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CADTH Reimbursement Recommendation

Elranatamab (Elrexfio)

Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Sponsor: Pfizer Canada ULC

Final recommendation: Reimburse with conditions

Summary

What Is the CADTH Reimbursement Recommendation for Elrexfio?

CADTH recommends that Elrexfio should be reimbursed by public drug plans for the treatment of adult patients with relapsed or refractory multiple myeloma (MM) who have received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy if certain conditions are met.

Which Patients Are Eligible for Coverage?

Elrexfio should only be covered to treat patients aged 18 years and older with relapsed or refractory MM who have received at least 3 prior treatments, have disease that has not responded to their last treatment, have not received prior B-cell maturation antigen (BCMA)–targeted treatment, and are in relatively good health. Elrexfio should not be reimbursed for the treatment of those patients whose MM is affecting their brain or spinal cord or those showing signs that the tissue layers protecting the brain and spinal cord are affected by MM. It also should not be reimbursed for the treatment of those with amyloidosis (a buildup of a protein, amyloid, in organs) that is not secondary to MM, those with POEMS (polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes) syndrome, and those with plasma cell leukemia.

What Are the Conditions for Reimbursement?

Elrexfio should only be reimbursed if it is prescribed and administered by health professionals at treatment centres with adequate medical resources and personnel, and if the price of Elrexfio is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Elrexfio may result in response to treatment, delay in the spread of cancer, and allow patients to live longer.
- Elrexfio may meet some patient needs because it may be an effective treatment option with manageable side effects.
- Based on CADTH's assessment of the health economic evidence, Elrexfio does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Elrexfio is estimated to cost the public drug plans approximately $87 million over the next 3 years. However, the actual budget impact is uncertain.

Summary

Additional Information

What Is MM?

MM is a cancer of plasma cells (i.e., white blood cells) in the bone marrow. In 2022, approximately 4,000 people in Canada were diagnosed with MM.

Unmet Needs in MM

MM is an incurable disease with a poor prognosis. MM often does not respond to initial treatments and will relapse, so the patient will need to try many different treatments. There is a need for additional treatment options that allow patients to live longer, delay the spread of cancer, improve quality of life, and reduce side effects.

How Much Does Elrexfio Cost?

Treatment with Elrexfio is expected to cost approximately $28,000 per patient per 28-day cycle on a weekly dosing schedule. If patients switch to a 2-week dosing schedule after 24 weeks of treatment, 28-day treatment costs per patient are $14,000.

Recommendation

The pCODR Expert Review Committee (pERC) recommends that elranatamab be reimbursed for the treatment of adult patients with relapsed or refractory (r/r) multiple myeloma (MM) who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy and without prior exposure to B-cell maturation antigen (BCMA)–directed therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One ongoing phase II, noncomparative, open-label trial (MagnetisMM-3) demonstrated that treatment with elranatamab may result in benefits in objective response rate (ORR) for adult patients with r/r MM who have received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody and no prior exposure to BCMA-directed therapy. The ORR in patients without (cohort A) and with (cohort B) prior exposure to BCMA-directed therapy were 61.1% (95% confidence interval [CI], 51.8% to 69.6%; P < 0.0001) [redacted] respectively. [redacted], respectively; however, the results were considered clinically meaningful by the clinical experts and pERC in only cohort A. Although the progression-free survival (PFS) and overall survival (OS) data were immature and associated with uncertainty due to the noncomparative design of the trial in both cohorts, the results in cohort A were considered promising by pERC. In cohort A, after a median duration of follow-up of 14.7 months, the median PFS was not reached (95% CI, 9.9 to not estimable) and the Kaplan-Meier estimated probability of PFS at 12 months was 56.6% (95% CI, 46.7% to 65.3%); the median OS was not reached (95% CI, 13.9% to not estimable) and the probability of being alive at 12 months was 63.0% (95% CI, 53.7% to 70.9%). Despite uncertainty in the results of the indirect treatment comparisons and real-world evidence (RWE) cohort studies due to methodological limitations, there was consistency in the direction of effects for PFS, OS, and complete response rate favouring elranatamab over real-world physician's choice of treatment in patients without prior exposure to BCMA-directed therapy.

Patients identified a need for accessible and effective treatment options, beyond third line, that delay disease progression, prolong survival, improve quality of life, and have manageable side effects. Given the totality of the evidence, pERC concluded that elranatamab could be an effective and more accessible treatment option that may delay disease progression and prolong survival in patients without prior BCMA-directed therapy. While recognizing the uncertainty in the evidence, pERC acknowledges that elranatamab could be more accessible compared to the relevant comparator chimeric antigen receptor (CAR) T-cell therapy.

Using the sponsor submitted price for elranatamab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for elranatamab was $208,582 per quality-adjusted life-year (QALY) gained compared with treatment of physician's choice in the submitted population. At this ICER, elranatamab is not cost-effective at a $50,000 per QALY willingness-to-pay threshold. A price reduction is required for elranatamab to be considered cost-effective at this threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Elranatamab should be reimbursed in adult patients aged 18 years or older who meet all the following criteria: 1.1. documented diagnosis of MM 1.2. documented evidence of progressive disease within the previous 6 months 1.3. received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody 1.4. no prior exposure to BCMA-directed therapy 1.5. refractory to their last treatment 1.6. good performance status.	In the MagnetisMM-3 trial, treatment with elranatamab demonstrated a clinical benefit in adult patients with a documented diagnosis of MM who had received at least 3 prior lines of therapy, including a proteasome inhibitor and an immunomodulatory agent, and an anti-CD38 antibody without prior BCMA-directed therapy (cohort A). Patients in the MagnetisMM-3 trial had documented progressive disease, and an ECOG performance status of 0 or 1. Results in patients with prior BCMA-directed therapy (cohort B) did not demonstrate there was a meaningful clinical benefit.	pERC acknowledged that clinicians may consider using elranatamab for patients with an ECOG performance status ≥ 2 at their discretion.
2. Elranatamab should not be initiated in patients with active CNS involvement or exhibiting signs of meningeal involvement of MM, amyloidosis, POEMS syndrome, or plasma cell leukemia.	The MagnetisMM-3 trial excluded patients with active CNS involvement or exhibiting signs of meningeal involvement of MM, primary amyloidosis, or plasma cell leukemia.	–
Discontinuation		
3. Treatment with elranatamab should be discontinued upon the occurrence of any of the following, whichever occurs first: 3.1. disease progression 3.2. unacceptable toxicity.	Treatment with elranatamab in the MagnetisMM-3 trial was given until disease progression or unacceptable toxicity, whichever occurred first.	–
Prescribing		
4. Elranatamab should be administered by health professionals at treatment centres with adequate medical resources and personnel to manage severe reactions, including cytokine release syndrome and neurologic toxicities.	To ensure that elranatamab is prescribed only for appropriate patients and adverse events are managed in an optimized and timely manner.	pERC recognized that tocilizumab must be readily available for the treatment of CRS.
Pricing		
5. A reduction in price.	The ICER for elranatamab is $208,582 per QALY gained when compared to treatment	–

Reimbursement condition	Reason	Implementation guidance
	of physician's choice. A price reduction of at least 72% would be required for elranatamab to achieve an ICER of $50,000 per QALY gained compared to treatment of physician's choice. Due to the limitations of the indirect comparative evidence, it was noted that higher price reductions may be required. Given the absence of evidence presented, the cost of elranatamab should also not exceed that of teclistamab, if funded.	
Feasibility of adoption		
6. The feasibility of adoption of elranatamab must be addressed.	At the submitted price, the budget impact of elranatamab is expected to be greater than $40 million in year 3 ($40,176,258).	—
7. The organizational feasibility of jurisdictions having specialized treatment centres with the infrastructure and resources required to administer elranatamab and manage adverse events must be addressed.	The limited availability of specialized treatment centres may limit access to elranatamab.	The product monograph recommends monitoring patients for CRS and neurologic toxicity, including ICANS, and states that elranatamab should be administered by a health care professional with appropriate medical support to manage these severe reactions.

CNS = central nervous system; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group; ICANS = immune effector cell-associated neurotoxicity syndrome; ICER = incremental cost-effectiveness ratio; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; MM = multiple myeloma; POEMS = polyneuropathy, organomegaly, endocrinopathy, myeloma protein, and skin changes; QALY = quality-adjusted life-year.

Discussion Points

- It is noted that there is a significant unmet need for effective treatments for patients with r/r MM in the fourth line and later setting who have not received BCMA-directed therapy. The available efficacy and safety evidence was from a noncomparative phase II trial that is associated with uncertainty. However, based on the totality of the evidence, elranatamab has the potential to reduce morbidity and mortality associated with r/r MM in patients without prior BCMA-directed therapy.
- pERC also carefully considered the unmet needs of patients with r/r MM who have previously received BCMA-directed therapy. The data from cohort B in the MagnetisMM-3 trial (with prior exposure to BCMA-directed therapy) was discussed and pERC noted that, overall, the results for patients in cohort B were not as favourable as cohort A (no prior exposure), and clinical experts noted that there may not be a clinically meaningful benefit from treatment in this group. Therefore, pERC could not conclude that elranatamab confers a clinically meaningful benefit in patients previously treated with BCMA-targeted therapy (e.g., CAR T-cell therapy or antibody-drug conjugate such as belantamab).

- pERC noted that in the MagnetisMM-3 trial, patients could change from weekly dosing of elranatamab to dosing every 2 weeks after they received at least 24 weeks of treatment and had achieved a response (i.e., a partial response or better that has been maintained for at least 2 months).
- pERC discussed the comparative evidence submitted by the sponsor, which included 2 unanchored matching-adjusted indirect comparisons (MAICs) and 2 RWE cohort studies of elranatamab relative to real-world physicians' choice of treatment, ciltacabtagene autoleucel, and teclistamab. As previously discussed, there was consistency in the direction of effects for PFS, OS, and complete response rate favouring elranatamab over real-world physician's choice of treatment in patients without prior exposure to BCMA-directed therapy, although there were limitations with this evidence. In the MAICs, there was heterogeneity in the populations and studies that could not be accounted for in the analyses; the RWE studies included a high risk of residual confounding and time-related biases. pERC noted that although elranatamab was favoured over teclistamab for ORR and PFS in the MAICs, the efficacy estimates remain uncertain. pERC noted that indirect evidence suggested that treatment with elranatamab was inferior to ciltacabtagene autoleucel for PFS and OS in the MAICs; however, the methodological limitations limit the certainty of these findings. pERC also noted that the MAICs and RWE cohort studies did not include patients with prior exposure to BCMA-directed therapy, which represents a gap in the available comparative evidence for this population.
- pERC noted that patients and clinicians highlighted improvement in health-related quality of life (HRQoL) as an important outcome and treatment goal for patients with r/r MM. Although pERC was unable to draw definitive conclusions regarding the effects of elranatamab on HRQoL due to the absence of a comparator and formal statistical testing as well as the open-label design of the trial, they noted that the descriptive assessments suggest HRQoL was maintained with elranatamab.
- pERC acknowledged that patients expressed a need for treatments that have fewer side effects. pERC noted that the most frequently reported notable harms were infections (71% of patients overall) and cytokine release syndrome (CRS) (59% of patients overall), and study treatment discontinuation due to treatment-emergent adverse events (TEAEs) was [redacted] pERC indicated that the adverse events (AEs) in the MagnetisMM-3 trial could be manageable; however, access to supportive treatments for AEs is needed (e.g., tocilizumab to treat CRS of any grade). No safety outcomes were included in any of the MAICs; therefore, pERC could not draw definitive conclusions about the safety of elranatamab relative to other treatments currently available.
- pERC noted that challenges remain regarding the implementation of elranatamab and the systems needed to optimize timely access and deliverability of elranatamab in the real-world setting. Initial doses of elranatamab must be administered at specialized treatment centres with the infrastructure and resources required to administer the treatment and manage AEs. However, a limited number of centres in Canada have the expertise and resources to deliver elranatamab and manage CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). It is possible that qualified centres will not be available in all jurisdictions. There may be a need for greater availability of inpatient hospital beds for drug monitoring and toxicity management. pERC considered that some patients may be unable to travel outside the province or country to receive therapy.

- pERC noted that Health Canada indication for elranatamab is for the treatment of r/r MM after receiving at least 3 prior lines of therapy. Patients are generally exposed to a proteasome inhibitor, an immunomodulatory agent, and anti-CD38 monoclonal antibody in earlier lines of therapy. The patient groups and the clinical experts expressed that patients who are resistant or intolerant to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody should be eligible to receive elranatamab at the point that these therapies are no longer effective or appropriate regardless of what line of therapy it is in; however, this would be outside of the Health Canada indication and therefore pERC could not recommend this.
- pERC discussed the cost-effectiveness of elranatamab versus ciltacabtagene autoleucel. It was noted that relative to elranatamab, ciltacabtagene autoleucel was associated with higher costs, but may also provide higher benefit. However, the comparative effectiveness is highly uncertain based on the available evidence. Given ciltacabtagene autoleucel is currently under negotiation at pan-Canadian Pharmaceutical Alliance (pCPA) and may not be displaced by elranatamab if funded, pERC noted that the cost-effectiveness of elranatamab relative to physician's choice was the more relevant comparison.

Background

MM is a plasma cell cancer characterized by clonal proliferation of malignant plasma cells (B cells) and overproduction of the abnormal immunoglobulin monoclonal protein (M protein). In 2022, it was estimated that 4,000 people in Canada were diagnosed with MM and 1,650 people in Canada died of MM. The 5-year survival for patients with MM is estimated to be approximately 50%, and although survival rates have improved in recent years due to advances in therapeutic options, MM remains incurable. The majority of patients with MM will relapse, and many patients' MM will become refractory to commonly used therapies. Patients with r/r MM often undergo multiple rounds of treatment, with the duration of remission, depth of response, PFS, and OS decreasing with each subsequent line of therapy. According to the clinical experts we consulted, the main treatment goals for patients with r/r MM are to prolong survival, improve symptoms, minimize toxicities, and maintain or improve HRQoL. Therapies for the treatment of patients with r/r MM, and the sequencing of these treatments, depends on eligibility for autologous stem cell transplant at diagnosis, age, comorbidities, previous treatments, prior toxicities, and line of therapy. According to the Cancer Care Ontario Joint Clinical Practice Guidelines and American Society for Clinical Oncology, treatment for r/r MM includes triplet therapy consisting of proteasome inhibitors, immunomodulatory drugs, or monoclonal antibodies. There is no preferred therapy for r/r MM in the fourth line and beyond settings; at this stage of the disease, patients may be treated with proteasome inhibitors, immunomodulatory drugs, and anti-CD38 and in some cases receive more than 1 proteasome inhibitor or immunomodulatory drugs, further limiting treatment options in later-lines of therapy.

Elranatamab injection has been approved by Health Canada for the treatment of adult patients with r/r MM who have received at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last

therapy. Elranatamab is a bispecific antibody comprised of humanized anti-BCMA and anti-CD3-epsilon targeting arms paired on an IgG2a backbone with nullified Fc binding function, which leads to a longer half-life. Elranatamab binds to both BCMA-expressing MM cells and T cells, effectively creating a bridge between them. Activated T cells release perforin and granzyme B leading to cytolysis of MM cells. The recommended dosing schedule for elranatamab, via subcutaneous injection, is 12 mg on day 1 and 32 on day 4 of week 1, followed by a full treatment dose of 76 mg administered weekly from week 2 to week 24. For patients who have received at least 24 weeks of treatment and have achieved a response (i.e., an International Myeloma Working Group [IMWG] response category of partial response or better with responses persisting for at least 2 months), the dose interval should transition to an every 2-week schedule.

Sources of Information Used by the Committee

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

- a review of 1 phase II, open-label, multicentre, noncomparative, nonrandomized trial in patients with r/r MM
- patients' perspectives gathered by 1 patient group, Myeloma Canada
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with r/r MM
- input from 2 clinician groups, including the Canadian Myeloma Research Group (CMRG) and Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee (OH-CCO's Drug Advisory Committees)
- a review of the pharmacoeconomic model and report submitted by the sponsor
- a review of the indirect evidence from 2 indirect treatment comparisons submitted by the sponsor
- a review of 3 RWE studies addressing gaps in the pivotal evidence.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to our call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

We received 1 patient group submission from Myeloma Canada. Myeloma Canada conducted both patient and caregiver surveys from September 26 to October 23, 2023, across Canada and internationally via email and social media. A total of 67 complete responses to the patient survey were received, of which 38 responses were recorded based on the respondent's eligibility criteria (receiving treatment with an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody). Among these 38 patients, 24 were eligible for the drug under review and 14 had experience with it. A total of 32 caregivers responded to

the caregiver survey, of whom 11 responses were recorded (8 based on eligibility and 3 based on experience with elranatamab). Upon verifying their eligibility for, or experience with, elranatamab, respondents were divided into 4 subsets:

- patients (n = 24) who would currently be eligible for treatment with elranatamab
- patients (n = 14) who have received or are currently receiving treatment with elranatamab
- caregivers (n = 8) of patients who would currently be eligible for treatment with elranatamab
- caregivers (n = 3) of patients who have received or are currently receiving treatment with elranatamab.

Regarding receiving prior lines of therapy, 13 patients and 3 caregivers indicated 3 lines of therapy, 6 patients and 5 caregivers indicated 4 lines, 6 patients and 1 caregiver chose 1 line, and 5 patients and 2 caregiver respondents indicated 5 lines of therapy or more.

Patient respondents indicated that among their daily activities and quality of life, their ability to work was the most significantly impacted by symptoms associated with myeloma, followed by ability to travel and to exercise. Regarding the most significant financial implication of myeloma treatment on patients and their household, 24 of 49 respondents (both patients and caregivers) identified loss of income or pension funds due to absence from work, disability, or early retirement, and 20 of 49 respondents chose travel parking costs. Patient respondents felt that interruption of life goals or accomplishments had the greatest impact on their quality of life, followed by loss of sexual desire and anxiety or worry. Patient and caregiver respondents identified the following factors as the most important to myeloma treatment: quality of life, manageable side effects, effectiveness of treatment (especially in achieving remission and having a durable response), and treatment accessibility or portability (including fewer or minimal visits to the hospital or cancer centre). Infections were identified as the most important aspect to control identified by patients, followed by mobility and kidney problems.

In terms of treatment outcomes, 12 of the 23 respondents who would currently be eligible for treatment with elranatamab rated improved quality of life as extremely important, 6 as very important, and 5 as somewhat important. In addition, 17 of the 23 patients rated the aspect of life extension while considering a myeloma treatment as extremely important, and 4 as very important. When asked about their tolerance of the most common side effects in patients who receive elranatamab, these patients perceived pneumonia, ICANS, upper respiratory tract infections, CRS, and infections were considered to be the least tolerable side effects, followed by peripheral neuropathy, other infections, and COVID-19. Regarding the impact of dosing schedule of elranatamab (weekly injections for at least 24 weeks, with the possibility of then switching to every 2 weeks) on the quality of life, 11 out of 24 patients chose negative impact, indicating it would limit patients' ability to travel or require a relocation (near their cancer centre) for the duration of treatment.

A total of 17 respondents (14 patients and 3 caregivers) indicated having experience with elranatamab. Among these, 12 respondents (10 patients and 2 caregivers) received elranatamab as monotherapy, 4 patients received elranatamab in combination with another drug, and 1 caregiver was unsure. All 14 patients who have received or are currently receiving treatment with elranatamab mentioned they were admitted to

the hospital at some point in the initial step-up dosing period. Regarding the most frequently experienced elranatamab side effects, all 14 patients rated cough as the least bearable side effect, followed by CRS, neutropenia, and upper respiratory tract infections. Most of these patients mentioned the overall side effects while receiving elranatamab were manageable and found elranatamab effective in controlling their myeloma.

Clinician Input

Input From Clinical Experts Consulted by CADTH

Unmet Needs

The clinical experts indicated that because almost all patients with r/r MM will become refractory to their therapy and continue on to next line of therapy, the unmet needs of patients would be new effective treatments, with curative potential, that are tolerable by targeting a different mechanistic pathway. Both clinical experts highlighted that the balance between treatment efficacy, minimizing toxicities, and quality of life would be important.

Place in Therapy

The clinical experts agreed that because of elranatamab's novel mechanism of action, it would provide an additional treatment option for patients who are refractory to other standard of care treatments. They noted that elranatamab is a new class of treatment for which there should be no existing drug resistance and, given its unique mechanism of action and toxicity profile, it should create a treatment synergy with other current families of myeloma treatments. However, they noted that given the lack of direct evidence, it is not known as yet if elranatamab is more effective than other therapies.

Patient Population

The clinical experts agreed that the patients best suited for elranatamab would be those with disease that is triple-class refractory (TCR). One of the clinical experts noted that patients most likely to respond to this therapy would be those with a stronger and more intact immune system, and patients with significant pre-existing cytopenias may not be ideal candidates as they may worsen during treatment and predispose patients to infection. The experts did not note any issues or challenges related to diagnosis or misdiagnosis of r/r MM and identifying patients likely to respond. Patients would be identified during routine cancer follow-up based on biochemical (serum protein electrophoresis, serum free light chain) or other evidence of relapse.

Assessing the Response Treatment

The clinical experts agreed that in clinical practice, standard clinical response criteria can be used to determine whether a patient with r/r MM is responding or progressing on treatment. The clinical experts noted that achieving a durable objective response lasting 6 to 12 months would be a sign of successful treatment, and such a response would be associated with reduction in disease-related symptoms, bone pain, fatigue, and transfusion requirements. They noted that toxicities, especially cytopenias such as neutropenia, infections, CRS, and hypogammaglobulinemia, would need to be monitored.

Discontinuing Treatment

The clinical experts indicated that treatment with elranatamab should be discontinued if the patient experiences disease progression (as defined radiologically or biochemically), loss of response, unacceptable toxicity such as grade 3 or 4 infection or CRS, light chains or renal dysfunction or increasing transfusion requirement.

Prescribing Considerations

The clinical experts noted that patients receiving elranatamab should be under the care of a specialist (hematologist, oncologist) familiar with myeloma and the use of bispecific antibodies, and who can manage toxicity associated with the therapy. They noted that elranatamab can be given in most centres experienced with myeloma therapy, and the first few doses usually require hospitalization.

Clinician Group Input

Clinician group input on the review of elranatamab was received from 2 clinician groups — CMRG and OH-CCO Drug Advisory Committees. A total of 33 clinicians (26 from CMRG and 7 from OH-CCO's Drug Advisory Committees) provided input for this submission.

Both CMRG and OH-CCO's Drug Advisory Committees emphasized that the overall treatment goals are to delay progression, improve OS, minimize adverse effects, control the disease and associated symptoms, and improve quality of life. While discussing the unmet needs of patients, CMRG highlighted that myeloma remains incurable and patients eventually become refractory to all available funded agents, which was similar to the input clinical experts consulted by CADTH. CMRG emphasized that the highest unmet need consists of patients with advanced disease who have received multiple lines of treatment and have already received the 3 major classes of drugs (triple-class exposed or refractory) including an immunomodulatory drug, a proteasome inhibitors, and anti-CD38 monoclonal antibody. Another unmet need noted by OH-CCO Drug Advisory Committees is to achieve ease of administration (i.e., subcutaneous injection and no need for apheresis) with elranatamab.

Similar to the clinical experts consulted by CADTH, both clinician groups agreed that elranatamab could be another option for patients who have been triple-class exposed (TCE). CMRG further stated that this treatment would be used late in the current lines of myeloma treatment (i.e., after failure of multiple agents). Moreover, CMRG added that elranatamab is not expected to impact the sequencing of agents earlier in the disease course or lead to a major change in treatment algorithms before patients become triple-class exposed or refractory.

CMRG indicated that patients with a good performance status, minimal or no comorbidities, relatively low tumour burden, adequate organ function, and satisfactory blood counts are the most likely to have the best outcomes with elranatamab. CMRG noted that overall, patients with poor disease-related prognostic factors, such as extramedullary myeloma and high-risk cytogenetics, should be eligible for the treatment under review.

OH-CCO Drug Advisory Committees noted that treatment responses with elranatamab are based on standard myeloma response measures, CRS and ICANS toxicity grading scales. CMRG elaborated that responses

are based on the monoclonal protein markers in the serum and/or urine, bone marrow biopsy, and, in some instances, by imaging studies (standardized IMWG). CMRG added that clinically meaningful responses usually correlate with at least a partial remission by IMWG Consensus Criteria, including improvement in symptoms (cessation of bone destruction with less pain, fractures and need for radiotherapy), improvement in energy and better ability to perform activities of daily living. Both CMRG and OH-CCO Drug Advisory Committees agreed upon that treatment discontinuation is based on ongoing efficacy or response, disease progression, and long-term tolerability or significant toxicities.

Given that prior anti-BCMA exposure does not preclude responsiveness to subsequent anti-BCMA therapy, CMRG would suggest that patients with prior anti-BCMA therapy who did not progress during it (i.e., nonrefractory to anti-BCMA therapy) be allowed access to elranatamab.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs. Refer to Table 2 for details.

Table 2: Responses to Questions From the Drug Programs

Drug program implementation questions	Clinical expert response
Relevant comparators	
MagnetisMM-3 is an open-label, single-arm, phase II trial. The CADTH submission is based on data from cohort A which did not allow prior BCMA-directed therapies. Relevant comparators that are funded in some or most jurisdictions include pomalidomide-dexamethasone (with or without cyclophosphamide, Pd or PCd), carfilzomib-dexamethasone (with or without cyclophosphamide, Kd or KCd), and selinexor-bortezomib dexamethasone (SVd). How does elranatamab compare to Pd or PCd, Kd or KCd, or SVd?	The CADTH team noted that the comparison between elranatamab and relevant comparators is to be addressed in the clinical review report. The clinical experts noted that, to their knowledge, the direct comparative efficacy and safety between elranatamab and relevant comparators is unknown. pERC noted that the indirect treatment comparisons and RWE cohort studies did not provide evidence compared to Pd or PCd, Kd or KCd, or SVd specifically (i.e., comparators were a basket of real-world physicians' choice of treatment).
Ciltacabtagene autoleucel (cilta-cel) is also used in this setting; however, it is under active negotiation at the time of this input. The CADTH reimbursement conditions for cilta-cel specified that it should not be reimbursed in patients who have received prior treatment with therapy targeting BCMA.	Comment from the drug plans to inform pERC deliberations.
Considerations for initiation of therapy	
The elranatamab submission was based on the MagnetisMM-3 trial cohort A, which did not allow prior BCMA-directed therapy. Should patients previously treated with BCMA-directed therapy (e.g., belantamab, cilta-cel) be eligible for elranatamab? Should patients treated with elranatamab be eligible CAR	The clinical experts noted that although the results for cohort B (patients with prior BCMA-directed treatments) were not as promising as cohort A (patients with no prior BCMA-directed treatments), patients with previous BCMA-directed therapy should be eligible for elranatamab. The clinical experts indicated that there are no data to support whether patients treated with elranatamab would benefit from subsequent CAR T-cell therapy. The clinical experts noted that the target of the treatments is the same; however, the T cells are

Drug program implementation questions	Clinical expert response
T-cell therapy (e.g., cilta-cel)? What evidence is there to support the above sequences?	activated through a different mechanism with CAR T-cell therapy and may be active when elranatamab-activated T cells fail. The clinical experts noted that, to their knowledge, there is no evidence to support the previously stated sequences. Although pERC acknowledged that clinical experts thought it would be reasonable to consider patients previously treated with BCMA-targeted therapy (e.g., CAR T-cell therapy) eligible for elranatamab, pERC also noted that there is limited evidence to support this. pERC additionally noted that there was no evidence included in this review to support the appropriateness of CAR T-cell therapy in patients previously treated with elranatamab.
Are 3 prior lines of therapy required if a patient is refractory to a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody as part of an earlier line therapy (e.g., by second line)?	The clinical experts thought that 3 prior lines of therapy should not be required, and it would be more reasonable for patients to have been treated with a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody, or refractory to these therapies. They indicated that with current therapies, they are combining multiple classes of antimyeloma drugs to treat patients. Upon progression, patients have fewer options with current standard of care drugs, and therefore, the clinical experts thought that access to anti-BCMA therapy in these situations would be reasonable, although these patients were not included in the MagentisMM-3 trial. pERC noted that there is no evidence reviewed to inform the use of elranatamab in earlier lines of therapy. Aligned with the Health Canada–approved indication, the reimbursement request for elranatamab is for the treatment of adult patients with r/r MM who have received at least 3 prior lines of therapy, including proteosome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy. pERC acknowledged the clinical experts' opinion that patients who are resistant to proteosome inhibitors, an immunomodulatory agent, and an anti-CD38 antibody (i.e., all 3), or intolerant to any of them and resistant to the others, should be eligible to receive elranatamab, regardless of the line of therapy it is in; however, this would be outside of the Health Canada indication and therefore pERC could not recommend this.
Considerations for discontinuation of therapy	
The product monograph has specific recommendations for restarting after dose delays, some of which require a readministration of step-up dosing.	Comment from the drug plans to inform pERC deliberations.
Considerations for prescribing of therapy	
Elranatamab must be administered according to a step-up dosing schedule to minimize the risk and severity of CRS and ICANS: 12 mg SC on day 1 and 32 mg SC on day 4 of week 1 cycle 1, followed by 76 mg SC once weekly in 28-day cycles. After 6 cycles, patients who have achieved and maintained a partial response or better for at least 2 months can be transitioned to once every 2-week dosing (starting cycle 7, day 1).	The clinical experts noted that it would be reasonable for patients to switch back to weekly dosing if patients begin to have disease burden that does not qualify as progressive disease. pERC agreed with the clinical experts, and further noted treatment should be subsequently discontinued if there was disease progression when patients were back on weekly dosing.

Drug program implementation questions	Clinical expert response
The trial allowed patients to go back to weekly dosing if the patient subsequently begins to have a disease burden that does not yet qualify as progressive disease according to IMWG criteria. Can pERC confirm what the dosing schedule should be?	
Teclistamab is under review for a similar indication. Should the reimbursement criteria for elranatamab be aligned with that of teclistamab?	The clinical experts indicated that it would be reasonable for the 2 drugs to have similar reimbursement criteria if they are recommended for reimbursement by pERC.
Generalizability	
The trial included patients with ECOG ≤ 2. Should elranatamab be used in patients with the following: • CNS disease that is under treatment or controlled • plasma cell leukemia or amyloidosis?	The clinical experts noted that, although there are no data from the MagnetisMM-3 trial to answer this question, it would be reasonable to use elranatamab in patients with CNS disease that is under treatment or controlled, and plasma cell leukemia or amyloidosis. They noted that CNS myeloma is not common, and both plasma cell leukemia and amyloidosis are diseases mediated by plasma cell clones that express BCMA and therefore elranatamab would likely have activity. pERC noted that patients with CNS disease that is under treatment or controlled, and plasma cell leukemia or amyloidosis were excluded from the MagnetisMM-3 trial; however, pERC agreed with the clinical experts who expressed that elranatamab can be used in patients with secondary amyloidosis as a complication of multiple myeloma.
At the time of funding, should patients receiving alternative therapies (e.g., Pd or PCd, Kd or KCd, or SVd) be eligible to switch to elranatamab?	The clinical experts noted that the option could be provided, especially for patients not responding or not responding well or experiencing toxicities associated with the alternative treatments. They noted that if a patient is responding to 1 of these drug combinations, they would likely maximize and maintain the response as long as possible. pERC agreed with clinical experts that physicians usually would not switch patients off effective treatments until they no longer work; however, patients can be switched to another drug if the existing treatment stops working.
Funding algorithm (oncology only)	
Complex therapeutic space with multiple lines of therapy, subpopulations, or competing products.	Comment from the drug plans to inform pERC deliberations.
Under what clinical circumstances would elranatamab be preferred over teclistamab or over cilta-cel and vice-versa? There may be interest in sequencing elranatamab with other BCMA-directed agents.	One of the clinical experts noted that they would likely prioritise cilta-cel before a bispecific if there are no clinical or logistical issues. The clinical experts noted that the toxicity profile and likelihood of CRS could be a consideration. They indicated that elranatamab is given subcutaneously which could be an advantage over the other therapies where infusion access is limited, although elranatamab still needs to be given in a trained infusion or chemotherapy unit. They also noted that using a bispecific over CAR T-cell therapy may be necessary when geographic access or capacity is an issue and where immediate treatment is required.

Drug program implementation questions	Clinical expert response
	pERC agreed that treatment selection would rely on patient and logistical factors.
Care provision issues	
Elranatamab is supplied as single-use vials of 44 mg and 76 mg (both with a similar concentration of 40 mg/mL). A step-up dosing of 12 mg and 32 mg is required during initiation and during restarts which would result in drug wastage. The drug may need to be initiated in the inpatient setting, in which case, the drug cost would be outside of the drug program budget in some provinces.	Comment from the drug plans to inform pERC deliberations.
CRS and ICANS can occur with elranatamab, although the severity and incidence appeared to be low in the trial. The funding of tocilizumab needs to be incorporated as part of any implementation to ensure that sites have tocilizumab available to manage CRS and ICANS. Other therapies (i.e., anakinra) may be required to treat ICANS.	Comment from the drug plans to inform pERC deliberations.
The monograph states that elranatamab should be administered by a health care professional with access to appropriate medical support to manage severe reactions, including CRS and neurologic toxicity. Is it safe to administer elranatamab in the outpatient setting?	The clinical experts noted that based on the very low frequency of grade 3 or greater CRS reported in the MagnetisMM-3 trial, it seems that CRS can be managed as an outpatient, as long as the treating clinicians are experienced in diagnosing and managing CRS. They indicated that patients who are at high risk for CRS (i.e., large disease burden, elevated creatinine) could be monitored more closely, perhaps as an inpatient. pERC acknowledged that the clinical experts noted that patients starting treatment with elranatamab will receive the first 2 to 3 doses in the hospital, and after that they can safely receive ongoing therapy in an outpatient setting on a case-by-case basis. pERC highlighted that hospitalization may likely be needed for patients who have CRS requiring tocilizumab.
System and economic issues	
There is concern about feasibility of adoption (budget impact and capacity) but there is uncertainty on what the uptake for elranatamab will be.	Comment from the drug plans to inform pERC deliberations.
There are additional costs associated with the requirement of tocilizumab for CRS, which impact drug program budgets (acute care). Additional resources would also be required for the management of infections, which can be quite severe.	Comment from the drug plans to inform pERC deliberations.
Generic pomalidomide is available, and confidential pricing exists for carfilzomib and selinexor	Comment from the drug plans to inform pERC deliberations

BCMA = B-cell maturation antigen targeted; CAR = chimeric antigen receptor; cilta-cel = ciltacabtagene autoleucel; CNS = central nervous system; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group; ICANS = immune effector cell-associated neurotoxicity syndrome; IMWG = International Myeloma Working Group; pERC = pan-Canadian Oncology Drug Review Expert Committee; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

One ongoing trial, MagnetisMM-3 (N = 187), met the inclusion criteria for the systematic review conducted by the sponsor. The objective of MagnetisMM-3 was to assess the efficacy and safety of elranatamab 76 mg, subcutaneous injection, in adults with r/r MM. The trial enrolled adults who did (cohort B) or did not (cohort A) have previous experience with BCMA-directed treatment; whose disease was refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody; and whose disease was relapsed or refractory to their last antimyeloma regimen. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of less than or equal to 2, and adequate bone marrow, hepatic, and renal functions. The 2 noncomparative cohorts were analyzed separately. Patients received elranatamab 76 mg, subcutaneous injection, once a week on a 28-day cycle with a 2 step-up priming dose regimen of 12 mg on day 1 and 32 mg on day 4 during the first week. Patients who received once a week dosing for at least 6 cycles and achieved a partial response or better persisting for at least 2 months had their dosing interval changed to once every 2 weeks. The outcomes relevant to this review included the primary outcome of ORR by blinded independent central review (BICR) per IMWG criteria, and secondary outcomes of PFS, OS, complete response rate (CRR), duration of response (DOR), and safety. HRQoL via European Organization for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire (EORTC QLQ-MY20) was included as an exploratory outcome. The trial population was predominately white (62%), with similar proportion of male and female patients who had a mean age of 67 years. Most patients had a ECOG performance status score of 1 (59%) and 0 (35%), indicating good overall performance, Revised International Staging System (R-ISS) disease stage of II (57%), standard cytogenetic risk (67%), and prior stem cell transplant (75%). Patients had received an average of 6 prior lines of therapy, and 46% had penta-drug refractory disease (refractory to at least 2 proteasome inhibitors, 2 immunomodulatory drugs, and 1 anti-CD38 antibody). [redacted]

Efficacy Results

Only those efficacy outcomes and analyses of subgroups identified as important to this review are reported. Efficacy and safety data were evaluated at a planned analysis data cut-off date of October 14, 2022, and additional follow-up data to a cut-off date of March 14, 2023.

Objective Response Rate

At the March 14, 2023, data cut-off, with a median follow-up of 14.7 months, the ORR in cohort A was 61.1% (95% confidence interval [CI], 51.8% to 69.6%; P < 0.0001) and [redacted]. These findings were consistent with the results at the 9-month analysis (data cut-off date of October 14, 2022). In cohort A, the ORR results were consistent across subgroups by age, baseline cytogenetics risk, prior stem cell transplant, and number of prior lines of therapy. Although, lower ORRs were observed in patients with R-ISS stage III. [redacted].

Progression-Free Survival by Blinded Independent Central Review

[redacted]. The median follow-up for PFS was 14.7 months for cohort A and [redacted]. The median PFS was not reached (95% CI, 9.9 to not estimable) in cohort A and [redacted] The probability of being event-free at 12 months in cohort A was [redacted]

Overall Survival

By the March 14, 2023, data cut-off, the OS data were immature. A total of [redacted]. Median OS was not yet reached in cohort A and was [redacted]. The probability of being alive at 12 months in cohort A was [redacted].

Duration of Response and Complete Response Rate

By the March 14, 2023, data cut-off, the median DOR was not reached among responders in both cohorts, with [redacted] of all patients censored at the time of the analysis. The probability of patients remaining in response at 12 months was 75.5% (95% CI, 58.8% to 80.9%) in cohort A and [redacted] A complete response or better was achieved in 43 (35.0%; 95% CI, 26.6% to 44.1%) patients in cohort A and [redacted].

Harms Results

Safety data were evaluated at the data cut-off date of March 14, 2023. All patients in the trial reported at least 1 TEAE. The most frequently reported TEAEs in both cohorts were CRS (59%), anemia (54%), neutropenia (45%), and diarrhea (39%). In both cohorts, 74% of patients experienced 1 or more serious TEAE. The type and number of events were similar in both cohorts, with the most frequently reported being COVID-19 pneumonia (13%), and CRS (12%). Study treatment discontinuation due to TEAEs occurred in [redacted] of patients and were similar in both cohorts. In cohort A and B, 45% and [redacted], respectively. Most deaths in both cohorts were attributed to disease progression. In the total population, the most frequently reported notable AEs were infections ([redacted]) and CRS [redacted] followed by peripheral neuropathy [redacted] hypogammaglobulinemia [redacted], and ICANS ([redacted]). All CRS events were grade 1 or 2 in severity, and only a single CRS event occurred at a dose greater than or equal to 4. The median time from the most recent elranatamab dose to CRS onset was 2 days and the median time to resolution was also 2 days. In general, the harms results of the MagnetisMM-9 trial were similar to the MagnetisMM-3 trial. According to the clinical experts, infection-related hospitalizations, hypogammaglobulinemia as measured by need for IV or subcutaneous immunoglobulin, and neurotoxicities were considered important outcomes, although they were not reported in the trials. As such, this represents a gap in the available evidence.

Critical Appraisal

The primary limitation of the MagnetisMM-3 trial was the absence of a comparator group to assess the efficacy and harms of elranatamab, and therefore the interpretation of the results is limited to its single-arm design. As such, it is difficult to make causal conclusions, in particular to what extent the observed effects were attributable to elranatamab. The open-label design introduces a potential bias in the assessment of ORR, PFS, DOR, and CRR, and a potential reporting bias of the subjective outcomes HRQoL

and safety. Although, this bias was mitigated by use of BICR for ORR, PFS, DOR, and CRR. To minimize the risk of differential measurement error, the trial performed tumour assessments using IMWG criteria and radiographic scans were assessed by BICR. Sample size and power calculations were based on ORR which had a prespecified hypothesis that was tested; however, all other analyses were descriptive. These included PFS, OS, DOR, and CRR, and the exploratory HRQoL outcome EORTC QLQ-MY20, which are deemed clinically important outcomes for the disease. The sample sizes for the subgroup analyses were small, and not adjusted for multiplicity, which also made it difficult in interpreting the results. Although the trial met its primary objective of assessing ORR, there was limited supporting evidence from important secondary outcomes, notably the immature data for PFS and OS. Given the importance of these outcomes to patients and clinicians, longer follow-up for the PFS and OS analyses would have been preferred to determine the clinical value of treatment with elranatamab. In addition, patients were permitted to receive posttreatment anticancer medications after study treatment had been discontinued (33% of all patients), which may influence the assessment of OS. The results of the EORTC QLQ-MY20 questionnaire were subjected to bias potentially due to incomplete reporting or missing data, which could have influenced the results toward the null. Therefore, the potential differences on patient's quality of life remains uncertain.

In general, the population requested for reimbursement aligns with the Health Canada indication, and the dosing and administration of elranatamab was consistent with the Health Canada–approved product monograph. According to the clinical experts we consulted, the inclusion and exclusion criteria and baseline characteristics of the MagnetisMM-3 trial were generalizable to adults with r/r MM in the Canadian setting. Although, the clinical experts noted that the trial did not include patients with a poor ECOG performance status, which is not entirely representative of patients with r/r MM in clinical practice. The trial included outcomes that were important to patients and clinicians. The patient group indicated that stopping disease progression, prolonging life, improving HRQoL, and reducing treatment side effects are important to them. Although, assessing HRQoL as an exploratory outcome is a limitation to the evidence because no definitive conclusions can be drawn.

GRADE Summary of Findings and Certainty of the Evidence

Methods for Assessing the Certainty of the Evidence

For pivotal studies and randomized controlled trials identified in the sponsor's systematic review, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to assess the certainty of the evidence for outcomes considered most relevant to inform the CADTH expert committee's deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.

Although GRADE guidance is not available for noncomparative studies, the CADTH review team assessed pivotal single-arm trials for study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, and publication bias to present these important considerations. Because the lack of a comparator arm does not allow for a conclusion to be drawn on the effect of the intervention versus any comparator, the certainty of evidence for single-arm trials started at very low certainty with no opportunity for rating up.

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:

- response outcomes (ORR, DOR, CRR)
- survival outcomes (PFS, OS)
- HRQoL outcomes (EORTC QLQ-MY20 functional and symptom scale scores).

Results of GRADE Assessments

Table 3 presents the GRADE summary of findings for elranatamab.

Table 3: Summary of Findings for Elranatamab for Patients With R/R MM

Outcome and follow-up	Patients (study), N	Effect (95% CI)	Certainty	What happens
Objective response				
Proportion of patients who had OR (PR or better) Median follow-up: 14.7 months	123 (1 noncomparative trial: cohort A)	611 per 1,000 (518 to 696)	Very low[a]	The evidence is very uncertain about the effect of elranatamab on OR when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a]	The evidence is very uncertain about the effect of elranatamab on OR when compared with any comparator.
Progression-free survival				
Probability of PFS at 12 months; median PFS (months) Median follow-up: 14.7 months	123 (1 noncomparative trial: cohort A)	566 per 1,000 (467 to 653); median PFS not reached (9.9 to NE)	Very low[a]	The evidence is very uncertain about the effect of elranatamab on PFS when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a]	The evidence is very uncertain about the effect of elranatamab on PFS when compared with any comparator.
Overall survival				
Probability of OS at 12 months; median OS (months) Median follow-up: 14.7 months	123 (1 noncomparative trial: cohort A)	630 per 1,000 (537 to 709); median OS not reached (13.9 to NE)	Very low[a]	The evidence is very uncertain about the effect of elranatamab on OS when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a]	The evidence is very uncertain about the effect of elranatamab on OS when compared with any comparator.

Outcome and follow-up	Patients (study), N	Effect (95% CI)	Certainty	What happens
Duration of response				
Probability of remaining in response (PR or better) at 12 months; median DOR (months) Median follow-up: 14.7 months	75 (1 noncomparative trial: cohort A)	753 per 1,000 (631 to 839); median DOR not reached (NE to NE)	Very low[a]	The evidence is very uncertain about the effect of elranatamab on DOR when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a]	The evidence is very uncertain about the effect of elranatamab on DOR when compared with any comparator.
Complete response				
Proportion of patients who had CR or better Median follow-up: 14.7 months	123 (1 noncomparative trial: cohort A)	350 per 1,000 (266 to 441)	Very low[a]	The evidence is very uncertain about the effect of elranatamab on CR or better when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a]	The evidence is very uncertain about the effect of elranatamab on CR or better when compared with any comparator.
EORTC QLQ-MY20 scale scores				
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on body image when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on body image when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on future perspective when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on future perspective when compared with any comparator.

Outcome and follow-up	Patients (study), N	Effect (95% CI)	Certainty	What happens
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on disease symptoms when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on disease symptoms when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on side effects of treatment when compared with any comparator.
[redacted]	[redacted]	[redacted]	Very low[a,b]	The evidence is very uncertain about the effect of elranatamab on side effects of treatment when compared with any comparator.

CI = confidence interval; CR = complete response; DOR = duration of response; EORTC QLQ-MY20 = European Organization for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire; NE = not estimable; NR = not reported; OR = objective response; OS = overall survival; PFS = progression-free survival; PR = partial response.

Notes: Effect estimates are based on the MagnetisMM-3 trial data cut-off date of March 14, 2023.

Data are based on the data cut-off date of March 14, 2023.

[a]In absence of a comparator arm, conclusions about efficacy relative to any comparator cannot be drawn and certainty of evidence started at very low.

[b]Rated down 1 level for risk of bias due to large amount of missing outcome data.

Source: MagnetisMM-3 Clinical Study Report.[32] Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

No long-term extension studies were submitted by the sponsor.

Indirect Comparisons

Description of Studies

In absence of direct comparative evidence of elranatamab versus relevant comparators, 2 MAICs were conducted by the sponsor. The objective of MAIC 1 was to assess the relative treatment effect of elranatamab, using data from cohort A of the MagnetisMM-3 trial, compared to physicians' choice of treatment based on aggregated data from the CMRG database in patients with TCE or r/r MM. The outcomes assessed included PFS and OS.

The objective of MAIC 2 was to assess the relative treatment effect of elranatamab compared to teclistamab from the MajesTEC-1 trial, physicians' choice of treatment from prospective RWE studies LocoMMotion and MAMMOTH, idecabtagene vicleucel from the KarMMa trial, and ciltacabtagene autoleucel from the CARTITUDE-1 trial in patients with TCE or r/r MM. Because idecabtagene vicleucel is not used in Canada, as

per the participating drug plans and the clinical experts consulted by CADTH, comparisons to this treatment were not included in this report. The outcomes assessed included ORR, PFS, OS, and CRR. Both MAICs used the same methods to match study populations and quantify the relative effect of treatments using hazard ratios (HRs) with 95% CIs. Prognostic variables and effect modifiers were identified through a systematic literature review and validated with clinical expert opinion.

Efficacy Results

The results of both MAICs were generally in favour of elranatamab compared to relevant comparators, except for ciltacabtagene autoleucel. In MAIC 1, the PFS and OS favoured elranatamab versus physicians' choice of treatment, although the proportional hazards assumption was violated for both outcomes, which could have biased the estimates. In MAIC 2, the ORR favoured elranatamab versus teclistamab and physicians' choice of treatment. For PFS, the HR favoured elranatamab versus teclistamab and physicians' choice of treatment and crossed the null for elranatamab versus ciltacabtagene autoleucel. For OS, the HR crossed the null for elranatamab versus teclistamab, favoured ciltacabtagene autoleucel versus elranatamab, and favoured elranatamab versus physicians' choice of treatment. The proportional hazards assumption was violated in most comparisons for both OS and PFS, except for the comparison to teclistamab. For CRR, the effect crossed the null for elranatamab versus teclistamab, and favoured elranatamab versus physicians' choice of treatment.

Harms Results

The MAICs did not include harms, therefore no conclusions could be drawn on the relative safety of elranatamab versus relevant comparators from this evidence.

Critical Appraisal

Both MAICs 1 and 2 used the same methods to indirectly compare treatments, and their rationale and objectives were reported. In both MAICs, the authors did not report a systematic literature search, describe their methods for data extraction, or conduct quality assessment of the included studies. The MAICs included relevant outcomes identified by the CADTH team (ORR, PFS, OS, CRR), however important outcomes such DOR, HRQoL and safety were not included in the comparisons. The CMRG database did not capture DOR, HRQoL and safety outcomes, and therefore these outcomes were not included in MAIC 1. As such their indirect comparative assessment remain unknown.

Across the included studies, there were similarities and notable differences in study design, inclusion and exclusion criteria, outcome definitions and patient characteristics. For MAIC 2, a key difference of comparing elranatamab to teclistamab, ciltacabtagene autoleucel, and physician's choice of treatment based on the LocoMMotion study was that these studies included patients who had TCE MM, while the MagnetisMM-3 trial enrolled patients who had TCR MM. Because patients with TCE MM are potentially in better health than patients with TCR MM, the treatment comparisons against these drugs would have been subjected to certain degree of uncertainty in favour of the comparators. To account for between study differences in patient baseline characteristics, several relevant prognostic variables and effect modifiers were matched in the weighting process, with separate sets of variables used across treatment comparisons and outcomes. These variables were selected based on a systematic literature search and clinical expert input; however,

the authors did not differentiate prognostic variables from effect modifiers and used them collectively in the weighting process. For MAIC 1 (elranatamab versus physicians' choice), ISS disease stage and cytogenetic risk could not be adjusted in the analyses for PFS and OS because the definitions did not align across the MagnetisMM-3 trial and CMRG study. The authors noted that, at the feasibility stage, because the definitions of ISS disease stage and cytogenetic risk were not comparable between the 2 studies, they were not included in the indirect treatment comparison. In the CMRG study, patient-level data regarding these 2 variables was captured at diagnosis, rather than at the start of the trial period, because it was defined in MagnetisMM-3 trial. In addition, extramedullary disease was not adjusted in the analysis because it was not reported in the CMRG study. For MAIC 2, these 2 important variables were missing for 2 comparisons: in the comparison of physician's choice of treatment from MAMMOTH, extramedullary disease was not adjusted for, and in comparison, with physician's choice of treatment from LocoMMotion, cytogenetic risk was not adjusted for. Not adjusting for these differences could introduce residual confounding due to unreported or unobserved cross-study differences, although the direction or extent of bias is unclear. For MAIC 1, following the weighting process, the effective sample size (ESS) for OS declined by approximately 34% of the original sample size compared with physician's choice of treatment. For the PFS comparison with physician's choice of treatment, the ESS declined by approximately 33% of the original sample size. For MAIC 2, following adjustment, the ESS for OS declined by 37% in the comparison with teclistamab; 73% in the comparison with ciltacabtagene autoleucel, 45% in the comparison with physician's choice of treatment (LocoMMotion), and 20% in the comparison with physician's choice of treatment (MAMMOTH), of the original sample size. These reductions in the ESS meant the final matched patient population was more selective than the original patient population and may lead to large uncertainty in estimated treatment effects, although the magnitude and direction of potential bias is unclear. For MAIC 1, the proportional hazards assumption was violated for both PFS and OS outcomes, and for MAIC 2, the assumption was violated in most comparisons for PFS and OS outcomes. These violations could have led to biased treatment effect estimates. In addition, because both MAICs only included cohort A from the MagnetisMM-3 trial and the Health Canada indication is for patients with and without prior exposure to BCMA-directed therapies, there is no indirect comparative evidence for the use of elranatamab in patients who have received prior BCMA-directed therapy. Due to these limitations in the MAICs and uncertainty in their estimates, no definitive conclusions could be drawn on the relative treatment effects of elranatamab versus relevant comparators.

Studies Addressing Gaps in the Evidence From the Systematic Review

This section summarizes 2 retrospective cohort studies with external control arms (Study C1071024 and Study C1071031) and 1 phase I/II dosing study (MagnetisMM-9) that were submitted to provide comparative evidence of elranatamab versus other active treatments RWE external cohort studies (Study C1071024 and Study C1071031).

Description of Studies

A retrospective cohort Study C1071024 was conducted to compare the efficacy outcomes ORR, TTR, and DOR observed in the participants of study MagnetisMM-3 (with at least 9 months of follow-up) and real-world (RW) patients selected from 2 US-based oncology electronic health record databases, Flatiron Health and COTA. Study C1071031 is the continuation of Study C1071024 with an available follow-up of

MagnetisMM-3 trial participants of approximately 15 months. Study C1071031 aimed to compare the PFS and OS in participants of study MagnetisMM-3 treated with elranatamab versus RW patients with TCR MM treated with RW physician's choice of therapy. Study C1071031 also assessed patient-reported outcomes (EORTC QLQ-MY20) using other studies, Study C1071013 and Study C1071014, as the data sources for the external cohort. Patients were considered eligible for selection into the external control arm if they had MM that was refractory to at least 1 proteasome inhibitors, 1 immunomodulatory drug, and 1 anti-CD38 and started at least 1 new treatment since the documentation of TCR status. The date of initiation of the first regimen after TCR MM eligibility was defined as the index date in establishing the external control arms from the Flatiron Health and COTA databases. Patients were only eligible if they had an index date occurring between November 16, 2015, and June 30, 2022.

For the main analysis in Study C1071024 and Study C1071031, differences in baseline and key covariate characteristics between participants in MagnetisMM-3 and each external control arm were balanced using inverse probability treatment (IPT) weighting.

Between February 2021 and January 2022, MagnetisMM-3 cohort A enrolled 123 patients with TCR MM, who were included the main analysis for Study C1071031. For the external control arms for Study C1071024 and Study C1071031, 239 patients with TCR MM were selected from the COTA database and 152 patients from the Flatiron database. Median follow-up times for included patients were [redacted] months in MagnetisMM-3 cohort A, [redacted] months for patients with TCR MM from the COTA database, and [redacted] months for patients with TCR MM from the Flatiron database.

A systematic literature review was conducted to identify variables most strongly and consistently correlated with outcomes in real-world data studies conducted among patients with r/r MM and some additional variables were included in the analysis as confounders. To control baseline confounding, propensity scores were estimated using logistic regression models.

For the patient-reported outcomes (EORTC QLQ-MY20) analysis, a total of [redacted] patients from prospective cohort studies C1071013 and C1071014 were included. Baseline characteristics were compared between participants of MagnetisMM-3 and Study C1071013 and Study C1071014. Most baseline characteristics between Study C1071013 and Study C1071014 were generally similar, although compared to the MagnetisMM-3 population, the population from the observational studies had higher proportions of ISS stage III ([redacted]), ECOG score of 2 [redacted], and high-risk cytogenetics ([redacted] A higher proportion of participants in MagnetisMM-3 had extramedullary disease compared to patients from the observational studies [redacted]

Efficacy Results

Progression-Free Survival (Study C1071031)

During the study periods, PFS events (disease progression or death) were identified for [redacted] in the MagnetisMM-3 population, [redacted] in the COTA population, and [redacted] in the Flatiron population. Median PFS was longer with elranatamab versus RW standard of care (SOC) in the COTA database both before weighting [redacted] and after IPT weighting [redacted] In the restricted mean

survival time analyses, the average PFS was longer with elranatamab versus RW SOC in the COTA database at 9, 12, 15, 18, and 24 months using both weighted and unweighted analyses. Similarly, the average PFS time was longer with elranatamab versus RW SOC in the Flatiron database.

Overall Survival (Study C1071031)

During the study periods, deaths were identified for [redacted] in the MagnetisMM-3 population, [redacted] from the COTA population, and [redacted] from the Flatiron population. Median OS was longer with elranatamab versus RW SOC in the COTA database both before weighting [redacted] and after IPT weighting [redacted]. In the restricted mean survival time analyses, the average OS time was longer with elranatamab versus RW SOC in the COTA database at 12, 15, 18, and 24 months using the unweighted analyses, and was also longer at 9, 12, 15, 18, and 24 months using the IPT weighted analyses. Similarly, the average OS time was longer with elranatamab versus RW SOC in the Flatiron database at 9, 12, 15, 18, and 24 months using the unweighted analyses.

Objective Response Rate (Study C1071024)

The ORR was higher for elranatamab compared to RW SOC in both unweighted and IPT weighted analyses. In the unweighted analyses, the ORR was 61% (95% CI, 51%.8 to 69.6%) in the MagnetisMM-3 population, [redacted] in the COTA population, and [redacted] in the Flatiron population, with higher values observed in MagnetisMM-3 versus COTA ([redacted] and versus Flatiron [redacted]. Similarly, after adjusting for baseline confounding using IPT weighting, higher ORR was observed in MagnetisMM-3 versus COTA [redacted] and versus Flatiron [redacted]

Duration of Response (Study C1071024)

Among patients who achieved an objective response, the median DOR was longer with elranatamab compared to RW SOC from both databases. In the unweighted analysis, improved DOR was observed with elranatamab in MagnetisMM-3 compared with RW SOC in the COTA database [redacted] and in the Flatiron database [redacted] After accounting for the baseline confounding in the IPT weighted analysis, improved DOR was still observed with elranatamab in MagnestisMM-3 compared with RW SOC in the COTA database [redacted] and in the Flatiron database [redacted]

Patient-Reported Outcomes (MagnetisMM-3 Versus C1071013 and C1071014)

The least square mean difference values for the disease symptoms and side effects modules were inconclusive.

Harms Results

Safety data were not evaluated.

Critical Appraisal

Patients were compared using IPT weighting and doubly robust methods in attempt to minimize the impact of confounding on the results. It should be noted that this method cannot control for substantial differences resulting from different study designs between the 2 cohorts (randomized controlled trial versus retrospective registry review). The MagnetisMM-3 trial is a phase II, open-label, single-arm trial,

whereas the external control arms were derived from longitudinal real-world cohorts from electronic health records in the US. For the retrospective cohorts, there was concern of potential time-related bias (e.g., treatment changes and informative censoring) due to likely unequal possibility of dropouts for outcome assessment. The definition of censoring in the PFS analysis was not equivalent between participants of the MagnetisMM-3 trial and patients identified from RW sources, which is a potential source of measurement error in PFS measurements that may have biased the comparative effectiveness estimates in favour of the SOC treatment group. There might be important unknown or unmeasured residual confounding in the external control arms that were either not documented or could not be accounted for. Although the sponsors made IPT weighting, a few characteristics were not well-balanced in the comparison of the MagnetisMM-3 and Flatiron populations (ECOG, time since initial MM diagnosis, Charlson Comorbidity Index, number of lines of therapy before the index date, and history of stem cell transplant). Therefore, there remains also a potential risk of residual confounding. The sponsors recognized that unlike clinical trial settings, which use specifically defined outcomes and scheduled assessments, RW data are subject to inconsistent assessments and evaluations of treatment response. The sponsors noted further limitations on data quality of real-world data such as key variables were either unavailable or not similarly reported; missing data and the accuracy of recorded data may introduce an information bias and residual confounding; and applying eligibility criteria from a clinical trial to an RW database requires adjustments, which could impact the comparability of the populations. Well-defined, reliable, and clinically meaningful outcomes that are typically used in randomized trials may be particularly difficult to ascertain and evaluate in a real-world data source that is being considered for an externally controlled trial. As a general consideration, outcomes of interest are more likely to be recorded in clinical records when events are objective and/or require immediate medical attention, which might have led to the omission of some important outcomes in the RWE cohort, which may bias the results. In addition, the sponsors did not evaluate the consistency of timing of outcome assessments in the treatment arm compared to the external control arms. For the analysis of PRO (EORTC QLQ-MY20), participation in the C1071013 and C1071014 studies was dependent on physicians' and patients' ability and willingness to participate, which may impact patient representativeness and be a source of self-selection bias.

The patients selected from these RW databases to generate the external cohorts are highly selective in nature and may not reflect the general population. It is not possible to know whether the results may have differed if data from different r/r MM studies or databases had been used. Numerous therapies were used in the real-world clinical practice groups from the MagnetisMM-3 trial cohort and the external cohorts, of which, many may not be relevant to clinical practice in Canada. Additionally, treatment regimens reported from these sources were included from 16 November 2015 until 30 June 2022 (index date) and may not be reflective of current treatment standards. The clinical experts consulted by CADTH indicated that the patient population included in the external control arms based on the US COTA and Flatiron Health databases may differ from the general population in Canada. The sponsors conducted a subgroup analysis according to treatments providing the rationale that treatments included in the analysis aligned with the "relevant comparators" for this submission. However, according to the clinical experts consulted by CADTH, some important comparators (e.g., pomalidomide, bortezomib, dexamethasone, belantamab) used in Canada are

missing from the RW treatment list used for the subgroup analysis. Furthermore, the clinical experts also noted that some of treatments included are not commonly used in Canada.

MagnetisMM-9 Trial

Description of Studies

The phase I/II MagnetisMM-9 trial was conducted to evaluate a dosing regimen with 2 step-up priming doses and longer dosing intervals of elranatamab. The primary objective was to assess the safety of a priming dose regimen that involves premedication and 2 step-up priming doses administered within the first week of elranatamab treatment in r/r MM participants who are refractory to at least 1 proteasome inhibitors, 1 immunomodulatory drug, and 1 anti-CD38 monoclonal antibody. At the time of submission, data were only available for an interim analysis up to July 29, 2022, at which point patients had only been enrolled in part 1 and part 2A dose level 1; efficacy data are only available for patients from part 1 and safety data were only available for patients from part 1 and part 2A dose level 1. Both sets of patients received the same first cycle (premedication, 2 step-up priming doses of elranatamab [4 mg and 20 mg], and 76 mg doses of elranatamab); patients in part 1 continued elranatamab 76 mg weekly for 6 cycles, while patients in part 2A dose level 1 received elranatamab 116 mg every 2 weeks for cycles 2 to 6. Additional doses were considered in the MagnetisMM-9 design but are not summarized because data for those groups were not yet available. The primary outcome of MagnetisMM-9 was the rate of Grade 2 or higher CRS during cycle 1 in adult patients with TCR MM, which was evaluated against an a priori assumption that the mean Grade 2 or higher CRS rate would be 35%. Outcomes in MagnetisMM-9 were analyzed descriptively and without a hierarchical testing strategy; several efficacy outcomes (duration of complete response, PFS, OS, and minimal residual disease) were immature at the time of submission and are not summarized because data were not available at the time of interim data cut-off date. The main inclusion and exclusion criteria for MagnetisMM-9 were similar to the eligibility criteria of the pivotal MagnetisMM-3 trial. The baseline demographic characteristics and clinical characteristics of patients who enrolled in MagnetisMM-3 and MagnetisMM-9 were generally consistent with the characteristics of patients who have heavily pretreated r/r MM.

Efficacy Results

At the latest data cut-off date (July 29, 2022), efficacy data were not available for MagnetisMM-9. At this time, the trial included [redacted] patients, [redacted] of patients were receiving treatment, and [redacted] were under follow-up. In the overall population, median treatment duration was [redacted] in MagnetisMM-9; the median treatment duration in part 1 of MagnetisMM-9 [redacted] was comparable to that in the overall MagnetisMM-3 population. Median cumulative dose was higher in MagnetisMM-3 than in MagnetisMM-9 [redacted]), which reflects the shorter time on treatment in MagnetisMM-9 at the data cut-offs. However, relative dose intensities were similar between MagnetisMM-3 [redacted] and MagnetisMM-9 [redacted]. No major differences were observed in the proportions of patients with dose reductions or interruptions in MagnetisMM-3 [redacted] and MagnetisMM-9 [redacted], which were predominantly due to AEs. A smaller proportion of patients re-escalated to the 76 mg or 116 mg doses of elranatamab in MagnetisMM-9. Patients in the overall populations of MagnetisMM-9 had heavily pretreated MM (median: [redacted]) that was refractory to the last line of therapy. Most patients [redacted] had MM that was classified as being TCR. Similar to the MagnetisMM-3 trial, infection

prophylaxis was common in MagnetisMM-9, most frequently involving antiviral medication [redacted] and medication to prevent *Pneumocystis jirovecii* pneumonia [redacted].

Harms Results

All harms data reported in this section are from the data cut-off date of July 29, 2022. All patients in the trial reported at least 1 TEAE. The most frequently reported TEAEs in part 1 were CRS [redacted], anemia [redacted], neutropenia [redacted], diarrhea [redacted], decreased appetite [redacted], pyrexia [redacted] and fatigue [redacted]. The most frequently reported TEAEs in part 2A dose level 1 were CRS ([redacted], anemia ([redacted]), neutropenia ([redacted]), diarrhea ([redacted]), fatigue ([redacted]), decreased appetite ([redacted]), injection site reaction ([redacted]), thrombocytopenia ([redacted]) and pain in extremity ([redacted]). In the total population, [redacted] of patients experienced at least 1 serious TEAE. The most frequently reported serious AEs in both part 1 and part 2A dose level 1 were CRS ([redacted] respectively). Study treatment discontinuation due to TEAEs in part 1 were [redacted] in part 2A dose level 1. The most common TEAEs leading to discontinuation of elranatamab included septic shock [redacted] and peripheral sensory neuropathy ([redacted]) for part 2A dose level 1, and neutropenia ([redacted]) for part 1. In part 1 and part 2A dose level 1, [redacted] of patients died, respectively. Most deaths in both cohorts were attributed to other reasons [redacted]). The primary end point of MagnetisMM-9 was the rate of [redacted] during cycle 1 (combining patients from part 1 and part 2A), which was [redacted].

Critical Appraisal

MagnetisMM-9 was an open-label, single-arm, phase I/II trial. The primary limitation of MagnetisMM-9 was the absence of a comparator group against which the benefits and harms of elranatamab could be compared. Single-arm trials are subject to several limitations that complicate their interpretation. Efficacy outcomes in MagnetisMM-9 were analyzed descriptively. The primary outcome for MagnetisMM-9, the rate of Grade 2 or higher CRS during cycle 1, was evaluated against an a priori assumption. Efficacy data were immature. The trial was open label, which can result in a risk of bias in the measurement of the outcomes, particularly for subjective harms.

The baseline demographic characteristics and clinical characteristics of patients who enrolled in MagnetisMM-3 and MagnetisMM-9 were generally consistent with the characteristics of patients who have heavily pretreated r/r MM. Dose adjustments were allowed in the trial and the methods were outlined in the protocol. Dose adjustments or modifications are anticipated in a clinical practice setting to manage AEs while maintaining drug benefit.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adult patients with relapsed or refractory multiple myeloma, who have received at least 3 prior lines of therapy including a PI, an IMiD, and an anti-CD38 mAb, and who have demonstrated disease progression on the last therapy.
Treatment	Elranatamab
Dose regimen	Step-up dosing 12 mg on day 1 followed by 32 mg on day 4; 76 mg is given once weekly thereafter. For patients who have received 24 weeks of treatment and have achieved a response (i.e., a partial response or better that has been maintained for at least 2 months), the dose interval should transition to an every 2-week schedule.
Submitted price	Elranatamab, 40 mg/mL solution for subcutaneous injection, single-use vials: $4,053 for 44 mg/1.1 mL and $7,000 for 76 mg/1.9 mL ($3,684 per mL).
Submitted treatment cost	The first 28-day costs of elranatamab are $25,053. Every 28 days after this, the costs are $28,000. If patients switch to an every 2-week dosing schedule after 24 weeks of treatment, 28-day treatment costs per patient are $14,000.
Comparators	• Mix of currently reimbursed combination therapies (referred to as physicians' choice): Kd (carfilzomib-dexamethasone), KCd (carfilzomib-cyclophosphamide-dexamethasone), Pd (pomalidomide-dexamethasone), PCd (pomalidomide-cyclophosphamide-dexamethasone), and other combinations of PI, IMiD, and mAb based on the CMRG study • Cilta-cel • SVd (selinexor-bortezomib-dexamethasone) (scenario analysis only)
Perspective	Publicly funded health care payer in Canada
Outcomes	QALYs, life-years
Time horizon	Lifetime (20 years)
Key data sources	• Elranatamab: single-arm, phase II MagnetisMM-3 trial • Physicians' choice: retrospective real-world evidence CMRG study • Cilta-cel: single-arm phase Ib/II CARTITUDE-1 trial
Key limitations	• The comparative efficacy of elranatamab vs. relevant comparators is uncertain due to an absence of head-to-head clinical trial data comparing elranatamab to comparator treatments, as well as lack of robust long-term clinical data. • The sponsor assumed nearly all patients would discontinue elranatamab before 2.5 years but maintain an indefinite treatment benefit, such that no patients would experience progression beyond 2.5 years. Based on clinical expert feedback, this extrapolation of trial data was considered highly unlikely and likely overestimates the benefit of elranatamab while underestimating elranatamab treatment costs. • The generalizability of the trial population to clinical practice in Canada is unclear due to differences in patient characteristics, such as performance status, comorbidities, and age. It is uncertain how these factors may influence the magnitude of benefit for elranatamab relative to physicians' choice. • The sponsor assumed that 100% of patients would switch to every 2 weeks dosing after 24

Component	Description
	weeks of treatment with elranatamab, which led to underestimated drug acquisition costs of elranatamab. • Once weekly dosing of carfilzomib was considered more commonly used than the twice weekly dosing assumed by the sponsor. Because weekly dosing is associated with lower costs due to less frequent dosing, the cost of the Kd regimen was overestimated. • The cost used for a 4 mg pomalidomide capsule ($425) was higher than the cost cited in the pCPA generic categories report as well as some jurisdictions in Canada ($125). • The sponsor assumed a reduction in dose would reduce drug costs. However, a reduction in dose may not reduce costs as elranatamab vials are single use. • Clinical evidence informing a comparison to SVd was highly uncertain. Cost-effectiveness vs. SVd is therefore unknown.
CADTH reanalysis results	• In reanalysis, CADTH modelled an alternative extrapolation of progression-free survival and time to treatment discontinuation, adjusted the proportion of patients switching to every 2 weeks elranatamab dosing based on trial data, updated the cost of pomalidomide, assumed carfilzomib was administered weekly rather than twice weekly, and adjusted the relative dose intensity to reflect dose interruptions only. • In the CADTH base case, elranatamab was more effective (incremental QALYs: 1.03) and more costly (incremental costs: $215,242) compared to physicians' choice. This resulted in an ICER of $208,582 per QALY gained. Relative to cilta-cel, elranatamab was found to be less costly and less effective (incremental costs = −$359,929; incremental QALYs: −1.34). • A price reduction of 72% would be required for elranatamab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained compared to physicians' choice.

cilta-cel = ciltacabtagene autoleucel; CMRG = Canadian Myeloma Research Group; IMiD = immunomodulatory drug; KCd = carfilzomib-cyclophosphamide-dexamethasone; KD = carfilzomib-dexamethasone; mAb = monoclonal antibody; PCd = pomalidomide-cyclophosphamide-dexamethasone; pCPA = pan-Canadian Pharmaceutical Alliance; PI = proteasome inhibitor; QALY = quality-adjusted life-year; SVd = selinexor-bortezomib-dexamethasone.

Budget Impact

CADTH identified the following limitations in the sponsor's base case: the calculation of the budget impact analysis (BIA) is uncertain, the proportion of patients with newly diagnosed multiple myeloma receiving therapy in fourth line is uncertain, the market uptake of elranatamab may be underestimated, and allocation of market shares to clinical trials is inappropriate.

CADTH conducted reanalyses of the BIA by revising the calculation of drug costs, revising the size of the eligible patient population, increasing the market uptake of elranatamab, and removing clinical trial market shares. The CADTH reanalysis of the BIA estimated that the 3-year budget impact of reimbursing elranatamab for the treatment of adult patients with r/r MM who have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory drug, and an anti-CD38 monoclonal antibody would be $15,819,100 in year 1, $30,815,799 in year 2, and $40,176,258 in year 3, for a 3-year cumulative total of $86,811,158. CADTH conducted scenario analyses to address remaining uncertainty. Assuming a 50% reduction in the eligible patient population resulted in a decrease of the elranatamab estimated 3-year budget impact to $43,898,028. Assuming higher uptake of elranatamab increased the 3-year BIA to $134,727,659.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Phillip Blanchette, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Michael Crump, Dr. Jennifer Fishman, Mr. Terry Hawrysh, Dr. Yoo-Joung Ko, Dr. Christian Kollmannsberger, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: April 9, 2024

Regrets: One expert committee member did not attend.

Conflicts of interest: Two expert committee members did not participate due to considerations of conflict of interest.

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