • high-risk cytogenetics?	The clinical experts confirmed that these patient populations should be considered for IsaVRd on a case-by-case basis. pERC agreed with the clinical experts. However, pERC and the clinical experts noted that amyloidosis is a different disease from myeloma and patients with monoclonal gammopathy of undetermined significance or smouldering myeloma would not be treated; thus, treatment with IsaVRd is not warranted in these populations. The clinical experts noted that delivery of treatment would vary depending on the situation (e.g., may start oral treatments only in patients aged > 80 years, and add on other treatments if tolerated). A frailty assessment would also be better than age itself. Age does contribute to frailty, but it is not unto itself the only definition of frailty.
Considerations for continuation or renewal of therapy	
Should cyclophosphamide be added to IsaVRd upon biochemical progression, given the clinical practice of adding cyclophosphamide to other myeloma regimens to prolong the response.	pERC agreed with the clinical experts that adding cyclophosphamide is not recommended because it is generally used as a bridging therapy and only adds more toxicity without an expectation of real benefit.
Should treatments be resumed if prolonged treatment breaks occur?	The clinical experts confirmed that treatment should be resumed if progression has not occurred before the prolonged treatment break. pERC agreed with the clinical experts.
If one of the drugs is discontinued, can the other drugs in the regimen be continued until disease progression or unacceptable toxicity?	The clinical experts confirmed that if one of the drugs in the regimen is discontinued, then the treatment can continue with the other drugs in the regimen until disease progression or unacceptable toxicity. pERC agreed with the clinical experts.

Implementation issues	Response
Considerations for prescribing of therapy	
The dosing schedule for VRd in the IMROZ trial appears different from that used in jurisdictions in Canada (weekly at a dose of 1.3 mg/m^2 to 1.5 mg/m^2). Are there alternative dosing schedules for bortezomib or VRd that can be used?	pERC and the clinical experts noted that bortezomib should be dosed at the Canadian and international standard of once weekly.
Rapid infusion for isatuximab has been adopted by some jurisdictions to save on chair time.	This is a comment from the drug plans to inform pERC deliberations, although pERC and the clinical experts highlighted that this should be conducted when possible.
Generalizability	
On a time-limited basis, should isatuximab be added to patients receiving VRd?	pERC agreed with the clinical experts that this should be considered for this patient population.
Funding algorithm	
Under what clinical circumstances would IsaVRd be preferred over daratumumab-based regimens and vice versa? Note: If the patient's disease progresses on an anti-CD38 biologic, then the patient would not be eligible for any downstream anti-CD38 biologic.	The clinical experts noted that IsaVRd would be a substitute for daratumumab-based regimens and the choice would come down to patient and clinician preference on a case-by-case basis. pERC also noted that efficacy and safety of IsaVRd has not been demonstrated in patients older than 80 years, although pERC agrees that use in this population according to clinician judgment on a case-by-case basis is acceptable.
Care provision issues	
Isatuximab interferes with blood compatibility testing; hence, the product monograph recommends that patients undergo phenotyping before the first isatuximab infusion.	This is a comment from the drug plans to inform pERC deliberations.
System and economic issues	
In the trial, prophylactic administration of G-CSF was given at the investigator's discretion if there was recurrent neutropenia or if there were serious neutropenic complications.	This is a comment from the drug plans to inform pERC deliberations.
Confidential prices exist for daratumumab.	This is a comment from the drug plans to inform pERC deliberations.

DCyBorD = daratumumab-cyclophosphamide-bortezomib-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVMP = daratumumab-bortezomib-melphalan-prednisone; ECOG PS = Eastern Cooperative Oncology Group Performance Status; G-CSF = granulocyte colony-stimulating factor; IsaVRd = isatuximab-bortezomib-lenalidomide-dexamethasone; MRD = minimal residual disease; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; Rd = lenalidomide-dexamethasone; VRd = bortezomib-lenalidomide-dexamethasone.

Clinical Evidence

Systematic Review

Description of Studies

The systematic review included 3 reports of 1 pivotal trial (IMROZ). IMROZ is an ongoing, prospective, international (no sites in Canada), multicentre, open-label, parallel-group, phase III randomized controlled trial to assess the clinical benefit of IsaVRd compared to VRd alone in patients with newly diagnosed MM

who are not eligible for ASCT. A total of 446 patients were randomized in a 3:2 ratio to IsaVRd (n = 265) or VRd (n = 181). Randomization was stratified by country (China versus other countries), age (younger than 70 years versus 70 years or older), and Revised International Staging System (R-ISS) stage I to II versus stage III versus not classified (i.e., inconclusive fluorescence in situ hybridization [FISH] unless the randomization stratum could be determined based on lactate dehydrogenase, albumin, and beta-2 microglobulin only). Patients in the IsaVRd group received isatuximab 10 mg/kg IV in 42-day cycles (cycles 1 to 4) or 28-day cycles (after 4 cycles) in combination with VRd. Patients were treated until they died, experienced disease progression or unacceptable toxicity, or they decided to discontinue study treatment. The primary outcome was PFS, and the key secondary outcomes included MRD and OS. During the continuous treatment period, patients randomized to the VRd group who had confirmed progressive disease during the VRd portion of the continuous treatment period (as assessed by the investigator) could cross over to the IsaVRd group. Harms, including treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events (AEs) of special interest, were also measured and reported. Patient-reported outcomes (e.g., HRQoL) were also measured.

The average age of patients was 71.5 years (standard deviation = 4.8 years); 53.1% of patients were male and 46.9% were female. Most patients (89.0%) had an ECOG PS of 0 or 1. The most common ISS stage at study entry was stage I (53.0%), followed by stage II (31.1%) and stage III (15.2%). The MM subtype at baseline was most frequently IgG (64.1%), and the R-ISS stage at study entry was most frequently stage II (n = 286; 64.1%). The median time from initial diagnosis to randomization was 1.18 months. The main reason for transplant ineligibility was age 65 years or older (95.7%).

Unless otherwise specified, all data reported are from the second interim analysis for the IMROZ trial corresponding with a data cut-off date of September 26, 2023, and reported for the intention-to-treat population. This data cut-off corresponds with the planned second PFS interim analysis cut-off date (i.e., date when 167 PFS events [75% information fraction] from the global population were expected to be observed). At the data cut-off date of September 26, 2023, a total of 162 PFS events were observed, as determined by an independent review committee (IRC). The median follow-up time at this data cut-off point was 59.73 months (range, 0.17 to 68.99 months).

Efficacy Results

At the data cut-off date of September 26, 2023, 78 (43.1%) patients in the VRd group and 84 (31.7%) patients in the IsaVRd group experienced PFS events. The median PFS was 54.34 months (95% CI, 45.21 months to not calculable) in the VRd group and not reached in the IsaVRd group. The HR was 0.596 (98.5% CI, 0.406 to 0.876) in favour of the IsaVRd group compared to the VRd group. At 60 months, the PFS probability was 45.2% in the VRd group and 63.2% in the IsaVRd group. The risk difference at 60 months was 18.0% (95% CI, 6.5% to 29.5%). The results for sensitivity analyses (e.g., without censoring for further antimyeloma treatment, using investigator assessment of response, without censoring of progression or death occurring at least 13 weeks after the last valid disease assessment), and planned subgroup analyses (e.g., by age, sex, race, geographic location) were consistent with the primary analysis.

At the interim analysis, 128 deaths had occurred (VRd group = 59; IsaVRd group = 69) representing an OS information fraction of 63%. The median OS was not calculable at the data cut-off date for the IsaVRd or VRd groups (HR = 0.776; 99.97% CI, 0.407 to 1.48). OS was not formally analyzed due to an earlier failure of the statistical hierarchy (the final OS analysis will be conducted when there are 202 deaths). The OS event-free probability at 60 months was 66.3% in the VRd group and 72.3% in the IsaVRd group, representing an absolute risk difference of 5.9% (95% CI, –3.3% to 15.2%).

The overall response rate was similar in the VRd and IsaVRd groups (92.3% versus 91.3%; OR = 0.888; 95% CI, 0.439 to 1.794). The CR rate (consisting of patients with stringent CR and CR) was statistically significant in favour of IsaVRd (odds ratio = 1.656; 95% CI, 1.097 to 2.500) with a CR or better in 74.7% of patients in the IsaVRd group compared with 64.1% in the VRd group. The MRD negativity rate for patients with a CR was statistically lower in the VRd group (40.9%) compared with the IsaVRd group (55.5%; OR = 1.803, 95% CI, 1.229 to 2.646). The rate of very good partial response or better based on IRC assessment was 82.9% in the VRd group and 89.1% in the IsaVRd group (odds ratio = 1.729; 95% CI, 0.994 to 3.008). The P value did not cross the multiplicity-adjusted efficacy boundary of 0.025. Most (> 90%) patients in both treatment groups achieved a tumour response.

HRQoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Completion rates were more than 90% of patients to cycle 14, and more than 80% at each cycle among patients remaining in follow-up; however, the total number of patients declined over time. Global health status remained stable throughout the treatment period, with no apparent differences between groups regarding change from baseline.

Harms Results

Most patients had a TEAE (IsaVRd group = 99.6%; VRd group = 98.3%), with the most frequently reported TEAEs (≥ 10% of patients) in the IsaVRd and VRd treatment groups being peripheral sensory neuropathy (54.4% versus 60.8%), diarrhea (54.8% versus 48.6%), constipation (35.7% versus 40.9%), upper respiratory tract infection (34.2% versus 33.7%), peripheral edema (32.7% versus 32.6%), fatigue (34.6% versus 26.5%), and cataracts (38.0% versus 25.4%).

More individuals in the IsaVRd group had a grade 3 or greater TEAE compared with those in the VRd group (91.6% versus 84.0%). Similarly, more patients in the IsaVRd group had treatment-emergent SAEs than in the VRd group (70.7% versus 67.4%). The most frequently reported SAE (≥ 10% of patients in either treatment group) was pneumonia (29.7% in the IsaVRd group versus 21.0% in the VRd group).

TEAEs leading to definitive treatment discontinuation were reported in 22.8% of patients receiving IsaVRd and 26.0% of patients receiving VRd. The most frequent reason for definitive treatment discontinuation in the IsaVRd and VRd groups was due to COVID-19 pneumonia (3.0% versus 0.6%).

There were 128 deaths reported (IsaVRd group = 26.2%; VRd group = 32.6%). AEs accounted for 11.0% in the IsaVRd group and 6.1% in the VRd group.

Infusion reactions and infections were notable harms of interest to this review. Infusion reactions were more frequent with IsaVRd compared to VRd (23.6% versus 1.1%). The rate of infections was similar across

groups, occurring in 91.3% patients in the IsaVRd group and 86.7% patients in the VRd group, consisting primarily of pneumonia, upper respiratory tract infections, and COVID-19 infections.

Critical Appraisal

The randomization method and allocation concealment in the IMROZ trial were considered adequate. However, IMROZ was an open-label trial, and the lack of blinding may have biased results, particularly for subjective, patient-reported outcomes (e.g., HRQoL), harms reporting, or willingness to remain in the trial. Objective outcomes, such as death, and assessment of outcomes such as PFS were conducted by a blinded IRC, and therefore were unlikely to have been influenced by lack of blinding. Even so, there was an exploratory component to this trial in which patients in the VRd control arm were allowed to cross over to the IsaVRd arm after disease progression was confirmed. Multiplicity was controlled in the key secondary outcomes with the use of a hierarchical testing procedure; however, early failure of the hierarchy meant that statistical testing was not conducted for OS, one of the key secondary outcomes, and no inferences could be drawn about differences between groups for this outcome. HRQoL was not included in the hierarchy and differences between groups were not tested statistically; therefore, no conclusions could be drawn about this outcome. Although the IMROZ trial is still ongoing, the available results were based on a planned interim analysis, with an information fraction of 75% for PFS; therefore, there is a risk of overestimation of the primary effect for PFS. However, because of the statistically significant difference observed between the groups and the calculation of the 98.5% CIs, the potential for overestimation is unlikely to alter the conclusions. In the analysis of PFS, 18.8% of patients in the VRd group and 23.8% in the IsaVRd group were censored due to not having a valid disease assessment in the 13 weeks before the data cut-off date (i.e., missed 2 or more scheduled disease assessments). Because the reason for missed assessments is not known, there is a potential for risk of bias due to informative censoring. There was no sensitivity analysis addressing this issue, and the direction of potential bias cannot be ascertained. At the data cut-off date, the OS information fraction was 63%. This is important because although PFS can be viewed as a surrogate for OS, death is not an immediate consequence of treatment failure because further lines of treatment can prolong life. Furthermore, the OS analysis is confounded by crossovers (the risk of bias may be toward the null). As the trial progressed, more patients discontinued treatment or died. This may have led to attrition bias for outcomes analyzed based on change in scores, such as HRQoL, or incidence of AEs, which were only documented for patients still being followed. For the latter, results were additionally reported after adjustment for the duration of exposure.

The IMROZ trial excluded patients older than 80 years and those with ECOG PS greater than 2; however, some patients with ECOG PS of 2 or greater were enrolled. The clinical experts noted that the efficacy of VRd in the trial was higher than would normally be expected, which could be the result of a learning curve in jurisdictions that use VRd regularly. Further, in the IMROZ trial, bortezomib was not dosed at the Canadian and international standard of once weekly. Finally, while the study was conducted in 96 sites (21 countries), none of the sites were in Canada.

GRADE Summary of Findings and Certainty of the Evidence

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- PFS: median, 18 months, 36 months, 60 months
- OS: median, 60 months
- HRQoL using the EORTC QLQ-C30: change from baseline
- number of individuals with SAEs: up to the data cut-off date.

Table 3: Summary of Findings for IsaVRd Versus VRd for Patients With Multiple Myeloma

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	Interpretation
			IsaVRd	VRd	Difference		
Survival outcomes (median follow-up = 59.7 months; range, 0.17 to 68.99 months)							
Probability of PFS by IRC at 18 months	446 (1 RCT)	[redacted]	882 per 1,000 (835 per 1,000 to 916 per 1,000)	796 per 1,000 (726 per 1,000 to 850 per 1,000)	86 more per 1,000 (13 per 1,000 to 159 more per 1,000)	Moderate[a]	IsaVRd likely results in an improvement in PFS compared to VRd.
Probability of PFS by IRC at 36 months	446 (1 RCT)	[redacted]	761 per 1,000 (702 per 1,000 to 809 per 1,000)	664 per 1,000 (583 per 1,000 to 732 per 1,000)	97 more per 1,000 (5 per 1,000 to 189 more per 1,000)	Moderate[a]	IsaVRd likely results in an improvement in PFS compared to VRd.
Probability of PFS by IRC at 60 months	446 (1 RCT)	[redacted]	632 per 1,000 (562 per 1,000 to 694 per 1,000)	452 per 1,000 (356 per 1,000 to 542 per 1,000)	180 more per 1,000 (65 to 295 more per 1,000)	Moderate[a]	IsaVRd likely results in an improvement in PFS compared to VRd.
Probability of OS by IRC at 60 months	446 (1 RCT)	[redacted]	723 per 1,000 (661 per 1,000 to 775 per 1,000)	663 per 1,000 (585 per 1,000 to 731 per 1,000)	59 more per 1,000 (33 fewer per 1,000 to 152 more per 1,000)	Low[b]	IsaVRd may result in an improvement in OS compared to VRd.
Patient-reported outcomes (HRQoL)							
EORTC QLQ-C30 global health status Follow-up: up to 90	446 (1 RCT)	NA	NA	The mean difference between groups in change from baseline in assessments using the EORTC QLQ-C30 was not tested statistically. The mean global health status appeared		Low[c]	IsaVRd may result in little to no difference in global health status compared to VRd

Outcome and follow-up	Patients (studies), N	Relative effect (95% CI)	Absolute effects (95% CI)			Certainty	Interpretation
			IsaVRd	VRd	Difference		
days after the last study treatment				relatively stable over time in both groups with wide overlapping CIs.			
Safety outcomes (treatment-emergent SAEs)							
SAEs Follow-up: up to 20 days after the last dose of study treatment[d]	444 (1 RCT)	RR = 1.05 (0.92 to 1.19)	707 per 1,000 (648 per 1,000 to 762 per 1,000)	674 per 1,000 (601 per 1,000 to 742 per 1,000)	33 more per 1,000 (54 fewer per 1,000 to 121 more per 1,000)	Moderate[e]	IsaVRd likely results in an increase in SAEs compared to VRd

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Core 30; HRQoL = health-related quality of life; IRC = independent review committee; IsaVRd = isatuximab-bortezomib-lenalidomide-dexamethasone; NA = not applicable; OS = overall survival; PFS = progression-free survival; RCT = randomized controlled trial; RR = risk ratio; SAE = serious adverse event; VRd = bortezomib-lenalidomide-dexamethasone.

Note: Study limitations (which refer to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

[a]No threshold of clinical importance could be established; effects were appraised using the null. Rated down 1 level for study limitations; 18.8% of patients in the VRd group and 23.8% in the IsaVRd group were censored due to not having a valid disease assessment in the 13 weeks before the data cut-off date (i.e., missed 2 or more scheduled disease assessments). Because the reason for missed assessments is not known, there is a potential for risk of bias due to informative censoring.

[b]Rated down 1 level for study limitations; results are from an interim analysis where OS was not formally tested, there is a risk of bias due to confounding as a result of crossover of patients from the VRd to the IsaVRd group postprogression, and there is a potential for risk of bias due to informative censoring. No threshold of clinical importance could be established; effects were appraised using the null. Rated down 1 level for imprecision; the point estimate suggests benefit and the CI includes no difference and potential harm.

[c]Rated down 2 levels for study limitations; there is risk of bias due to a lack of blinding and a subjective outcome as well as substantial missing outcome data.

[d]For patients in the VRd group who crossed over, the follow-up was to the crossover date minus 1 day.

[e]No threshold of clinical importance could be established; effects were appraised using the null. Rated down 1 level for imprecision; the point estimate suggests harm and the CI includes no difference and potential benefit (i.e., lesser harm than VRd).

Long-Term Extension Studies

There is no long-term extension phase planned for the IMROZ trial. The IMROZ trial remains ongoing with an anticipated completion date of June 30, 2027. No other long-term extension studies were included in the submission.

Indirect Comparisons

Description of Studies

Unanchored MAICs were used as the source of ITC to compare individual patient data for IsaVRd from the IMROZ trial to aggregate data from studies of DRd, Rd, DVMP, and DCyBorD. For the comparison with CyBorD (Flatiron data source), a nonrandomized comparison using inverse probability weighting methods was used because individual patient data were available for each arm.

Efficacy Results

Progression-Free Survival

The MAIC of IsaVRd versus DRd resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

The MAIC of IsaVRd versus DVMP resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

The MAIC of IsaVRd versus DCyBorD resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

The MAIC of IsaVRd versus Rd using data from the MAIA trial resulted in HRs of [redacted] at 1 year and [redacted] at 5 years. Using data from the FIRST trial, the HR was [redacted] at 1 year and [redacted] at 5 years.

The observational comparison of IsaVRd versus CyBorD resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

Overall Survival

The MAIC of IsaVRd versus DRd resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

The MAIC of IsaVRd versus DVMP resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

There were no data available to compare OS for IsaVRd versus DCyBorD.

The MAIC of IsaVRd versus Rd using data from the MAIA trial resulted in HRs of [redacted] at 1 year and [redacted] at 5 years. Using data from the FIRST trial, the HR was [redacted] at 1 year and [redacted] at 5 years.

The observational comparison of IsaVRd versus CyBorD resulted in HRs of [redacted] at 1 year and [redacted] at 5 years.

Harms Results

Harms were not evaluated in the submitted ITCs.

Critical Appraisal

The ITC analyses were preceded by a feasibility appraisal, and the decision to use MAICs and inverse probability weighting as the ITC method of choice (instead of network meta-analysis) was adequately justified. However, the unanchored nature of the comparisons imposes an unrealistic assumption that all prognostic factors and effect modifiers are adequately adjusted for. The choice of the adjustment factors was based on internal expert opinion and availability and completeness of data in the trials. An assessment of the potential magnitude of residual confounding was not presented for any comparison, therefore the extent of potential bias is unknown. The adjustment methods used cannot overcome methodological or design differences across the comparators which can introduce bias (e.g., region or setting, length of follow-up, outcome definitions [event and censoring rules, schedule and method of assessments], cointerventions, subsequent treatments). Important outcomes for decision-making, such as HRQoL and AEs, were not

included in the analyses even though the MAIC included real-world evidence that could have provided important insights and generation of hypotheses for future confirmation. The OS data from the IMROZ trial is still immature and final data will not be available until 2027, so any MAIC based on this is premature. Generalizability may be an issue due to the small sample size remaining after the exclusions and matching in some of the analyses.

Studies Addressing Gaps in the Evidence From the Systematic Review

No studies addressing gaps were submitted.

Economic Evidence

Cost and Cost-Effectiveness

Table 4: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with newly diagnosed multiple myeloma who are not eligible for ASCT
Treatment	Isatuximab in combination with VRd
Dose regimen	Cycle 1 (42-day cycle): isatuximab (10 mg/kg) is dosed weekly on days 1, 8, 15, 22, and 29 Cycles 2 to 4 (42-day cycles): isatuximab (10 mg/kg) is dosed every 2 weeks on days 1, 15, and 29 Cycles 5 to 17 (28-day cycles): isatuximab (10 mg/kg) is dosed every 2 weeks on days 1 and 15 Cycles 18 and beyond (28-day cycles): isatuximab (10 mg/kg) is dosed every 4 weeks on day 1
Submitted price	Isatuximab: $757.90 per 100 mg/5 mL Isatuximab: $3,789.49 per 500 mg/25 mL
Submitted treatment cost	Cycle 1: $33,695 Cycles 2 to 4: $20,217 Cycles 5 to 17: $11,669 Cycles 18 and beyond: $5,835
Comparators	• CyBorD • DCyBorD • DRd • DVMP • Rd • VRd
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (29 years)

Component	Description
Key data sources	• Efficacy inputs for IsaVRd and VRd were informed by the IMROZ trial (data cut-off date: September 26, 2023). • Efficacy inputs for CyBorD, DCyBorD, DRd, DVMP, and Rd were derived from sponsor-submitted ITCs.
Key limitations	• The comparative clinical efficacy of IsaVRd, CyBorD, DCyBorD, DRd, DVMP, and Rd therapies is uncertain due to the lack of head-to-head evidence and limitations with the sponsor's ITCs. Factors such as unaddressed prognostic and effect-modifying variables, study design differences, reductions in effective sample size, and imprecision in estimates contribute to uncertainty in the modelled OS and PFS for these comparators. The CDA-AMC base case focused on comparing IsaVRd and DRd because the clinical experts identified DRd as the most relevant comparator and ITC limitations restricted other comparisons. • The long-term OS benefit of IsaVRd is highly uncertain due to immature data from the IMROZ trial and reliance on extrapolated survival projections. These projections suggest a curative effect among patients receiving IsaVRd that is not supported by evidence, with the majority of predicted OS benefits (82%) occurring beyond the observed trial period. • Subsequent therapy costs are highly uncertain due to the sponsor's use of a single one-time cost for all patients transitioning to the postprogression health state. This approach likely overestimates costs by not accounting for treatment duration and prior therapy exposure. Clinical experts noted that treatment selection is typically influenced by previous therapies, rendering the sponsor's assumption unrealistic. • The sponsor used median duration of treatment as a proxy for median TTD, assuming a time-invariant relationship between median PFS and duration of treatment. This approach may not accurately represent the true TTD distribution and does not account for censoring, potentially leading to an overestimation of treatment persistence. For DRd, the sponsor applied the hazard ratio of TTD versus PFS from the MAIA trial to the IMROZ population, despite differences in trial populations, methodologies, and treatment regimens. This adds to the uncertainty in the TTD estimates. • The submitted model had transparency challenges due to the use of formulas to manage errors generated in the model, which made it difficult to track how key values were calculated. This limited the ability of CDA-AMC to thoroughly validate the model, introducing some uncertainty around the reliability of the results.
CDA-AMC reanalysis results	• The CDA-AMC base case was derived by assuming equal OS efficacy, excluding subsequent therapy costs, aligning TTD with PFS, and focusing on DRd as the primary comparator. • In the CDA-AMC base case, IsaVRd is associated with an ICER of $311,681 per QALY gained relative to DRd (incremental costs = $22,340; incremental QALYs = 0.07). A price reduction of 2.5% for isatuximab would be required for IsaVRd to be cost-effective compared with DRd at a WTP threshold of $50,000 per QALY gained.

ASCT = autologous stem cell transplant; CDA-AMC = Canada's Drug Agency; CyBorD = cyclophosphamide-bortezomib-dexamethasone; DCyBorD = daratumumab-cyclophosphamide-bortezomib-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; DVMP = daratumumab-bortezomib-melphalan-prednisone; ICER = incremental cost-effectiveness ratio; IsaVRd = isatuximab-bortezomib-lenalidomide-dexamethasone; ITC = indirect treatment comparison; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; Rd = lenalidomide-dexamethasone; TTD = time to treatment discontinuation; VRd = lenalidomide-dexamethasone-bortezomib; WTP = willingness to pay.

Budget Impact

CDA-AMC identified the following key limitations with the sponsor's analysis: inappropriate use of relative dose intensity to calculate drug acquisition costs, potential overestimation of market uptake for IsaVRd, and exclusion of subsequent therapy costs.

The CDA-AMC budget impact analysis base case increased relative dose intensity for all comparators to be 100%. The analysis indicates that funding IsaVRd for the treatment of adult patients with newly diagnosed

MM who are not eligible for ASCT resulted in cost savings of $3,304,157 in year 1, $2,016,456 in year 2, and $17,863,532 in year 3. This results in cumulative cost savings of $23,184,144 over 3 years.

pERC Information

Members of the Committee

Dr. Catherine Moltzan (Chair), Dr. Philip Blanchette, Dr. Kelvin Chan (Vice Chair), Dr. Matthew Cheung, Dr. Michael Crump, Annette Cyr, Dr. Jennifer Fishman, Dr. Jason Hart, Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Aly-Khan Lalani, Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Pierre Villeneuve, and Danica Wasney.

Meeting date: April 9, 2025

Regrets: One expert committee member did not attend.

Conflicts of interest: None

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Questions or requests for information about this report can be directed to Requests@CDA-AMC.ca.