

7.03 ELRANATAMAB,

**Solution for subcutaneous injection 44 mg in 1.1 mL
(40 mg per mL),**

**Solution for subcutaneous injection 76 mg in 1.9 mL
(40 mg per mL),**

Elrexio[®],

PFIZER AUSTRALIA PTY LTD.

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a dual General Schedule and Section 100 (Efficient Funding of Chemotherapy Program – Related Benefits) Authority Required (Telephone/Online) listing, for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy.
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care, represented by carfilzomib + dexamethasone (Cd; 51.0%), pomalidomide + dexamethasone (Pd; 46.5%) and selinexor + dexamethasone (Sd; 2.5%).

Table 1: Key components of the clinical issue addressed in the resubmission

Component	Description
Population	Patients with relapsed or refractory multiple myeloma who have received <u>at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and a CD38 monoclonal antibody.</u>
Intervention	Elranatamab administered by subcutaneous injection, with step-up doses of 12 mg on Day 1 and 32 mg on Day 4, followed by the full treatment dose of 76 mg once a week from Week 2 to Week 24. Patients who have achieved a response are recommended to transition to 76 mg every two weeks from Week 24, <u>with a further dose frequency reduction to 76 mg every 4 weeks recommended after at least 24 weeks of treatment with 76 mg every 2 weeks.</u> The PBAC noted that the dosing change to 76 mg every 4 weeks at <u>Week 49 was not yet approved by the TGA.</u>
Comparator	Standard of care, comprised of <u>Cd (51.0%), Pd (46.5%) and Sd (2.5%).</u>
Outcomes	Overall response rate by blinded independent central review (primary), progression-free survival, overall survival, overall response rate, complete response rate, duration of response, time to response, adverse events and health-related quality of life.
Clinical claim	Based on clinical evidence for elranatamab from the MagnetisMM-3 study, and clinical evidence for standard of care from the <u>ENDEAVOR (Cd), MM-003 (Pd), and STORM (Sd) studies:</u> <ul style="list-style-type: none"> • Elranatamab is superior in terms of efficacy compared with standard of care. • Elranatamab has a non-inferior, albeit different safety profile compared with standard of care.

Source: Table 1.1, p9 of the resubmission.

Abbreviations: Cd, carfilzomib + dexamethasone; Pd, pomalidomide + dexamethasone; Sd, selinexor + dexamethasone.

Changes compared to the July 2024 submission underlined.

2 Background

Registration status

2.1 Elranatamab was granted provisional TGA registration on 26 June 2024 for the following indication:

- Treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 3 prior therapies, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody and have demonstrated disease progression on the last therapy.
- The decision to approve this indication has been made on the basis of the overall response rate in a single arm study. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

2.2 An additional application was made to the TGA on 30 September 2024 requesting changes to the elranatamab product information. The changes include an update to the elranatamab dose frequency, with a recommendation for the dose frequency to be reduced from 76 mg every 2 weeks to 76 mg every 4 weeks from Week 49 (after completion of at least 24 weeks of treatment with elranatamab every 2 weeks).

Previous PBAC consideration

2.3 The PBAC did not recommend the PBS listing of elranatamab for the treatment of RRMM at the July 2024 PBAC meeting. A summary of the key matters of concern are provided in Table 2.

Table 2: Summary of key matters of concern

Matter of concern	How the resubmission addresses it
Comparator	
<p>The PBAC noted that the submission nominated SOC, represented by a basket of therapies as the comparator (Cd: 34%, Pd: 18%, ELd 18%, Cd + cyclo 11%, PBd 11% and Ld 8%). The PBAC considered the nominated basket of therapies, and the individual weightings applied to each therapy, did not reflect contemporary clinical practice and was inconsistent with the comparators used in recently recommended RRMM submissions (paragraphs 7.8 and 7.10).</p> <p>The PBAC previously noted that the nominated standard of care did not reflect contemporary clinical practice, with CLd and SBd not captured, and the impact of DBd as a second line only treatment not fully accounted for (paragraph 7.8).</p>	<p>Addressed.</p> <p>The resubmission nominated SOC, represented by Cd (51.0%), Pd (46.5%) and Sd (2.5%), as the main comparator.</p>
Proposed restriction	
<p>The PBAC considered that the data presented likely supported a listing in a later line than that proposed in the submission (paragraph 7.1).</p>	<p>Addressed.</p> <p>The proposed listing was updated to reflect patients who have received at least 3 prior lines of therapy that include a proteasome inhibitor, immunomodulatory drug and an anti-CD38 antibody (previously 3 prior therapies that include a proteasome inhibitor, immunomodulatory drug and an anti-CD38 antibody).</p>

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Matter of concern	How the resubmission addresses it
<p>The PBAC considered the role of elranatamab and the CAR T-cell therapy, ciltacabtagene autoleucl, both BCMA-directed therapies, in the treatment algorithm for RRMM was unclear (paragraph 7.7). The PBAC previously advised that a criterion should be added to the initial supply restriction preventing use in patients who have received a prior BCMA-directed therapy (paragraph 3.8).</p>	<p>Not addressed in the resubmission but addressed in the Pre-Sub-Committee Response (PSCR). The proposed restriction did not preclude use of elranatamab among patients who have received prior BCMA-directed therapy. The PSCR stated that if CAR T-cell therapy is available at the time of listing the sponsor would be willing to add a criteria restricting treatment among patients who have received prior BCMA-directed therapy.</p>
Clinical evidence	
<p>The PBAC noted that the treatments received by patients in the comparator arm (based on data from the COTA and Flatiron US databases) did not fully reflect the nominated standard of care. The PBAC considered that comparing the outcomes from MagnetisMM-3 with other clinicals trials may reduce the transitivity issues (paragraph 7.12).</p>	<p>Addressed. The resubmission presented unanchored ITCs of elranatamab versus the nominated SOC components using evidence from published clinical studies.</p>
<p>The PBAC considered that the data presented had limited applicability to the proposed third-line treatment setting (paragraph 7.14).</p>	<p>Addressed. The resubmission positioned elranatamab as a fourth or subsequent line therapy.</p>
<p>The PBAC noted the high rates of CRS and ICANS associated with elranatamab treatment. The PBAC also noted the high rates of anaemia, thrombocytopenia and lymphopenia compared to SOC. Overall, the PBAC considered that elranatamab was inferior in terms of safety compared to SOC (paragraph 7.15).</p>	<p>Not addressed. The clinical claim of non-inferior but different safety for elranatamab versus SOC was unchanged from the July 2024 submission. However, SOC in the resubmission was informed by a different mix of therapies (Cd, Pd and Sd).</p>
Economic analysis	
<p>The PBAC considered that the economic analysis presented in the submission was highly uncertain due to the treatment effect in the model, which was informed by the IPTW analysis of MagnetisMM-3 and COTA, being highly uncertain given the substantive transitivity issues across the studies, and the limited applicability to the proposed third line setting (paragraph 7.16).</p>	<p>Partially addressed. Treatment effects included in the model were based on the ITCs versus the nominated SOC (Cd, Pd and Sd). The results of the unanchored ITCs and unanchored MAICs were uncertain.</p>
<p>The PBAC noted the comparator arm was costed based on an assumed basket of therapies and weightings which may not reflect the pattern of replacement/displacement with elranatamab, and there was likely limited overlap of the basket of therapies with the treatments used in COTA (paragraph 7.16).</p>	<p>Addressed. The distribution of use for the SOC therapies was derived from an analysis of PBS data provided by the DUSC Secretariat (100% PBS sample).</p>
<p>The PBAC noted that the base case ICER presented in the submission was high and highly sensitive to a number of inputs including the treatment effect, the extrapolations of the treatment effect over time and the assumption that all patients would transition to dosing elranatamab every 2 weeks even though only two-thirds of patients transitioned to the less frequent dosing in MagnetisMM-3 (paragraph 7.16).</p>	<p>Partially addressed. The resubmission assumed that all patients would receive elranatamab according to the updated treatment regimen, with weekly dosing from Week 2 to 24, every 2 weeks dosing from Week 25 to Week 48, and every 4 weeks dosing from Week 49 onwards. The ESC noted the TGA application requesting the dose amendment was under evaluation. The base case ICER remained high and was highly sensitive to inputs including the time horizon, treatment effect and distribution of standard of care.</p>
Financial estimates	
<p>The PBAC previously considered that the DUSC Secretariat analyses of the 100% PBS data provided a more reasonable base for future utilisation estimates and noted that the potential introduction of CAR T-cell therapies may alter the uptake of elranatamab (paragraph 7.17).</p>	<p>Addressed. The results of the analysis of PBS data provided by the DUSC Secretariat were used to estimate the eligible population.</p>

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Matter of concern	How the resubmission addresses it
DUSC previously considered that the eligible population and the uptake rate for elranatamab were underestimated (paragraph 6.65).	Partially addressed. The results of the analysis of PBS data provided by the DUSC Secretariat were used to estimate the eligible population. However, uptake rates were unchanged in the resubmission.
The PBAC previously noted that the mean treatment duration for elranatamab applied in the financial estimates was overestimated relative to that applied in the economic evaluation (paragraph 6.69).	Addressed. The average treatment duration derived from the economic model (71 weeks) was used to derive the financial impact of listing elranatamab.
The DUSC previously considered that cost offsets associated with Cd (as a proxy for standard of care treatments) were overestimated, as elranatamab would displace rather than replace other therapies in the treatment algorithm (paragraph 6.65).	Addressed. The assumed proportion of substitution versus displacement of Cd (as a proxy for standard of care therapies) was reduced from 72.8% to 56.9%.

Source: Constructed during the evaluation with reference to the elranatamab July 2024 Public Summary Document and the current elranatamab resubmission.

Abbreviations: BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Cd, carfilzomib + dexamethasone; CD, cluster of differentiation; CLd, carfilzomib + lenalidomide + dexamethasone; CRS, cytokine release syndrome; cyclo, cyclophosphamide; DBd, daratumumab + bortezomib + dexamethasone; DUSC, Drug Utilisation Sub-Committee; ELd, elotuzumab + lenalidomide + dexamethasone; ICANS, immune effector cell-associated neurotoxicity syndrome; ICER, incremental cost-effectiveness ratio; IPTW, inverse probability of treatment weighting; ITC, indirect treatment comparison; Ld, lenalidomide + dexamethasone; MAIC, matching adjusted indirect comparison; PBd, pomalidomide + bortezomib + dexamethasone; Pd, pomalidomide + dexamethasone; RRMM, relapsed and/or refractory multiple myeloma; SBd, selinexor + bortezomib + dexamethasone; Sd, selinexor + dexamethasone; SOC, standard of care.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	No. of Rpts
ELRANATAMAB	<u>Public hospital</u> \$ published price \$ effective price <u>Private hospital</u> \$ published price \$ effective price	44 mg	Initial: 1
Available brands			
Elrexio (elranatamab 44 mg/1.1 mL injection, 1 vial)			
ELRANATAMAB	<u>Public hospital</u> \$ published price \$ effective price <u>Private hospital</u> \$ published price \$ effective price	76 mg	Continuing 1: 11 Continuing 2: 11 Continuing 3: 5 Grandfathered: 11
Available brands			
Elrexio (elranatamab 76 mg/1.9 mL injection, 1 vial)			
Category / Program: General Schedule and Section 100 – Efficient Funding of Chemotherapy (Related Benefits) – Schedule 2			
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners			
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)			
Indication: Relapsed or refractory multiple myeloma			
Treatment Phase: Initial treatment - dose requirement of 12 mg on Day 1 and 32 mg on Day 4			
Clinical criteria:			
The condition must be confirmed by a histological diagnosis			

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AND
Clinical criteria:
Patient must have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody
AND
Clinical criteria:
Patient must not have previously received this drug for this condition
Treatment criteria:
<p>Progressive disease is defined as at least 1 of the following:</p> <ul style="list-style-type: none"> (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause). <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein.</p> <p>Details of: the histological diagnosis of multiple myeloma; prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response, must be documented in the patient's medical records.</p> <p>Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records:</p> <ul style="list-style-type: none"> (a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration. <p>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records.</p> <p>Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy.</p>
Treatment Phase: Continuing treatment 1 - dose requirement of 76 mg every week from Weeks 2 to 24
Clinical criteria:
Patient must have previously received initial treatment with this drug for this condition,
AND

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Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Prescribing instructions:
Prescriber to adjust the number of repeats to either 10 or 11 in line with the stage of treatment.
Treatment Phase: Continuing treatment 2 - dose requirement of 76 mg every two weeks from Weeks 25 to 48
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Treatment Phase: Continuing treatment 3 - dose requirement of 76 mg every four weeks from Week 49 until disease progression or unacceptable toxicity
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition,
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Treatment Phase: Grandfathered treatment - transitioning from non-PBS to PBS-subsidised supply, dose requirement of 76 mg every week OR every two weeks OR every four weeks
Clinical criteria:
Patient must have received non-PBS-subsidised treatment with this drug for this condition prior to [PBS-listing date]
AND
Clinical criteria:
Patient must have met all initial treatment PBS eligibility criteria applying to a non-grandfathered patient prior to having commenced treatment with this drug, which are: (a) the condition was confirmed by histological diagnosis, (b) the patient must have received at least 3 prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody (c) the patient had never been treated with this drug,
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Administrative Advice:
Note: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

- 3.1 The resubmission proposed a special pricing arrangement for elranatamab, with an effective ex-manufacturer price (AEMP) of \$| for 1 x 44 mg vial and \$| for 1 x 76 mg vial. The requested effective price was approximately 5% lower than the price proposed in the July 2024 submission. The pre-PBAC response proposed an AEMP of \$| for 1 x 76 mg vial (a 7% price reduction compared to the price proposed in the resubmission).
- 3.2 The PBAC noted that the dosing of elranatamab every 4 weeks from Week 49 is not currently TGA approved (see paragraph 2.2).
- 3.3 The resubmission requested a dual General Schedule and Section 100 Efficient Funding of Chemotherapy listing. The Secretariat previously considered that as elranatamab is a subcutaneous injection, it should be listed under the General Schedule and the Section 100 Program (EFC – Related Benefits) Schedule 2 (paragraph 2.7, elranatamab, Public Summary Document (PSD), July 2024 PBAC meeting).

- 3.4 Compared to the July 2024 submission, the proposed restriction was updated to specify 3 prior lines of therapy rather than 3 prior therapies. The ESC considered that the change was reasonable, and consistent with the positioning of elranatamab as a fourth or subsequent line therapy. However, while the proposed initial treatment restriction specifies RRMM, the proposed initial treatment restriction does not include clinical criteria requiring patients to have experienced disease progression on their prior line of therapy. The TGA indication requires patients to have previously received at least 3 prior therapies, and demonstrated disease progression on the last therapy. Additionally, the MagnetisMM-3 study required patients to be relapsed or refractory to their last anti-myeloma therapy.
- 3.5 The proposed restriction does not preclude use in combination with other treatments. The ESC considered that the restriction should specify that treatment with elranatamab is as monotherapy to align with the clinical evidence presented in the resubmission.
- 3.6 The ESC considered that a prescribing instruction to the initial supply restriction stating that elranatamab is not PBS-subsidised if it is administered to an inpatient in a public hospital setting would be required.
- 3.7 The proposed restriction requires prior treatment with an anti-CD38 antibody treatment. Daratumumab is currently the only anti-CD38 antibody treatment listed on the PBS for multiple myeloma, and it is only PBS-listed for use as a second-line treatment. Patients who have not previously received treatment with daratumumab and are beyond second line treatment may not have a pathway to qualify for elranatamab treatment through the PBS.
- 3.8 The proposed restriction does not restrict treatment on the basis of prior B-cell maturation antigen (BCMA)-directed CAR-T cell therapy use. The PBAC previously advised that a criterion should be added to the initial supply restriction preventing use in patients who have received a prior BCMA-directed therapy (paragraph 3.8, elranatamab, PSD, July 2024 PBAC meeting). The Pre-Sub-Committee Response (PSCR) stated that if ciltacabtagene autoleucel (a CAR T-cell therapy) is available at the time of elranatamab listing, a criterion that excludes patients who have received prior BCMA-directed therapy would be reasonable.
- 3.9 The resubmission requested grandfather provisions to allow the approximately < 500 patients enrolled in a planned expanded access program to receive PBS treatment with elranatamab.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Multiple myeloma is a plasma cell malignancy characterised by the abnormal growth of clonal B-cells in the bone marrow. Proliferation of myeloma cells in the bone marrow is associated with bone destruction and bone marrow failure. Patients with multiple myeloma experience hypercalcaemia, fatigue, weight loss, anaemia, bone

pain, bone fractures, renal impairment, and are at higher risk of infections. An estimated 2,719 new cases of multiple myeloma are forecast in Australia in 2024 (1,637 males and 1,082 females; AIHW, 2024). The median age of patients with multiple myeloma in Australia in 2020 was 72.4 years, with a 5-year survival rate of approximately 60% (AIHW, 2024).

- 4.2 The population targeted in the resubmission is patients who are receiving a fourth or subsequent line of therapy, and who have previously received treatment with a proteasome inhibitor, immunomodulatory drug and an anti-CD38 monoclonal antibody (i.e., triple class exposed). In the pivotal elranatamab study (MagnetisMM-3), patients were required to be triple class refractory (i.e., refractory to at least one proteasome inhibitor, one immunomodulatory drug and one CD38 monoclonal antibody). The majority of patients in Cohort A of the MagnetisMM-3 study (70.7%) were penta-drug exposed (i.e., had prior exposure to 2 proteasome inhibitors, 2 immunomodulatory drugs and an anti-CD38 monoclonal antibody) and a large portion were penta-drug refractory (42.3%). The resubmission claimed that approximately 63-73% of patients with triple class exposed multiple myeloma are triple class refractory and approximately 20% are penta-drug refractory.
- 4.3 For patients with RRMM after 3 lines of prior therapy, the NCCN guidelines list CAR T-cell therapy (ciltacabtagene autoleucel or idecabtagene vicleucel) as the preferred treatment option, with bispecific antibodies (including elranatamab, talquetamab and teclistamab) listed as a preferred regimen for patients who have received at least four prior therapies that include a proteasome inhibitor, immunomodulatory drug and an anti-CD38 monoclonal antibody. Sd is recommended as an option after at least four prior therapies among patients whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody. The NCCN guidelines note that the choice of therapy for a specific patient depends on the context of clinical relapse, including prior treatments and the duration of response to prior treatments.
- 4.4 Elranatamab is an immunoglobulin G2 kappa (IgG2K) bispecific antibody targeting B-cell maturation antigen (BCMA) on B-cells and CD3 on T-cells. BCMA is a cell surface receptor that is overexpressed on malignant cells such as multiple myeloma cells. Simultaneous binding of elranatamab to BCMA and CD3 receptor on T-cells induces selective T-cell-mediated cytotoxicity of myeloma cells.
- 4.5 Elranatamab is administered via subcutaneous injection, with initial step-up doses of 12 mg on Day 1 and 32 mg on Day 4, followed by the full treatment dose of 76 mg once a week from Day 8. For patients who have received at least 24 weeks of treatment with elranatamab and who have achieved a response, it is recommended that the dosing frequency is reduced to 76 mg every two weeks. Treatment with elranatamab is ongoing until disease progression or unacceptable toxicity. Based on proposed changes to the Product Information, the resubmission has proposed a reduction in dose frequency from 76 mg every 2 weeks to 76 mg every 4 weeks from Week 49 onwards for patients who have received at least 24 weeks of treatment with elranatamab every 2 weeks. The updated dosing regimen was included in the

calculation of elranatamab treatment costs in the economic analysis and financial estimates. As noted above (see paragraph 2.2), the reduction in dosing frequency has not yet been approved by the TGA.

- 4.6 Due to the risk of severe reactions, hospitalisation is recommended for 48 hours after administration of the first step-up dose, and for 24 hours after administration of the second step-up dose. Supervision by a healthcare professional or hospitalisation is also recommended for subsequent treatment reinitiations¹. The economic analysis and financial estimates assumed that 96% of patients would initiate treatment with elranatamab in an inpatient setting and 4% would initiate treatment in an outpatient setting.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated standard of care, represented by Cd, Pd, and Sd, as the main comparator. The main arguments provided in support of this nomination were:
- There is no established standard of care in Australia for triple class refractory multiple myeloma, with various therapies and combination regimens used. The treatment regimens often include a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 monoclonal antibody.
 - The PBAC previously noted that Cd, Pd, and Sd were included as comparators in recently recommended submissions to PBAC and MSAC.
- 5.2 The PBAC previously noted that, since the PBS listing of daratumumab + bortezomib + dexamethasone (DBd) for use as a second line treatment, the PBAC has recommended applications for the listing of ELd, CLd and SBd for RRMM; and that Cd was included as the comparator in these submissions (paragraph 5.3, elranatamab, PSD, July 2024 PBAC meeting). Additionally, it was noted that Cd, Pd and Sd were accepted as comparators for the ciltacabtagene autoleucl submission which was recommended at the April 2024 MSAC meeting (paragraph 5.4, elranatamab, PSD, July 2024 PBAC meeting).
- 5.3 The resubmission used the results of an analysis of PBS dispensing data provided by the DUSC Secretariat (100% PBS sample, data to end of June 2024) to inform the relative distribution of the three nominated standard of care therapies in the fourth line treatment setting. The estimated distribution was Cd: 51%; Pd: 46.5%; and Sd: 2.5%. The evaluation considered the results of the analysis were uncertain, as combination therapy was not captured, making it difficult to determine whether patients were truly fourth line, or to identify combination treatment regimens used in the assumed fourth line setting. The PSCR stated that although the PBS data does not capture use of combination therapies, it determines the sequence of treatment

¹ The elranatamab PI contains recommendations for restarting therapy after dose delay. For patients receiving the full dose that have a delay of >12 weeks from the last initiation, reinitiation with the step-up doses is recommended.

initiation. Overall, the ESC considered that the distribution of therapies was likely reasonable.

- 5.4 Ciltacabtagene autoleucel, a CAR-T cell therapy targeting BCMA, was recommended by the MSAC in April 2024 for the treatment of adult patients with RRMM who have received at least 4 prior lines of therapy. The elranatamab sponsor previously argued that if elranatamab and ciltacabtagene autoleucel were both available, there may be some impact on uptake of ciltacabtagene autoleucel, but that ciltacabtagene autoleucel, due to its intensive nature, is only suitable for a limited population of RRMM patients (paragraph 5.4, elranatamab, PSD, July 2024 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (163), health care professionals (3) and organisations (3) via the Consumer Comments facility on the PBS website. The PBAC also recalled that there was input associated with the July 2024 submission from individuals (14), health care professionals (1) and organisations (3). The comments from individuals, the majority of whom would like access to elranatamab, described the clinical need for effective treatments for multiple myeloma. The individuals stated that elranatamab is a beneficial treatment option and potentially results in improved response rates and progression free and overall survival outcomes. The side effect profile was described as manageable, and individuals expressed a hope that elranatamab would result in an improved quality of life. The individuals also noted the prohibitive cost of elranatamab. The health professionals stated that elranatamab was an effective and fast-acting treatment that produced a sustained response in those undergoing treatment. They also noted that elranatamab does not require concomitant dexamethasone treatment, commented that adverse events were manageable and stated that elranatamab may be an alternative to CAR T-cell therapy.
- 6.3 Myeloma Australia's Medical and Scientific Advisory Group (MSAG) provided input. The PBAC noted that MSAG supported the listing of elranatamab in the fourth-line setting. MSAG stated that these patients are usually TCR, face limited treatment options and have poor survival outcomes. MSAG noted elranatamab provided a readily available treatment alternative to CAR-T therapies, particularly for those patients living in regional or remote areas. MSAG also stated that the side effect profile of elranatamab is manageable and predictable and that MSAG plans to write a guideline of the management of T-cell redirection therapies, including the clinical management of CRS and ICANs, in collaboration with the National CAR-T Patient Prioritisation Committee.

6.4 Input was also received from Myeloma Australia, the Leukaemia Foundation and Rare Cancers Australia. Myeloma Australia and the Leukaemia Foundation stated that elranatamab was a new class of therapy which was efficacious and well tolerated. Rare Cancers Australia stated that PBS listing of elranatamab would provide a more equitable and accessible treatment pathway for patients. All organisations described the need for additional treatment options for patients with RRMM.

Clinical studies

6.5 No head-to-head trials comparing elranatamab with Cd, Pd, or Sd were identified in the literature search. One single-arm study for elranatamab (MagnetisMM-3), one head-to-head trial of Cd versus Bd (ENDEAVOR), one head-to-head trial of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone (MM-003), and one single arm study of Sd (STORM) were identified.

6.6 The clinical claim was based on the following series of indirect comparisons:

- An unanchored indirect treatment comparison (ITC) of elranatamab (MagnetisMM-3) versus Cd (ENDEAVOR).
- An unanchored ITC and an unanchored matching adjusted indirect comparison (MAIC) of elranatamab (MagnetisMM-3) versus Pd (MM-003).
- An unanchored ITC and an unanchored MAIC of elranatamab (MagnetisMM-3) versus Sd (STORM).

6.7 Clinical evidence for the ENDEAVOR, MM-003 and STORM studies has previously been considered by the PBAC in RRMM submissions for Cd, Pd, and Sd.

6.8 Details of the studies presented in the submission are provided in Table 3.

Table 3: Studies and associated reports presented in the resubmission

Trial ID	Protocol title/publication title	Publication citation
Elranatamab studies		
MagnetisMM-3 (NCT04649359)	An open-label multicenter, non-randomized phase 2 study of elranatamab (Pf-06863135) monotherapy in participants with multiple myeloma who are refractory to at least one proteasome inhibitor, one immunomodulatory drug and one anti-Cd38 antibody.	Clinical study reports (October 2022, March 2023 and March 2024 data cuts).
	Tomasson MH, Iida S, Niesvizky R, Mohty M, et al. Long-term survival and safety of elranatamab in patients with relapsed or refractory multiple myeloma: update from the MagnetisMM-3 study.	<i>Hemasphere</i> 2024; 8(7): e136.
	Mohty M, Bahlis NJ, Nooka AK, DiBonaventura M, et al. Impact of elranatamab on quality of life: patient-reported outcomes from MagnetisMM-3.	<i>British Journal of Haematology</i> 2024; 204(5): 1801-1810.
	Lesokhin AM, Tomasson MH, Arnulf B, Bahlis NJ. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results.	<i>Nature Medicine</i> 2023; 29(9): 2259-2267.
Carfilzomib studies		
ENDEAVOR (NCT01568866)	Chng WJ, Goldschmidt H, Dimopoulos MA, Moreau P, et al. Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR.	<i>Leukemia</i> 2017; 31(6): 1368-1374.
	Dimopoulos MA, Goldschmidt H, Niesvizky R, Joshua D, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial.	<i>Lancet Oncology</i> 2017; 18(10): 1327-1337.

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Trial ID	Protocol title/publication title	Publication citation
	<p>Dimopoulos MA, Moreau P, Palumbo A, Joshua D, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study.</p> <p>Moreau P, Joshua D, Chng WJ, Palumbo A, et al. Impact of prior treatment on patients with relapsed multiple myeloma treated with carfilzomib and dexamethasone vs bortezomib and dexamethasone in the phase 3 ENDEAVOR study.</p> <p>Goldschmidt H, Moreau P, Ludwig H, Niesvizky R, et al. Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: secondary analysis of the phase 3 ENDEAVOR study.</p> <p>Dimopoulos M, Siegel D, White DJ, Boccia R, et al. Carfilzomib vs bortezomib in patients with multiple myeloma and renal failure: a subgroup analysis of ENDEAVOR.</p> <p>Ludwig H, Moreau P, Dimopoulos MA, Mateos MV, et al. Health-related quality of life in the ENDEAVOR study: carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed/refractory multiple myeloma.</p> <p>Orlowski RZ, Moreau P, Niesvizky R, Ludwig H, et al. Carfilzomib-dexamethasone versus bortezomib-dexamethasone in relapsed or refractory multiple myeloma: updated overall survival, safety, and subgroups.</p>	<p><i>Lancet Oncology</i> 2016; 17(1):27-38.</p> <p><i>Leukemia</i> 2017; 31(1): 115-122.</p> <p><i>Leukemia & Lymphoma</i> 2018; 59(6): 1364-1374.</p> <p><i>Blood</i> 2019; 133(2): 147-155.</p> <p><i>Blood Cancer Journal</i> 2019; 9(3): 23.</p> <p><i>Clinical lymphoma, myeloma & leukemia</i> 2019; 19(8): 522-530.</p>
Pomalidomide studies		
MM-003 (NCT01311687)	<p>Miguel JS, Weisel K, Moreau P, Lacy M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial.</p> <p>Moreau P, Weisel KC, Song KW, Gibson CJ, et al. Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS).</p> <p>Weisel KC, Dimopoulos MA, Moreau P, Lacy MQ, et al. Analysis of renal impairment in MM-003, a phase III study of pomalidomide + low-dose dexamethasone versus high-dose dexamethasone in refractory or relapsed and refractory multiple myeloma.</p> <p>Dimopoulos MA, Weise KC, Song KW, Delforge M, et al. Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone.</p> <p>San Miguel JF, Weisel KC, Song KW, Delforge M, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma.</p> <p>Weisel K, Dimopoulos M, Song KW, Moreau P, et al. Pomalidomide and low-dose dexamethasone improves health-related quality of life and prolongs time to worsening in relapsed/refractory patients with multiple myeloma enrolled in the MM-003 randomized phase III trial.</p> <p>Song KW, Dimopoulos MA, Weisel KC, Moreau P, et al. Health-related quality of life from the MM-003 trial of pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed and/or refractory multiple myeloma.</p>	<p><i>Lancet Oncology</i> 2013; 14(11): 1055-1066.</p> <p><i>Leukemia & Lymphoma</i> 2016; 57(12): 2839-2847.</p> <p><i>Haematologica</i> 2016; 101(7): 872-8.</p> <p><i>Haematologica</i> 2015; 100(10):1327-33.</p> <p><i>Haematologica</i> 2015; 100(10): 1327-33.</p> <p><i>Clinical lymphoma, myeloma & leukemia</i> 2015; 15(9): 519-30.</p> <p><i>Haematologica</i> 2015; 100(2): e63-67.</p>
	Morgan G, Palumbo A, Dhanasiri S, Lee D, et al. Overall survival of relapsed and refractory multiple myeloma patients after adjusting for crossover in the MM-003 trial for pomalidomide plus low-dose dexamethasone.	<i>British Journal of Haematology</i> 2015; 168(6): 820-3.

Trial ID	Protocol title/publication title	Publication citation
Selinexor studies		
STORM (NCT02336815)	Chari A, Vogl DT, Gavriatopoulou M, Nooka AK, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma.	<i>New England Journal of Medicine</i> 2019; 381(8): 727-738.
	Tremblay G, Daniele P, Breeze J, Li L, et al. Quality of life analyses in patients with multiple myeloma: results from the Selinexor (KPT-330) Treatment of Refractory Myeloma (STORM) phase 2b study.	<i>BMC Cancer</i> 2021; 21(1): 993.
	Vogl DT, Dingli D, Cornell RF, Huff CA, et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma.	<i>Journal of Clinical Oncology</i> 2018; 36(9): 859-866.
	Richardson PG, Jagannath S, Chari A, Vogl DT, et al. Overall survival with oral selinexor plus low-dose dexamethasone versus real-world therapy in triple-class-refractory multiple myeloma.	<i>eJHaem</i> 2021; 2(1): 48-55.

Source: Table 2.4, pp54-57 of the resubmission.
Selected citations relating to conference abstracts omitted.

6.9 The key features of the studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Elranatamab studies						
MagnetisMM-3	187	Phase 2, open-label, single-arm study; median follow-up of 28.4 months (Cohort A).	High	<ul style="list-style-type: none"> - Age ≥18 years with multiple myeloma - Measurable disease - Refractory to last anti-myeloma treatment - Refractory to ≥1 PI, IMiD and CD38 antibody - ECOG ≤2 - Cohort A: No prior BCMA-directed therapy - Cohort B: Prior BCMA-directed therapy 	<ul style="list-style-type: none"> - ORR by BICR (primary) - ORR by BICR baseline EMD status (key secondary) - CRR - Duration of response - PFS - OS - Time to response - MRD negativity rate - Adverse events - HRQoL (EORTC QLQ-C30, EORTC MY20, EORTC QLQ CIPN20, PGI-S and PGI-C). 	<ul style="list-style-type: none"> - PFS - OS - Adverse events - HRQoL (EQ-5D-5L)
Cd studies						
ENDEAVOR	929	Phase 3, open-label, randomised controlled trial; median follow-up of 4.3 months.	Unclear	<ul style="list-style-type: none"> - Age ≥18 years with multiple myeloma - Relapsing or progressing disease - Evaluable disease - 1 to 3 prior lines of therapy - At least partial response to at least 1 line of prior therapy - Refractory to last anti-myeloma treatment - ECOG ≤2 	<ul style="list-style-type: none"> - PFS by IRC (primary) - OS - ORR - Duration of response - Adverse events 	<ul style="list-style-type: none"> - PFS - OS - Adverse events

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Pd studies						
MM-003	455	Phase 3, open-label, randomised controlled trial; median follow-up of 10.0 months	High	<ul style="list-style-type: none"> - Age ≥18 years with multiple myeloma - Refractory or relapsed disease - Measurable disease - ≥2 treatment lines of anti-myeloma therapy - At least 2 consecutive cycles of prior treatment that included lenalidomide and bortezomib - Failed treatment with both lenalidomide and bortezomib - Adequate prior alkylator therapy - ECOG ≤2 	<ul style="list-style-type: none"> - PFS (primary) - OS (key secondary) - ORR - Time to progression - Time to response - Duration of response - Adverse events - HRQoL (EORTC QLQ-C30, EORTC MY20, EQ-5D). 	<ul style="list-style-type: none"> - PFS - OS - Adverse events
Sd studies						
STORM	123	Phase 2, open-label, single-arm study; median follow-up not reported.	High	<ul style="list-style-type: none"> - Age ≥18 years with multiple myeloma - Symptomatic disease - Evidence of disease progression - Measurable disease - 3 prior anti-myeloma regimens including an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib and a glucocorticoid - Refractory to the most recent treatment regimen - Refractory to previous anticancer treatments: glucocorticoids, proteasome inhibitor, immunomodulatory drug, and daratumumab - ECOG ≤2 	<ul style="list-style-type: none"> - ORR by IRC (primary) - Duration of response - Clinical benefit rate - Disease control rate - PFS - OS - Minimal response - Time to next treatment - Adverse events - HRQoL (FACT-MM) 	<ul style="list-style-type: none"> - PFS - OS - Adverse events

Source: Section 2.4, pp71-91; Section 2.6.1, pp179-187; Section 2.6.2, pp188-193; Section 2.6.3, pp194-198 of the resubmission.
Abbreviations: 5L, 5-level; BCMA, B-cell maturation antigen; BICR, blinded independent central review; Cd, carfilzomib + dexamethasone; CD, cluster of differentiation; CIPN, chemotherapy-induced peripheral neuropathy; CRR, complete response rate; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; EORTC, European Organization for Research and Treatment of Cancer; FACT-MM, Functional Assessment of Cancer Therapy – Multiple Myeloma; HRQoL, health-related quality of life; IMiD, immunomodulatory drug; IRC, independent review committee; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; Pd, pomalidomide + dexamethasone; PFS, progression-free survival; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PI, proteasome inhibitor; QLQ, quality of life questionnaire; Sd, selinexor + dexamethasone.

6.10 The clinical evidence for elranatamab was derived from the MagnetisMM-3 study, an ongoing, phase 2, open-label, single-arm study of elranatamab monotherapy. The MagnetisMM-3 study included patients who were both naïve to BCMA-directed therapies (Cohort A, 123 patients), and patients with previous BCMA-directed therapy exposure (Cohort B; 64 patients). The resubmission included results based on the March 2024 data cut.

Comparative effectiveness

Pivotal elranatamab study (MagnetisMM-3)

6.11 Table 5 presents the results for blinded independent review committee-assessed response for Cohorts A and B of the MagnetisMM-3 study.

Table 5: Blinded independent central review response results for the MagnetisMM-3 study

Outcome	Elranatamab (Cohort A) N=123	Elranatamab (Cohort B) N=64
Best overall response, n (%)		
- Stringent complete response (sCR)	20 (16.3)	0
- Complete response (CR)	26 (21.1)	9 (14.1)
- Very good partial response (VGPR)	23 (18.7)	12 (18.8)
- Partial response (PR)	6 (4.9)	1 (1.6)
- Minimal response (MR)	0	0
- Stable disease (SD)	21 (17.1)	18 (28.1)
- Progressive disease (PD)	22 (17.9)	17 (26.6)
- Not evaluable (NE)	5 (4.1)	7 (10.9)
Overall response rate (sCR + CR + VGPR + PR), n (%)	75 (61.0)	22 (34.4)
- 95% CI	51.8, 69.6	22.9, 47.3
Complete response rate (sCR + CR), n (%)	46 (37.4)	9 (14.1)
- 95% CI	28.8, 46.6	6.6, 25.0
VGPR or better response rate (sCR + CR + VGPR), n (%)	69 (56.1)	21 (32.8)
- 95% CI	46.9, 65.0	21.6, 45.7
Clinical benefit rate (sCR + CR + VGPR + PR + MR) rate, n (%)	75 (61.0)	22 (34.4)
- 95% CI	51.8, 69.6	22.9, 47.3
Participants on treatment, no progression, confirmed response	0	0
Responders on treatment, no progression, confirmed VGPR	0	0
Responders on treatment, no progression, confirmed CR	3 (2.4)	3 (4.7)

Source: Table 2.25, p110 of the resubmission.

Abbreviations: CI, confidence interval; CR, complete response; MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

6.12 Treatment with elranatamab was associated with overall response rates of 61.0% and 34.4% in Cohorts A and B, respectively. The complete response rates were 37.4% and 14.1%, respectively.

6.13 MRD negativity based on a sensitivity of 10^{-5} was achieved by 28 patients (22.8%) in Cohort A and 3 patients (4.7%) in Cohort B; MRD negativity (based on a sensitivity of 10^{-6}) was achieved by 19 patients (15.4%) in Cohort A and 2 patients (3.1%) in Cohort B.

6.14 The median duration of response was not reached in either cohort. Among 75 patients who achieved a response in Cohort A, the proportion of patients remaining event-free at 24 months was 66.9% (95% CI: 54.4%, 76.7%). Among 22 patients who achieved a response in Cohort B, the proportion of patients remaining event-free at 12 months was 69.8% (95% CI: 44.5%, 85.2%).

6.15 Table 6 presents the results for progression-free survival based on blinded independent central review for the MagnetisMM-3 study.

Table 6: Progression-free survival based on blinded independent central review in the MagnetisMM-3 study

	Elranatamab (Cohort A) N=123	Elranatamab (Cohort B) N=64
Median duration of follow-up (95% CI)	28.4 (28.0, 29.0)	27.7 (27.2, 28.4)
Participants with event, n (%)	58 (47.2)	41 (64.1)
- Progressive disease, n (%)	38 (30.9)	29 (45.3)
- Death, n (%)	20 (16.3)	12 (18.8)
Median PFS, months (95% CI)	17.2 (9.8, NE)	4.4 (1.9, 7.4)
KM estimate of proportion remaining event-free		
- 6 months, % (95% CI)	63.6 (53.9, 71.8)	39.9 (27.2, 52.3)
- 12 months, % (95% CI)	55.7 (45.8, 64.5)	32.1 (20.3, 44.5)
- 18 months, % (95% CI)	48.3 (38.4, 57.4)	27.8 (16.6, 40.2)
- 24 months, % (95% CI)	48.3 (38.4, 57.4)	27.8 (16.6, 40.2)

Source: Table 14.2.3.1, pp282-283 of the MagnetisMM-3 clinical study report (March 2024 data cut).

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; NE, not estimable; PFS, progression-free survival.

6.16 Median progression-free survival was 17.2 months in Cohort A (based on a median follow-up of 28.4 months) and 4.4 months for Cohort B (based on a median follow-up of 27.7 months). The proportion of patients remaining progression-free at 24 months was 48.3% in Cohort A and 27.8% in Cohort B.

6.17 Table 7 presents the results for overall survival for Cohorts A and B of the MagnetisMM-3 study.

Table 7: Overall survival results for the MagnetisMM-3 study

	Elranatamab (Cohort A) N=123	Elranatamab (Cohort B) N=64
Median duration of follow-up (95% CI)	28.4 (28.0, 29.0)	27.7 (27.2, 28.4)
Deaths, n (%)	64 (52.0)	39 (60.9)
Median OS, months (95% CI)	24.6 (13.4, NE)	11.3 (6.5, 22.2)
KM estimate of proportion remaining event-free		
- 6 months, % (95% CI)	75.4 (66.8, 82.1)	66.9 (53.8, 77.0)
- 12 months, % (95% CI)	62.2 (53.0, 70.2)	47.1 (34.3, 58.9)
- 18 months, % (95% CI)	52.1 (42.8, 60.6)	40.4 (28.1, 52.3)
- 24 months, % (95% CI)	50.4 (41.1, 58.9)	36.9 (24.9, 48.8)

Source: Table 14.2.7, p321 of the MagnetisMM-3 clinical study report (March 2024 data cut).

Abbreviations: CI, confidence interval; NE, not estimable; OS, overall survival.

6.18 Median overall survival was 24.6 months in Cohort A (based on a median follow-up of 28.4 months) and 11.3 months for Cohort B (based on a median follow-up of 27.7 months). The proportion of patients remaining alive at 24 months was 50.4% in Cohort A and 36.9% in Cohort B.

6.19 Among patients with 2-3 prior lines of therapy in Cohort A, the median overall survival was not reached (95% CI: NE) and was 14.9 months (95% CI: 10.1, NE) for participants with ≥ 4 prior lines. The Kaplan-Meier probability of being alive at 24 months was 76.7% (95% C: 55.3, 88.8) for patients with 2-3 prior lines of treatment and 43.3% (95% CI: 33.2, 53.0) for patients with ≥ 4 prior lines.

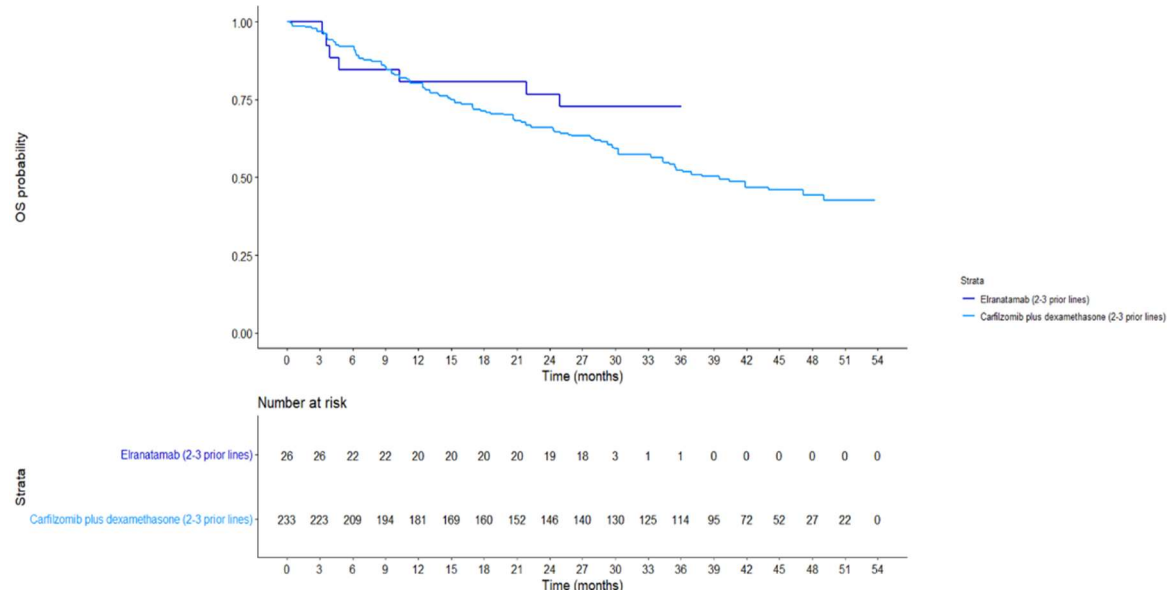
6.20 Updated quality of life outcome results based on the March 2024 data cut were available for the EORTC QLQ-C30, EORTC QLQ-MY20, QLQ-CIPN20 and EQ-5D. Due to the relatively small number of respondents at later time points for the quality-of-life survey instruments, the updated data was not considered to be informative.

- 6.21 For the EORTC QLQ-C30, group level scale scores worsened relative to baseline in the first 2 cycles for global quality of life, physical functioning, role functioning, social functioning, and financial difficulties, and then improved back to baseline levels. Group level scale scores for pain improved relative to baseline starting at day 1 of cycle 4, though the improvement was not maintained consistently. Group level scale scores for fatigue, nausea/vomiting, and appetite loss increased (worsened) and remained elevated until day 1 of cycle 6 and then decreased (improved) back to baseline levels. Group level domain scores were largely maintained over time for emotional functioning, cognitive functioning, dyspnoea, insomnia, constipation, and diarrhea with improvement beyond baseline at certain time points.
- 6.22 For the EQ-5D, there was no change from baseline over the course of the first nine cycles for the index score, except for an increase (improvement) at day 1 of cycle 11, day 1 of cycle 12 and day 1 of cycle 15 for Cohort A.

Unanchored indirect comparison of elranatamab (MagnetisMM-3) versus Cd (ENDEAVOR)

- 6.23 The resubmission noted differences in the MagnetisMM-3 and ENDEAVOR eligibility criteria, with the MagnetisMM-3 study including patients with RRMM that were triple class refractory, whereas the ENDEAVOR trial recruited patients with relapsing or progressing multiple myeloma disease who had received 1 to 3 prior lines of therapy.
- 6.24 Due to differences in the number of lines of therapy between trials, the resubmission presented a comparison based on the subgroup of patients in each study who had received 2 or 3 prior lines of therapy. The subgroup of patients in Cohort A of the MagnetisMM-3 study was small, with only 5 patients (4%) having received 2 prior lines of therapies, and 21 patients (17%) having received 3 prior lines of therapy. Due to the relatively small number of patients in the elranatamab subgroup, an unanchored MAIC versus the Cd subgroup was not considered feasible.
- 6.25 There were limited published patient characteristics for the subgroup of patients in the 2 to 3 prior lines subgroup of the ENDEAVOR study. The median age of patients in the MagnetisMM-3 study was higher (66 years versus 64 years), a lower proportion of patients had Stage I disease (23% versus 44%), and a higher proportion of patients had an ECOG score of 0 (58% versus 48%) compared to patients in the ENDEAVOR study.
- 6.26 Based on the unanchored ITC of progression-free survival, the hazard ratio favoured elranatamab but was not statistically significant (HR = 0.656; 95% CI: 0.303, 1.420; p=0.284). There was crossing of the curves at 7 months, with a higher proportion of patients treated with Cd compared to elranatamab remaining progression free prior to 7 months, and a lower proportion of patients treated with Cd compared to elranatamab remaining progression free after 7 months.
- 6.27 Figure 1 presents the results of the unanchored ITC of overall survival for elranatamab versus Cd, based on the subgroup of patients with 2 to 3 prior lines of treatment.

Figure 1: Unanchored indirect comparison of overall survival for elranatamab versus carfilzomib + dexamethasone



Source: Figure 2.24, p206 of the resubmission.
Abbreviations: OS, overall survival.

6.28 Based on the unanchored ITC of overall survival, the hazard ratio favoured elranatamab but was not statistically significant (HR = 0.673; 95% CI: 0.305, 1.484). There were multiple crosses of the overall survival curves prior to 12 months. Beyond 12 months, a higher proportion of patients treated with elranatamab remained progression free compared to Cd.

6.29 The results of the indirect comparison were considered uncertain for the following reasons:

- the small number of patients in the MagnetisMM-3 study subgroup with 2 to 3 prior treatments (n=26);
- differences in the eligibility criteria between the studies regarding prior treatment refractoriness;
- the limited availability of patient characteristics for the Cd subgroup;
- crossing of the progression-free survival and overall survival curves, and the lack of a statistically significant difference for the comparisons of progression-free survival and overall survival; and
- potential differences in the multiple myeloma treatments used, including prior therapies, and therapies used in the post-progression setting.

6.30 The pre-PBAC response acknowledged the limitations of the indirect comparison between elranatamab and Cd and stated that although the results should be interpreted with caution, the comparison offered valuable context regarding the treatment effect of elranatamab within the Australian RRMM landscape. In addition, the pre-PBAC response noted that elranatamab was associated with favourable

hazard ratios for progression free and overall survival compared to Cd and the results were trending towards statistical significance.

Unanchored MAIC of elranatamab (MagnetisMM-3) versus Pd (MM-003)

- 6.31 The resubmission noted differences in the MagnetisMM-3 and MM-003 eligibility criteria, with the MagnetisMM-3 study including patients with RRMM that were triple therapy refractory, whereas the MM-003 trial recruited patients with RRMM with at least 2 prior lines of therapy and who had previously failed treatment with bortezomib and lenalidomide. The resubmission noted that the majority of patients in the MagnetisMM-3 study (81%) had previously received treatment with pomalidomide. Patients who had previously received treatment with pomalidomide were excluded from the MM-003 trial. MM-003 was an older study, and the results may not reflect the current management of patients with RRMM given changes in the availability of standard of care treatments over time. Progression-free survival for the MM-003 study was based on investigator assessment (assessment by blinded independent review committee were not included in the trial).
- 6.32 Of the identified prognostic and treatment effect modifier variables, high-risk cytogenetics, extramedullary disease status, penta-exposed and penta-refractory status were not adjusted for in the MAIC as they were not reported for the MM-003 trial. The resubmission noted that the exclusion of high-risk cytogenetics and extramedullary disease status from the MAIC may have introduced bias, as these variables were identified as key prognostic/treatment effect modifier variables based on expert clinical opinion. The resubmission also noted that previous exposure to pomalidomide could not be adjusted in the MAIC, as it would lead to a very small sample size.
- 6.33 Table 8 presents a comparison of the available baseline patient characteristics for Cohort A of the MagnetisMM-3 study and the Pd arm of the MM-003 trial.

Table 8: Comparison of patient characteristics for the MagnetisMM-3 and MM-003 studies

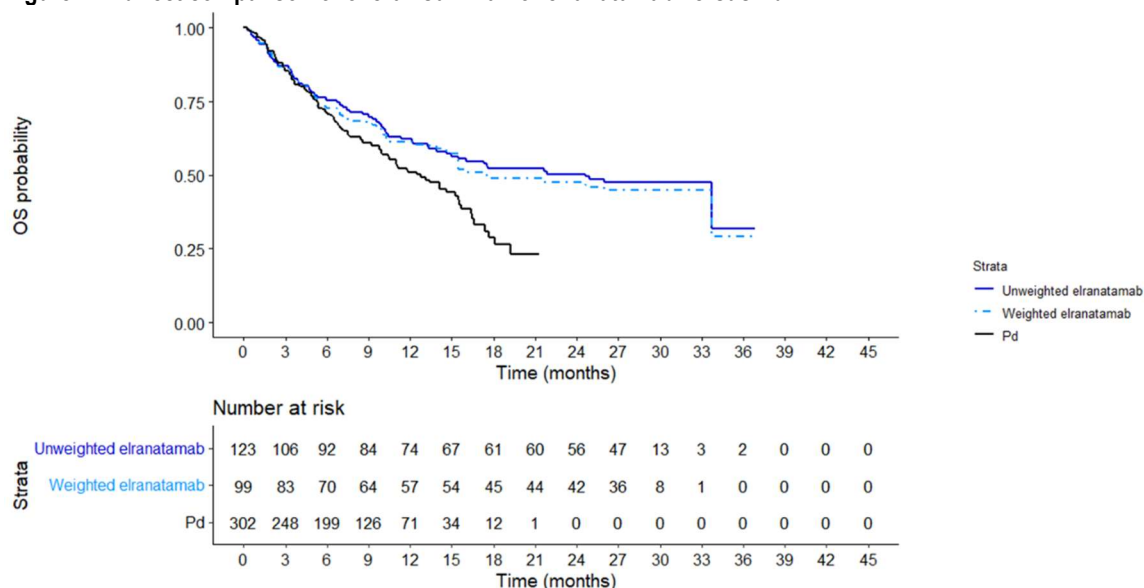
	MagnetisMM-3 Elranatamab (Cohort A) Unadjusted N=123	MM-003 Pd N=302	MagnetisMM-3 Elranatamab (Cohort A) Adjusted ESS=76
Age >75 years	21 (17%)	24 (8%)	8%
Male	68 (55%)	181 (60%)	60%
Median time from initial diagnosis, years	6.1	5.3	5.3
ISS disease stage			
- Stage I to II	82 (67%)	197 (65%)	65%
- Stage III	24 (20%)	93 (31%)	31%
- Missing	17 (14%)	12 (4%)	NR
>2 lines of prior therapy	118 (96%)	285 (94%)	94%
ECOG			
- 0 to 1	116 (94%)	248 (82%)	83%
- 2	7 (6%)	52 (17%)	17%
- Missing	0 (0%)	2 (<1%)	NR
Creatinine clearance <60 mL/min	37 (30%)	95 (31%)	31%

Source: Table 2.66, p210 of the resubmission; Table 1, p1 of the 'Elranatamab_ITC_Australia asks_DEC202024' document provided during the evaluation.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; ISS, International Staging System; Pd, pomalidomide + dexamethasone.

- 6.34 After matching for the available characteristics, the effective sample size for patients in the MagnetisMM-3 study was 76. Based on examination of the plot of patient weights, 3 patients received weights of around 4, and 1 patient included a weighting of around 6. The impact of the adjustment on other characteristics that were not selected for matching was unclear, as post-matching characteristics for variables that were not included for matching were not provided.
- 6.35 Table 9 presents the results of the unanchored ITC and unanchored MAICs for elranatamab versus Pd. A Kaplan-Meier plot of overall survival is presented in Figure 2.

Figure 2: Indirect comparison of overall survival for elranatamab versus Pd



Source: Figure 2.26, p211 of the resubmission.
Abbreviations: OS, overall survival; Pd, pomalidomide + dexamethasone.

Table 9: Results for the unanchored MAIC for elranatamab versus Pd

	ESS	HR (95% CI)	p-value
Progression-free survival			
Unanchored ITC	123	0.362 (0.257, 0.510)	≤0.001
Unanchored MAIC	76	0.385 (0.254, 0.584)	≤0.001
Overall survival			
Unanchored ITC	123	0.623 (0.446, 0.871)	0.006
Unanchored MAIC	76	0.658 (0.456, 0.949)	0.025

Source: Table 2.68, p211; Table 2.69, p212 of the resubmission.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; Pd, pomalidomide + dexamethasone.

- 6.36 Based on the unanchored ITC of progression-free survival, the hazard ratio favoured elranatamab, and the difference was nominally statistically significant. The results of the unanchored MAIC also favoured elranatamab, and the difference was nominally statistically significant.
- 6.37 Based on the unanchored ITC of overall survival, the hazard ratio favoured elranatamab, and the difference was nominally statistically significant. The results of the unanchored MAIC also favoured elranatamab, and the difference was nominally statistically significant.
- 6.38 Overall, the results of the indirect comparisons were suggestive of superiority for elranatamab compared to Pd, however, the results should be interpreted with caution due to the following reasons:
- the lack of patient characteristics reported for the MM-003 trial, which limited the number of prognostic/treatment effect modifier variables that could be matched in the MAIC;
 - potential differences in the multiple myeloma treatments used, including prior therapies, and therapies used in the post-progression setting; and

- differences in eligibility criteria between the studies.

Unanchored MAIC of elranatamab (MagnetisMM-3) versus Sd (STORM)

- 6.39 The resubmission noted differences in the MagnetisMM-3 and STORM eligibility criteria, with the MagnetisMM-3 study including patients who had RRMM that was triple class refractory whereas the STORM study included patients who had previously received ≥ 3 anti-myeloma regimens (including an alkylating agent, lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and a glucocorticoid), and who were refractory to glucocorticoids, a proteasome inhibitor, an immunomodulatory drug and daratumumab.
- 6.40 The resubmission noted extramedullary disease status was identified as a key prognostic variable based on the literature review and clinical expert opinion but was not reported for the STORM study.
- 6.41 Table 10 presents a comparison of the available baseline patient characteristics for Cohort A of the MagnetisMM-3 study and Sd in the STORM study.

Table 10: Comparison of patient characteristics between the MagnetisMM-3 and STORM studies

	MagnetisMM-3 Elranatamab (Cohort A) Unadjusted (N = 123)	STORM Sd (N = 122)	MagnetisMM-3 Elranatamab (Cohort A) Adjusted ESS=47
Age >75 years	21 (17%)	18 (15%)	15%
Male	68 (55%)	71 (58%)	58%
Median time from initial diagnosis, years	6.1	6.6	6.6
R-ISS disease stage			
- Stage I	28 (23%)	20 (16%)	16%
- Stage II	68 (55%)	78 (64%)	64%
- Stage III	19 (15%)	23 (19%)	19%
High risk cytogenetics			
- del(17p)/p53	19 (15%)	32 (26%)	26%
- t(4;14)	10 (8%)	17 (14%)	14%
- t(14;16)	2 (2%)	5 (4%)	4%
Median number of prior treatments	5	7	7
ECOG score			
- 0	45 (37%)	36 (30%)	30%
- ≥ 1	78 (63%)	82 (67%)	67%
Creatinine clearance ≥ 60 mL/min	72 (59%)	82 (67%)	67%
Penta-drug refractory	51 (41%)	83 (68%)	68%
Type of myeloma			
- IgG	65 (53%)	82 (67%)	67%
- Non-IgG	45 (37%)	40 (33%)	33%

Source: Table 2.72, p214 of the resubmission; Table 2, p3 of the 'Elranatamab_ITC_Australia asks_DEC202024' document provided during the evaluation.

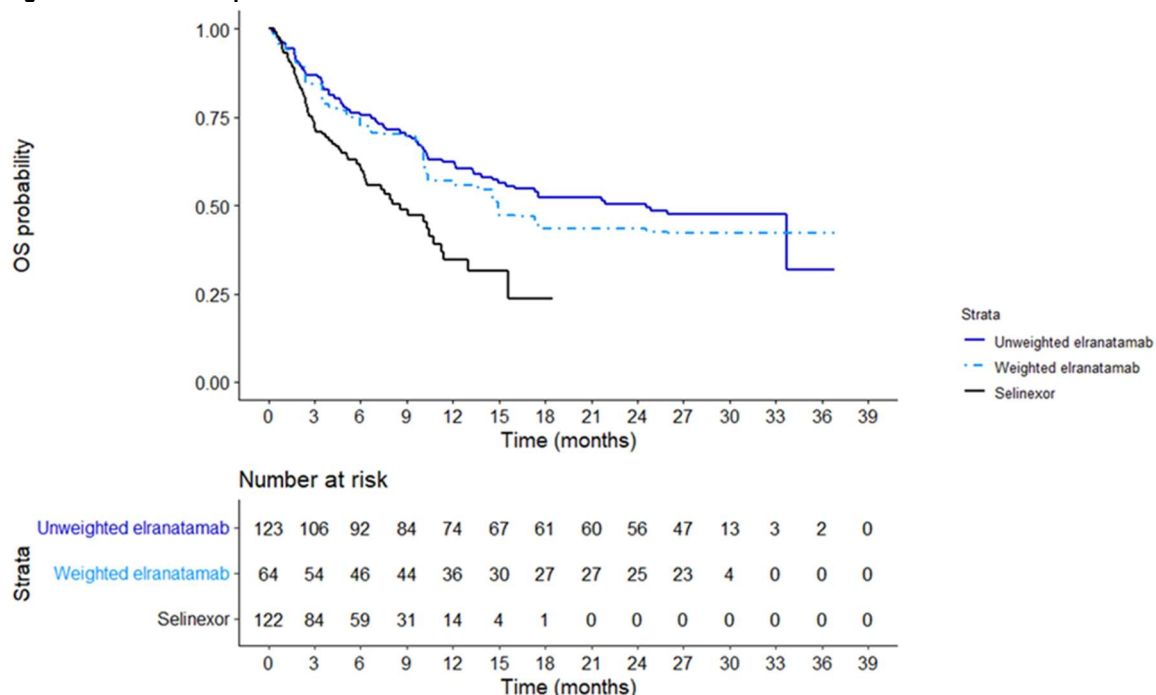
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IgG, immunoglobulin G; R-ISS, Revised International Staging System; Sd, selinexor + dexamethasone.

- 6.42 After matching based on the selected characteristics, the effective sample size for patients in the MagnetisMM-3 study was 47. Based on examination of the plot of patient weights, some patients had a relatively large weighting applied (6 patients received weights of between 4 to 6). The impact of the adjustment on other

characteristics that were not selected for matching was unclear, as post-matching characteristics for variables that were not included for matching were not provided.

6.43 Table 11 presents the results of the unanchored ITC and unanchored MAICs for elranatamab versus Sd. A Kaplan-Meier plot of overall survival is presented in Figure 3.

Figure 3: Indirect comparison of overall survival for elranatamab versus Sd



Source: Figure 2.28, p216 of the resubmission.
Abbreviations: OS, overall survival.

Table 11: Results for the unanchored MAIC for elranatamab versus Sd

	ESS	HR (95% CI)	p-value
Progression-free survival			
Unanchored ITC	123	0.481 (0.309, 0.749)	0.001
Unanchored MAIC	47	0.442 (0.238, 0.818)	0.009
Overall survival			
Unanchored ITC	123	0.491 (0.337, 0.716)	≤0.001
Unanchored MAIC	47	0.563 (0.348, 0.912)	0.020

Source: Table 2.69, p212; Table 2.75, p216 of the resubmission.

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; Sd, selinexor + dexamethasone.

6.44 Based on the unanchored ITC of progression-free survival, the hazard ratio favoured elranatamab, and the difference was nominally statistically significant. The results of the unanchored MAIC also favoured elranatamab, and the difference was nominally statistically significant.

6.45 Based on the unanchored ITC of overall survival, the hazard ratio favoured elranatamab, and the difference was nominally statistically significant. The results of the unanchored MAIC also favoured elranatamab, and the difference was nominally statistically significant.

- 6.46 Overall, the results of the indirect comparisons were suggestive of superiority for elranatamab compared to Sd, however, the results should be interpreted with caution due to the following reasons:
- the effective sample size after matching was relatively small;
 - differences in eligibility criteria between the studies;
 - potential differences in the multiple myeloma treatments used, including prior therapies, and therapies used in the post-progression setting; and
 - it was unclear whether all relevant prognostic and treatment effect modifier variables were matched in the unanchored MAICs.

Comparative harms

- 6.47 Compared to the July 2024 submission, the resubmission presented updated adverse event results based on a median follow-up of 28.4 months for Cohort A and 27.7 months for Cohort B.
- 6.48 Table 12 presents a summary of adverse events among patients in the MagnetisMM-3 study, based on the March 2024 data cut.

Table 12: Summary of adverse events in the MagnetisMM-3 study

	Cohort A N=123	Cohort B N=64	Total N=187
Median duration of follow-up, months (95% CI)	28.4 (28.0, 29.0)	27.7 (27.2, 28.4)	NR
Number of events, n	2275	978	3253
- Treatment related	959	349	1308
Any AE, n (%)	123 (100.0)	64 (100.0)	187 (100.0)
- Treatment related	112 (91.1)	59 (92.2)	171 (91.4)
Serious AE, n (%)	94 (76.4)	47 (73.4)	141 (75.4)
- Treatment related	47 (38.2)	19 (29.7)	66 (35.3)
Grade 3/4 AE, n (%)	89 (72.4)	42 (65.6)	131 (70.1)
- Treatment related	81 (65.9)	44 (68.8)	125 (66.8)
Grade 5 AE, n (%)	25 (20.3)	17 (26.6)	42 (22.5)
- Treatment related	4 (3.3)	2 (3.1)	6 (3.2)
AE leading to treatment discontinuation, n (%)	31 (25.2)	18 (28.1)	49 (26.2)
- Treatment related	23 (18.7)	9 (14.1)	32 (17.1)
AE leading to dose reduction, n (%)	36 (29.3)	9 (14.1)	45 (24.1)
- Treatment related	36 (29.3)	8 (12.5)	44 (23.5)
AE leading to treatment interruption, n (%)	96 (78.0)	45 (70.3)	141 (75.4)
- Treatment related	65 (52.8)	33 (51.6)	98 (52.4)
Grade 3/4 AE occurring in ≥5%, n (%)			
- Anaemia	46 (37.4)	33 (51.6)	79 (42.2)
- Neutropenia	61 (49.6)	22 (34.4)	83 (44.4)
- Thrombocytopenia	29 (23.6)	19 (29.7)	48 (25.7)
- Lymphopenia	31 (25.2)	20 (31.3)	51 (27.3)
- Leukopenia	17 (13.8)	7 (10.9)	24 (12.8)
- COVID-19 pneumonia	16 (13.0)	7 (10.9)	23 (12.3)
- Hypokalaemia	15 (12.2)	3 (4.7)	18 (9.6)
- Pneumonia	11 (8.9)	5 (7.8)	16 (8.6)
- Hypertension	9 (7.3)	5 (7.8)	14 (7.5)
- Sepsis	8 (6.5)	1 (1.6)	9 (4.8)
- SARS-CoV-2 test positive	7 (5.7)	2 (3.1)	9 (4.8)
- Asthenia	7 (5.7)	1 (1.6)	8 (4.3)
- Alanine aminotransferase increased	7 (5.7)	2 (3.1)	9 (4.8)
- Dyspnoea	3 (2.4)	5 (7.8)	8 (4.3)

Source: Table 19, p64, Table 20, p65; Table 21, pp66-69 of the MagnetisMM-3 clinical study report.

Abbreviations: AE, adverse event.

- 6.49 All patients experienced at least one adverse event, with 91% experiencing at least one treatment-related adverse event. The most commonly occurring adverse events in the overall population were cytokine release syndrome (58.8%), anaemia (53.5%), neutropenia (46.0%), diarrhoea (42.2%), thrombocytopenia (35.3%) and fatigue (29.9%).
- 6.50 Grade 3/4 adverse events occurred in 70% of the overall population. The most commonly occurring Grade 3/4 adverse events were anaemia (42.2%), neutropenia (44.4%), thrombocytopenia (25.7%), lymphopenia (27.3%), leukopenia (12.8%) and COVID-19 pneumonia (12.3%).
- 6.51 Fatal adverse events occurred in 42 patients (22.5%) in the overall population, with 6 events (3.2% of the overall population) considered to be related to treatment. The treatment-related fatal adverse events included cardiac arrest, failure to thrive, pneumonia pseudomonal, adenoviral hepatitis, and septic shock. One participant experienced a concurrent event of adenovirus infection and adenoviral pneumonia.

- 6.52 The product information for elranatamab includes a boxed warning for cytokine release syndrome (CRS) and neurologic toxicity including immune effector cell-associated neurotoxicity syndrome (ICANS). In the overall population of the MagnetisMM-3 study, 80 patients experienced Grade 1, 29 patients experienced Grade 2, and 1 patient experienced Grade 3 adverse events of CRS. The pre-PBAC response highlighted that the majority of CRS cases were low grade (96.5% were Grade 1/2). Two patients experienced Grade 1 events, 4 patients experienced Grade 2 events, and 2 patients experienced Grade 3 adverse events of ICANS. The pre-PBAC response highlighted that 60% of ICANS cases were low grade and were manageable.
- 6.53 In the overall population, a total of 8 patients (4.3%) developed ICANS events, including 2/4 patients (50%) who received 1 step-up dose of 44 mg elranatamab and 6/183 participants (3.3%) who received 2 step-up priming doses. The pre-PBAC response noted that the majority of patients who experienced CRS and ICANS did so during the first week of treatment when they were already in hospital.
- 6.54 Selected adverse event results for Cd, Pd and Sd reported in the respective study publications were presented in the resubmission. In general, comparison of adverse events between studies was impacted by limited reporting of adverse events for the comparator studies, differences in the included patient populations, and differences in the adverse event reporting periods between the studies.

Benefits/harms

- 6.55 The indirect comparisons presented in the resubmission did not allow for a robust comparison of the benefits and harms of elranatamab and standard of care. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.56 The submission described elranatamab as superior in terms of effectiveness and non-inferior but different in terms of safety compared to standard of care, represented by Cd, Pd and Sd.
- 6.57 The therapeutic conclusion presented in the submission was partially supported by the ESC, as outlined below:
- The ESC noted that the comparison of elranatamab versus Cd, which was assumed to represent 51.0% of the standard care therapy mix, was limited to an unanchored ITC of outcomes among a subgroup of patients with 2 to 3 prior lines of treatment. The ESC considered that although there was a trend towards elranatamab being superior in terms of efficacy compared to Cd, the data presented did not adequately support the claim for the reasons outlined in paragraph 6.29.
 - The ESC noted that the comparison of elranatamab versus Pd, which was assumed to represent 46.5% of the standard care therapy mix, was based on the results of an unanchored ITC and an unanchored MAIC. The ESC noted the limitations associated with this comparison (see paragraph 6.38); however, noted the results

of the unanchored MAICs demonstrated (nominally) statistically significant differences favouring elranatamab, and in each case there was a clear difference in the trajectory of the Kaplan-Meier overall survival curves. On balance, the ESC considered that the data presented supported the claim that elranatamab was superior in terms of efficacy compared to Pd.

- The ESC noted that the comparison of elranatamab versus Sd, which was assumed to represent 2.5% of the standard care therapy mix, was based on the results of an unanchored ITC and an unanchored MAIC. The ESC noted the limitations associated with this comparison (see paragraph 6.46); however, noted the results of the unanchored MAICs demonstrated (nominally) statistically significant differences favouring elranatamab, and in each case there was a clear difference in the trajectory of the Kaplan-Meier overall survival curves. On balance, the ESC considered that the data presented supported the claim that elranatamab was superior in terms of efficacy compared to Sd.
- While the resubmission presented the results for Cohort B of the MagnetisMM-3 study (patients with prior BCMA-directed therapy), no clinical claim in relation to patients with prior BCMA-directed therapy was made, and no estimates of comparative effectiveness were presented. The ESC noted that the results for Cohort B suggest that patients with prior BCMA-directed therapy experienced poorer outcomes with elranatamab.
- The ESC noted that the comparison of safety outcomes was impacted by the limited reporting of adverse events for the standard of care therapies, differences in the included patient populations, and differences in the adverse event reporting periods between the studies. Noting that elranatamab was associated with CRS and ICANs, the ESC considered that elranatamab was inferior compared to standard of care in terms of safety. The pre-PBAC response reiterated that elranatamab was not inferior to standard of care, but that it had a different adverse event profile to carfilzomib, pomalidomide and selinexor.

6.58 On balance, the PBAC considered that the claim that elranatamab had superior comparative effectiveness compared to Cd, Pd and Sd was reasonable.

6.59 The PBAC considered that the claim of non-inferior but different comparative safety was not adequately supported by the data.

Economic analysis

6.60 The resubmission presented a modelled economic evaluation comparing elranatamab with standard of care, for the treatment of patients with RRMM who have received at least three prior lines of therapy. The base case was derived as the weighted average of modelled results for elranatamab versus each of the nominated standard of care components (Cd: 51.0%; Pd: 46.5%; Sd: 2.5%). The economic evaluation was based on the updated results of the MagnetisMM-3 study for elranatamab, and the ENDEAVOR, MM-003 and STORM studies for Cd, Pd and Sd, respectively. Further, the PBAC noted that the economic evaluation incorporated 4-weekly dosing of elranatamab from

Week 49. The PBAC noted that this was not consistent with the current Product Information for elranatamab. The economic evaluation was presented as a stepped cost-effectiveness/cost-utility analysis.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Elranatamab versus standard of care, represented by the weighted average of results compared to Cd (51.0%), Pd (46.5%) and Sd (2.5%).
Time horizon	7 years in the base case versus a median follow-up of 28.4 months in the MagnetisMM-3 study. The ESC considered that the time horizon was long given the positioning of elranatamab as a fourth-line treatment. The ESC considered that a time horizon of 5 years would be more reasonable. The pre-PBAC response noted the PBAC have previously considered time horizons of 10 years to be appropriate in the second line treatment setting (carfilzomib, July 2017) and 5 years in the penta-refractory setting (selinexor, March 2022).
Outcomes	Quality-adjusted life years; life years.
Methods used to generate results	Partitioned survival analysis
Health states	Progression-free, progressed disease, dead.
Cycle length	1 week
Allocation to health states	Elranatamab: Progression-free survival and overall survival data based on the results of Cohort A from the MagnetisMM-3 study, with extrapolation using parametric functions. Standard of care: Progression-free survival and overall survival derived from extrapolated elranatamab survival curves, by application of hazard ratios obtained from the indirect comparisons presented in Section 2: <ul style="list-style-type: none"> - Unanchored indirect comparison of elranatamab (MagnetisMM-3) versus Cd (ENDEAVOR). - Unanchored MAIC of elranatamab (MagnetisMM-3) versus Pd (MM-003). - Unanchored MAIC of elranatamab (MagnetisMM-3) versus Sd (STORM).
Extrapolation method	Elranatamab: Progression-free survival, overall survival and time to treatment discontinuation data for elranatamab derived by extrapolation of Kaplan-Meier data using a parametric function (Weibull). Standard of care: Progression-free survival and overall survival curves derived by applying hazard ratios obtained from indirect comparisons of progression-free survival and overall survival for elranatamab versus each of the nominated standard of care component treatments to the extrapolated elranatamab progression-free survival and overall survival curves. Time to treatment discontinuation derived by fitting an exponential function to the median treatment duration for each of the nominated standard of care component treatments. 64% of the incremental QALYs and 15% of the incremental costs occur in the extrapolated period.
Health related quality of life	Progression-free and progressed disease health state utilities based on a post hoc analysis of EQ-5D-5L data for Cohort A of the MagnetisMM-3 study. Adverse event disutilities derived from a post hoc analysis of the MagnetisMM-3 study, the 2018 daratumumab NICE submission (TA510), and Howell et al. (2022).
Primary treatment cost	Based on the proposed effective price of elranatamab, and the published prices for carfilzomib, pomalidomide, selinexor and dexamethasone. Treatment regimen for elranatamab based on the updated treatment regimen (including reduced dose frequency to every 4 weeks beyond Week 49). Treatment regimens for standard of care therapies based on eviQ protocols.
Subsequent treatment costs	Medicine costs and administration costs derived based on an assumption that 40.8% of patients would receive subsequent treatment. Duration of treatment based on patient-months spent in post-progression survival, capped at the reported median duration of subsequent treatment reported for the MagnetisMM-3 study. Assumed a mix of 5 subsequent treatment regimens: ELd (20.0%), Cd + cyclo (11.4%), Pd (20.0%), Cd (37.1%) and PBd (11.4%).

Source: Section 3, pp229-280 of the resubmission.

Abbreviations: Cd, carfilzomib + dexamethasone; cyclo, cyclophosphamide; Eld, elotuzumab + lenalidomide + dexamethasone; MAIC, matching adjusted indirect comparison; PBd, pomalidomide + bortezomib + dexamethasone; Pd, pomalidomide + dexamethasone; QALY, quality-adjusted life year; Sd, selinexor + dexamethasone.

6.61 A partitioned survival approach was used to distribute patients between the model health states. Progression-free survival and overall survival curves for each of the

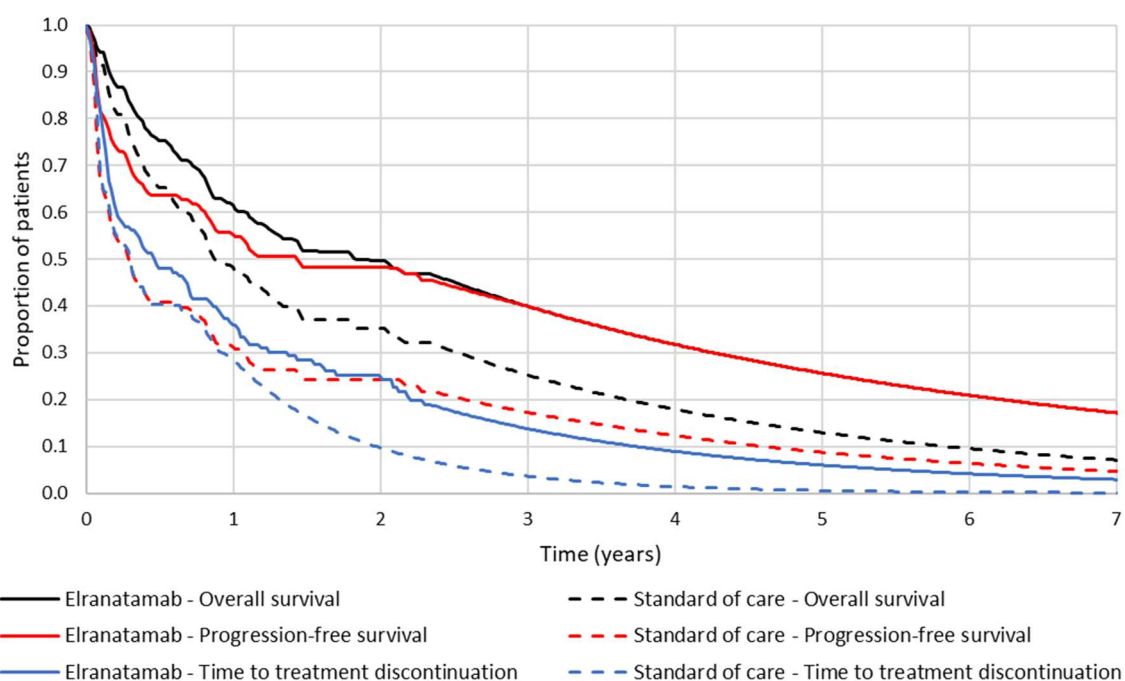
standard of care components were generated by applying the hazard ratios obtained from the indirect comparisons to the extrapolated progression-free survival and overall survival curves for elranatamab. The results of the indirect comparisons were associated with a substantial amount of uncertainty. While the results of the MAICs versus Pd and Sd were nominally statistically significant, the results of the indirect comparisons versus Cd did not achieve statistical significance.

- 6.62 In the model, the progression-free survival curves were capped by the overall survival curves to ensure that modelled progression-free survival did not exceed the modelled overall survival. Similarly, the time to treatment discontinuation curves were capped by the progression-free survival curves to ensure that the modelled time to treatment discontinuation curve did not exceed the modelled progression-free survival. Capping of the progression-free survival curve resulted in progression-free survival and overall survival for the elranatamab arm that was similar from 2 years onwards, and identical from 3 years onwards (see Figure 4 below). As a consequence, all of the patients in the elranatamab arm surviving beyond 3 years remain progression-free.
- 6.63 This suggests that the selected combination of progression-free survival and overall survival extrapolations were not appropriate. The PSCR stated that of the seven parametric extrapolations considered, the Weibull, exponential and Gamma distributions were deemed the most clinically plausible as the other appeared to overestimate progression free and overall survival and that the Weibull model demonstrated the best fit to the Kaplan Meier data. The ESC noted that although the parametric distributions were conservative, the results were not clinically plausible and introduced a high degree of uncertainty.
- 6.64 The duration of subsequent treatment in each treatment arm was assumed to be the lower of 7.98 months (the median duration of subsequent treatment observed among patients in the MagnetisMM-3 study) and the modelled patient-months of post-progression survival. The ESC noted that the capping of progression-free survival in the elranatamab arm resulted in a substantially shorter duration of post-progression survival, a shorter duration of subsequent treatment, and a lower cost of subsequent treatment for elranatamab compared to the other treatments. The ESC considered that the assumed differences in post-progression treatment costs were not adequately justified in the resubmission. The PSCR stated that despite the capping of the progression-free survival curve, the difference in post-progression costs between the treatment arms was less than \$10,000 per average patient.
- 6.65 While no capping of progression-free survival was observed in the standard of care arm over the 7-year time horizon, capping of the modelled time to treatment discontinuation curve by the modelled progression-free survival arm was present in the standard of care arm during the initial 6 months.
- 6.66 In general, the ESC noted that the modelled results were constrained by the assumption of fixed treatment effects for elranatamab versus standard of care (due to the application of hazard ratios to the extrapolated elranatamab data to obtain progression-free survival and overall survival for the standard of care arm), and the

occurrence of capping effects when various alternative extrapolation functions were used.

- 6.67 The proportion of patients in the elranatamab arm remaining progression-free at 5 years (26%) was substantially higher than the proportion of patients in the standard of care arm remaining progression free (7%).
- 6.68 The proportion of patients in the elranatamab arm remaining alive at 5 years (26%) was also substantially higher than the proportion of patients in the standard of care arm remaining alive (12%).
- 6.69 Further, the ESC noted that approximately 17% of patients in the elranatamab arm remained alive/progression free at the time horizon of 7 years, which the ESC considered lacked clinical plausibility.

Figure 4: Partitioned survival approach used in the resubmission



Source: Constructed during the evaluation using the Section 3 economic model Excel workbook (based on the model traces for the elranatamab arm).

6.70 Table 14 summarises the key drivers of the economic model.

Table 14: Key drivers of the model

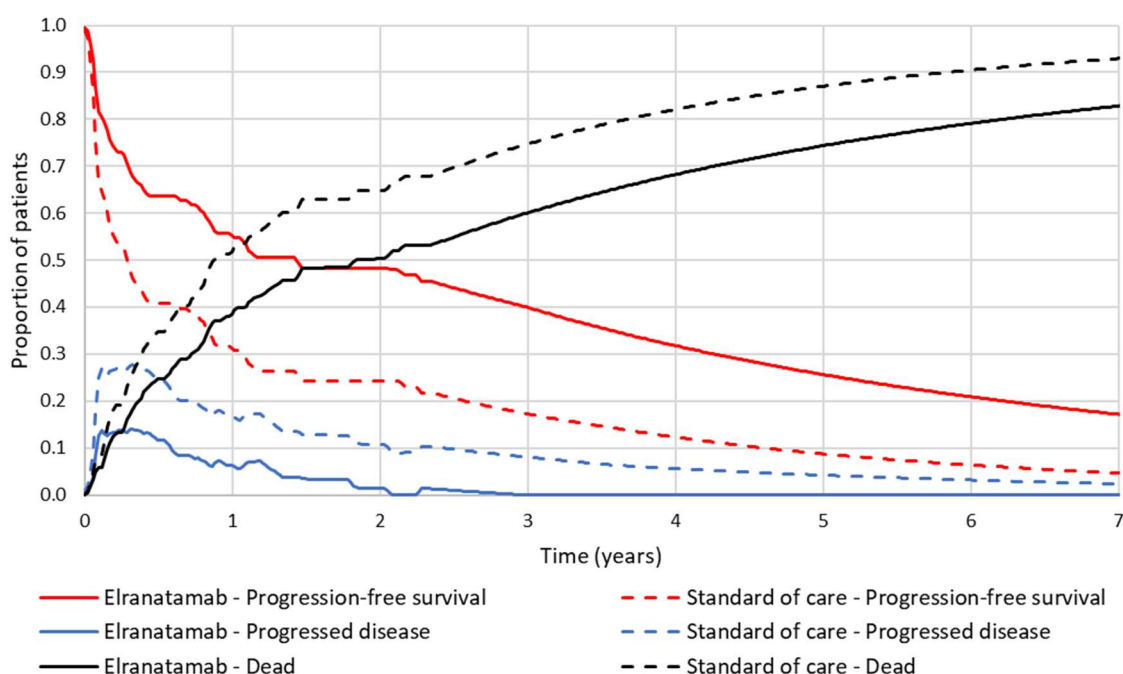
Description	Method/Value	Impact
Comparative effectiveness	Progression-free survival and overall survival curves for each of the standard of care components were generated by applying the hazard ratios obtained from the indirect comparisons to the extrapolated progression-free survival and overall survival curves for elranatamab. While the results of the MAICs versus Pd and Sd were nominally statistically significant, the results of the indirect comparisons versus Cd did not achieve statistical significance.	High, favours elranatamab.
Extrapolation	Due to the capping of the progression-survival curve by the overall survival curve, the progression-free survival and overall survival curves for the elranatamab arm were similar from 2 years onwards and identical from 3 years onwards, resulting in all elranatamab patients remaining progression-free from 3 years, and a lower duration of post-progression survival in the elranatamab arm, with lower associated subsequent treatment costs.	High, favours elranatamab.
Time horizon	Extrapolation of the clinical evidence and the associated comparative effectiveness was associated with a large degree of uncertainty.	Moderate, favours elranatamab.
Treatment adherence	The assumed treatment adherence for elranatamab (79%) was lower than the treatment adherence assumed for carfilzomib (93% for once weekly and 87% for twice weekly regimen) and pomalidomide (90%). Differences in treatment adherence between clinical studies may be due to other factors (e.g., differences in patient populations), and may not reflect treatment adherence in Australian clinical practice.	Moderate, favours elranatamab

Source: Constructed during the evaluation using the Section 3 economic model Excel workbook.

Abbreviations: Cd, carfilzomib + dexamethasone; MAIC, matching adjusted indirect comparison; Pd, pomalidomide + dexamethasone; Sd, selinexor + dexamethasone.

6.71 Figure 5 presents model traces for the elranatamab and standard of care arms.

Figure 5: Model traces for elranatamab and standard of care



Source: Constructed during the evaluation using the Section 3 economic model Excel workbook.

Standard of care traces derived from the weighted average proportion of patients in the progression-free, progressed and dead states for the nominated standard of care therapies (carfilzomib + dexamethasone: 51.0%; pomalidomide + dexamethasone: 46.5%; selinexor + dexamethasone: 2.5%).

6.72 Table 15 presents the results of the stepped economic evaluation based on published prices and 4-weekly dosing of elranatamab from Week 49.

Table 15: Results of the stepped economic evaluation

Step and component	Elranatamab	Standard of care	Increment
Step 1: Modelled analysis over 28.4 months. Results for comparators derived using hazard ratios obtained from indirect comparisons. ICER weighted based on nominated standard of care comparator distribution.			
Costs	\$█	\$87,828	\$█
Life years	1.486	1.202	0.283
Incremental cost per life year gained			\$█ ¹
Step 2: Time horizon increased to 7 years. Elranatamab progression-free survival, overall survival and time to treatment discontinuation extrapolated using parametric functions.			
Costs	\$█	\$101,026	\$█
Life years	2.828	1.947	0.881
Incremental cost per life year gained			\$█ ²
Step 3: Incorporation of health state utilities and adverse event disutilities.			
Costs	\$█	\$101,026	\$█
QALYs	2.367	1.599	0.768
Incremental cost per QALY gained			\$█ ³
Step 4: Inclusion of discounting for costs and outcomes.			
Costs	\$█	\$96,293	\$█
QALYs	2.096	1.445	0.651
Incremental cost per QALY gained			\$█³

Source: Table 3.27, p270 of the resubmission.

Abbreviations: QALY, quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$115,000 to < \$135,000

² \$45,000 to < \$55,000

³ \$55,000 to < \$75,000

6.73 Based on the economic model, treatment with elranatamab was associated with an incremental cost per QALY of \$55,000 to < \$75,000 compared to standard of care. Extrapolation of the time horizon to 7 years had the largest impact on the ICER. The PBAC noted that if 2-weekly dosing was applied from Week 24, i.e. no reduction in dosing to 4-weekly at Week 49, the ICER increased by █% to \$115,000 to < \$135,000 per QALY.

6.74 The difference in total costs between treatment arms was primarily driven by drug costs (acquisition and administration) for elranatamab in the progression-free health state, which were partly offset by drug acquisition costs for standard of care in the progressed disease state.

6.75 The difference in health outcomes between treatment arms was primarily driven by the difference in overall survival.

6.76 In the model, 64% of the incremental QALYs, 20% of the incremental primary medicine costs, 1% of the incremental primary medicine administration costs, 64% of the incremental disease management costs, 0% of the incremental adverse event management costs, 12% of the subsequent medicine costs and 12% of the subsequent medicine administration costs were accrued in the extrapolated period beyond 24.8 months.

6.77 For every patient treated with elranatamab versus standard of care and followed up for 7 years, the economic evaluation (without discounting) estimated that there would be:

- An additional 0.88 years of life lived.
- An additional 0.77 years of quality-adjusted life lived.
- Additional primary therapy costs of \$| (including administration costs), additional disease monitoring and adverse event costs of \$7,489, and a reduction in subsequent medicine costs of \$19,107 (including administration costs).

6.78 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 16.

Table 16: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change
Base case	\$	0.651	\$ ¹	-
Time horizon (base case: 7 years)				
5 years	\$	0.503	\$ ²	%
Discount rate (base case: 5% for costs and outcomes)				
0%	\$	0.768	\$ ¹	%
3.5%	\$	0.68	\$ ¹	%
Elranatamab progression-free survival extrapolation (base case: Weibull)				
Gamma	\$	0.652	\$ ¹	%
Exponential	\$	0.641	\$ ²	%
Elranatamab overall survival extrapolation (base case: Weibull)				
Gamma	\$	0.636	\$ ¹	%
Exponential	\$	0.593	\$ ¹	%
Elranatamab time to treatment discontinuation extrapolation (base case: Weibull)				
Gamma	\$	0.65	\$ ¹	%
Exponential	\$	0.651	\$ ¹	%
Log-logistic	\$	0.651	\$ ²	%
Standard of care distribution (base case: Cd: 51.0%; Pd: 46.5%; Sd: 2.5%)				
Cd 100%	\$	0.606	\$ ³	%
Pd 100%	\$	0.687	\$ ⁴	%
Sd 100%	\$	0.880	\$ ²	%
Progression-free survival hazard ratio (base case: Cd: 0.656 (95% CI: 0.303, 1.420); Pd: 0.385 (95% CI: 0.254, 0.584); Sd: 0.442 (95% CI: 0.238, 0.818))				
Cd hazard ratio = 0.303	\$	0.684	\$ ^{a 2}	%
Cd hazard ratio = 1.000	\$	0.645	\$ ^{a 1}	%
Cd hazard ratio = 1.420	\$	0.645	\$ ^{a 1}	%
Overall survival hazard ratio (base case: Cd: 0.673 (95% CI: 0.305, 1.484); Pd: 0.658 (95% CI: 0.456, 0.949); Sd: 0.563 (95% CI 0.348, 0.912))				
Cd hazard ratio = 0.305	\$	1.105	\$ ¹	%
Cd hazard ratio = 1.000	\$	0.362	\$ ⁵	%
Cd hazard ratio = 1.484	\$	0.074	\$ ⁶	%
Treatment adherence – elranatamab (base case: 79%)				
Decrease by 5% (74%)	\$	0.651	\$ ¹	%
Increase by 5% (84%)	\$	0.651	\$ ²	%
Treatment adherence – standard of care (base case: carfilzomib weekly 87%, twice weekly 93%; pomalidomide 90%; selinexor 72%)				
79% for all standard of care (same as elranatamab)	\$	0.651	\$ ²	%

Analyses	Incremental cost	Incremental QALY	ICER	% change
Elranatamab treatment regimen (base case: every 2 weeks from Week 25 to 48; every 4 weeks from Week 49)				
All patients remain on every 2 weeks dosing from Week 25	\$█	0.651	\$█ ⁴	█%
Subsequent treatment costs (base case: applied to 40.8%; cost based on duration of post-progression survival)				
Applied to 0%	\$█	0.651	\$█ ²	█%
Applied to 20.4%	\$█	0.651	\$█ ¹	█%

Source: Table 3.34, p276 of the resubmission; additional sensitivity analyses conducted during the evaluation using the Section 3 economic model Excel workbook.

Abbreviations: AR-DRG, Australian Refined Diagnosis-Related Group; Cd, carfilzomib + dexamethasone; CI, confidence interval; ICER, incremental cost-effectiveness ratio; Pd, pomalidomide + dexamethasone; QALY, quality-adjusted life year; Sd, selinexor + dexamethasone.

^a The results were impacted by capping of the modelled time to treatment discontinuation curve for carfilzomib + dexamethasone by the modelled progression-free survival.

The redacted values correspond to the following ranges:

- ¹ \$55,000 to < \$75,000
- ² \$75,000 to < \$95,000
- ³ \$5,000 to < \$15,000
- ⁴ \$115,000 to < \$135,000
- ⁵ \$95,000 to < \$115,000
- ⁶ \$455,000 to < \$555,000

6.79 The ESC noted that the model was most sensitive to the time horizon, the assumed progression-free survival extrapolation, the relative distribution of standard of care therapies, the treatment effect of elranatamab versus comparators on overall survival, elranatamab treatment adherence, elranatamab dosing frequency, and the costs associated with subsequent treatment. Due to the structure of the model, testing of alternative progression-free survival, overall survival and time to treatment discontinuation assumptions for elranatamab resulted in capping effects on progression-free survival and the time to treatment discontinuation curves in the elranatamab and standard of care arms.

Drug cost/patient/course

6.80 Table 17 presents a comparison of drug costs for elranatamab and standard of care therapies included in the economic model and financial estimates, assuming 4-weekly dosing of elranatamab from Week 49.

Table 17: Drug cost per patient per course for elranatamab and standard of care

	Elranatamab			Standard of care		
	Clinical evidence	Economic model	Financial estimates	Clinical evidence	Economic model	Financial estimates
Mean duration	10.7 months (46.7 weeks)	71.7 weeks ^a	71.0 weeks ^b	Not reported	Cd: 52.5 weeks Pd: 24.8 weeks Sd: 12.9 weeks	Cd: 39.9 weeks ^c
Cost/patient/week ^d	-	Week 1: \$█ Weeks 2-24: \$█ Weeks 25-48: \$█ Weeks 49+: \$█	Week 1: \$█ ^e Weeks 2-24: \$█ Weeks 25-48: \$█ Weeks 49+: \$█	-	Week 1: \$1,016.48 ^f Weeks 2-4: \$1,494.85 ^f Weeks 5+: \$1,627.04 ^f	\$1,275.57 ^{g,h}
Cost/patient/course	-	\$█	\$█	-	\$72,040 ^f	\$50,895 ^h

Source: Constructed during the evaluation using the Section 3 economic model and Section 4 financial implications Excel workbooks.

Abbreviations: Cd, carfilzomib + dexamethasone; NE, not estimable; Pd, pomalidomide + dexamethasone; Sd, selinexor + dexamethasone.

- ^a Mean treatment duration estimated from the proportion of patients on primary treatment over time in the economic model.
- ^b Treatment duration based on the modelled duration of treatment in the economic model.
- ^c Based on the treatment duration for Cd reported in the ENDEAVOR trial (Dimopoulos et al., 2016).
- ^d Inclusive of treatment adherence of 79% for elranatamab (79.12% in the financial estimates), 93% for Cd once weekly regimen, 97% for Cd twice weekly regimen, 90% for Pd, and 72%/78% for selinexor/dexamethasone for Sd.
- ^e Based on the average cost of 2 x 44 mg scripts, assuming a 40.1%/59.9% public/private hospital split, with costs included for all private hospital patients and 10% of public hospital patients (10% of public hospital patients assumed to receive treatment as outpatients).
- ^f Based on published prices, with a weighted average weekly cost (Cd 51.0%, Pd 46.5% and Sd 2.5%).
- ^g Average weekly cost over the assumed 39.9 weeks of treatment, based on a 63%/37% split between Cd weekly and twice weekly treatment regimens, and a 40.1%/59.9% public/private hospital split.
- ^h Based on the estimated effective price of carfilzomib, assumed to be 50% of the published AEMP.

Estimated PBS usage & financial implications

- 6.81 This resubmission was not considered by DUSC.
- 6.82 The resubmission used an epidemiological approach to estimate the utilisation and financial implications of listing elranatamab for the treatment of patients with RRMM who have received at least three prior lines of therapy that include a proteasome inhibitor, immunomodulatory drug, and an anti-CD38 antibody. The resubmission assumed a 50% rebate on the published price for carfilzomib.
- 6.83 Table 18 presents the key inputs relied on in the financial estimates.

Table 18: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value applied and source	Comment
Eligible population		
Prevalent multiple myeloma patients	5-year prevalence rate of 0.0276% reported by the AIHW (5-year period ending December 2018) to the forecast ABS population.	Unchanged from the July 2024 submission.
Proportion with triple class exposed disease	13.8%; based on an analysis of PBS dispensing data provided by the DUSC Secretariat (100% sample), which estimated that █ ¹ patients became triple class exposed (i.e., had a proteasome inhibitor, immunomodulatory drug and a CD38 antibody dispensed) in 2021/22, █ ¹ in 2022/23 (an increase of 17%) and █ ¹ in 2023/24 (an increase of 18%). The number of eligible patients in 2024/25 was assumed to increase by 19% from 2023/24, representing 13.8% of the prevalent population (█ ¹ ÷ █ ² = 13.8%).	Increased from 2.9% in the July 2024 submission. Although DUSC considered that 2.9% was markedly underestimated, the PBS dispensing data analysis did not determine if medicines were used in combination, and therefore some patients may not have received three prior lines of therapy. Other factors, such as the timing of availability of PBS treatments may have impacted the proportion with triple class exposed patients identified in the analysis. There may be additional patients that are not captured in the PBS dataset, such as patients who have previously received components of the 3 required therapies (a proteasome inhibitor, immunomodulatory drug and an anti-CD38 antibody) through an alternative source (e.g., privately funded or through a public hospital).
Proportion with triple class exposed disease initiating subsequent treatment	Yr 1: 40.8%; Based on an analysis of PBS dispensing data provided by the DUSC Secretariat (100% sample). Yr 2: █%; Yr 3: █%; Yr 4: █%; Yr 5: █%; Yr 6: █%; Assumption.	Reduced from 66.7% (all years) in the July 2024 submission. The PBS dispensing data analysis did not determine if medicines were used in combination. Some of the patients assumed to be initiating a subsequent treatment may have been receiving third line combination therapy. The assumption of a higher proportion of patients receiving fourth or later line therapy in Years 2 to 6 compared to Year 1 was not adequately justified.

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Data	Value applied and source	Comment
Treatment utilisation		
Elranatamab uptake rate	Yr 1: ■■■%; Yr 2: ■■■%; Yr 3: ■■■%; Yr 4: ■■■%; Yr 5: ■■■%; Yr 6: ■■■%; Assumption.	Unchanged from the July 2024 submission. DUSC previously considered that the estimates were an underestimate (para 6.65, elranatamab, PSD, July 2024 PBAC meeting). The PBAC previously considered that the potential introduction of CAR T cell therapies may alter the uptake of elranatamab (para 7.17, elranatamab, PSD, July 2024 PBAC meeting).
Grandfathered patients	■■■ ³ ; included in Year 1 of the financial estimates.	Increased from ■■■ ³ patients in the July 2024 submission. DUSC previously considered that the grandfathered patients were not relevant due to the prevalence-based approach adopted in the July 2024 submission (para 6.65, elranatamab, PSD, July 2024 PBAC meeting).
Proportion with substituted versus displaced standard of care (Cd)	Substituted: 56.9%; displaced: 43.1%; Derived based on an analysis of data reported by Fonseca et al. 2020, assuming 60% of elranatamab use as a fourth line treatment and 40% as a fifth line treatment.	It is unclear whether the derived proportions based on the Fonseca et al. data will accurately predict the relative impact of substitution versus displacement of Cd.
Initial treatment costs		
Elranatamab treatment adherence	79.12%; based on the median relative dose intensity reported for elranatamab in Cohort A of the MagnetisMM-3 study.	The assumed treatment adherence for elranatamab was lower than the treatment adherence assumed for Cd. Differences in treatment adherence between clinical studies may be due to other factors (e.g., differences in patient populations).
Cd treatment adherence	Weekly regimen: 92.7%; twice weekly regimen: 87.0%; Based on the average of the reported Cd mean relative dose intensities for the ARROW, CHAMPION-1 and ENDEAVOR trials (Moreau et al., 2020).	Differences in treatment adherence between clinical studies may reflect factors other than the underlying treatment (e.g., differences in patient populations).
Elranatamab treatment duration	71 weeks; based on the mean treatment duration for elranatamab in the economic model, which was estimated using parametric extrapolation of time to treatment discontinuation data for patients in Cohort A of the MagnetisMM-3 study.	In the financial model it was assumed that all patients receive elranatamab weekly (i.e., the more costly dose regimen) in the first 24 weeks, every 2 weeks from Week 25 to Week 48, and every 4 weeks from Week 49 onwards. The cost of elranatamab is likely to be overestimated, as a proportion of patients will discontinue treatment during the earlier, more frequent administration phases.
Cd treatment duration	39.9 weeks; median duration of carfilzomib treatment reported in the ENDEAVOR trial (Dimopoulos et al., 2016).	The use of the median treatment duration for carfilzomib was inconsistent with the treatment duration measure used for elranatamab (mean treatment duration).

Source: Section 4, pp281-305 of the resubmission; Section 4 financial implications Excel workbook.

Abbreviations: ABS, Australian Bureau of Statistics; AEMP, approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; Cd, carfilzomib + dexamethasone; CD, cluster of differentiation; DUSC, Drug Utilisation Sub-Committee; MBS, Medicare Benefits Schedule; Yr, Year.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² 5,000 to < 10,000

³ < 500

6.84 Table 19 presents the estimated use and financial implications of listing elranatamab on the PBS, assuming 4-weekly dosing from Week 49.

Table 19: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	█ ^{a 1}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Elranatamab 44 mg scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Elranatamab 76 mg scripts	█ ²	█ ²	█ ²	█ ²	█ ²	█ ³
Dexamethasone 4 mg scripts	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated financial implications of elranatamab						
Cost to PBS/RPBS less copayments	\$█ ⁴	\$█ ⁵	\$█ ⁴	\$█ ⁴	\$█ ⁶	\$█ ⁶
Estimated financial implications for Cd						
Cost offset to PBS/RPBS less copayments	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷	-\$█ ⁷
Net financial implications						
Net cost to PBS/RPBS	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁴	\$█ ⁴	\$█ ⁴
Net cost to MBS	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸
Net cost to the PBS/RPBS/MBS	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁴	\$█ ⁴	\$█ ⁴
July 2024 submission						
Number of patients treated	█ ^{b 1}	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Net cost to PBS/RPBS	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁸	\$█ ⁹

Source: Section 4 financial implications Excel workbook; Table 4.4.1, p150 of the July 2024 elranatamab commentary. Includes correction of error in the number of elranatamab scripts.

Abbreviations: Cd, carfilzomib + dexamethasone.

^a Includes < 500 grandfathered patients in Year 1.

^b Includes < 500 grandfathered patients in Year 1

The redacted values correspond to the following ranges:

¹ < 500

² 5,000 to < 10,000

³ 10,000 to < 20,000

⁴ \$30 million to < \$40 million

⁵ \$20 million to < \$30 million

⁶ \$40 million to < \$50 million

⁷ net cost saving

⁸ \$0 to < \$10 million

⁹ \$10 million to < \$20 million

6.85 The estimated net cost to the PBS/RPBS/MBS (after correction of errors) was \$30 million to < \$40 million in Year 1, increasing to \$30 million to < \$40 million in Year 6, a total cost of \$100 million to < \$200 million over the first 6 years of listing. The PBAC noted that if 2-weekly dosing from Week 24 was applied, with no change to 4-weekly dosing at Week 49, the net cost to the PBS/RPBS/MBS was \$30 million to < \$40 million in Year 1, increasing to \$40 million to < \$50 million in Year 6, and totalling \$200 million to < \$300 million over the first 6 years.

6.86 The ESC noted that the estimated financial implications associated with listing elranatamab on the PBS were considered uncertain due to the following reasons:

- The assumed prevalence of multiple myeloma (0.0276%; based on the period ending December 2018) was unchanged from the 2024 submission. However, updated AIHW data suggest a higher 5-year prevalence of 0.0299% for the period ending December 2020.
- Although the triple class exposed population was increased from 2.9% to 13.8%, the population might still be underestimated.

- A higher proportion of patients were assumed to initiate subsequent treatment in Years 2 to 6 (ranging from $\frac{1}{2}$ % in Year 2 to $\frac{1}{2}$ % in Year 6), based on the assumption that a greater number of patients will proceed to active treatment over time as newer/more effective treatments become available. However, this claim may not be reasonable.
 - Uptake rates associated with elranatamab were considered uncertain and may be underestimated in the context of fourth or later RRMM treatment. The PBAC previously considered that the potential introduction of CAR T-cell therapies may alter the uptake of elranatamab (paragraph 7.17, elranatamab, PSD, July 2024 PBAC meeting). The PSCR stated that the uptake rate in Year 1 was derived from the PBS 100% sample, in which 40.8% of patients with triple class refractory multiple myeloma became eligible for fourth-line treatment, after which uptake was assumed to increase gradually as patients and clinicians become more familiar with elranatamab.
 - The assumed treatment adherence for elranatamab (79%) was lower than the treatment adherence assumed for Cd (weekly regimen: 92.7%; twice weekly regimen: 87.0%). Differences in treatment adherence between clinical studies may be due to other factors (e.g., differences in patient populations), and the assumed treatment adherence may not reflect the treatment adherence for elranatamab and Cd in Australian clinical practice. However, the ESC noted these assumptions were consistent with the economic model.
 - It is unclear whether the derived proportions of substituted versus displaced standard of care (based on the Fonseca et al. data) will accurately predict the relative impact of substitution versus displacement of Cd.
- 6.87 The resubmission included costs associated with continuing treatment of < 500 grandfathered patients in Year 1 of the financial estimates (increased from < 500 in the July 2024 submission).
- 6.88 The resubmission assumed that all patients treated in the private hospital setting, and 90% of patients treated in the public hospital setting would receive the initial 2 step-up doses of elranatamab as inpatients. Drug costs and hospitalisation costs were not included in the financial estimates but would represent an additional cost to state/territory government health budgets.

Quality Use of Medicines

- 6.89 The proposed activities to support the quality use of medicines were unchanged from the July 2024 submission:
- Holding an elranatamab training certification course for clinicians and haematologists in the area of RRMM and associated adverse events.
 - Working with Myeloma Australia to identify outreach gaps and deliver training throughout Australia in regional centres to reach haematology nurses and other health care professionals.

- Development of elranatamab patient wallet cards to ensure the appropriate management of potential side effects and risks associated with elranatamab step-up dosing.
 - Development of training videos for health care professionals on how to administer elranatamab.
 - Development of an elranatamab website for health care professionals that includes patient materials on demand.
- 6.90 DUSC previously considered that cytokine release syndrome and ICANS are novel complications that are not well understood outside specialist centres, and that education of both patients and health care practitioners would be needed (paragraph 6.73, elranatamab, PSD, July 2024 PBAC meeting).

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended elranatamab for the treatment of patients with relapsed or refractory multiple myeloma (RRMM) who have received at least three prior lines of therapy, on the basis that it should be available only under special arrangements under the Section 100 Program (Efficient Funding of Chemotherapy – Related Benefits) and as a General Schedule listing. The PBAC considered that elranatamab was superior in terms of efficacy compared to standard of care, represented by carfilzomib plus dexamethasone (Cd), pomalidomide plus dexamethasone (Pd) and selinexor plus dexamethasone (Sd), but inferior in terms of safety. The PBAC considered that the revised economic model was reliable for decision making and noted that elranatamab would be cost effective with a price reduction. The PBAC considered that the estimated utilisation of elranatamab was uncertain and considered that a risk-sharing arrangement (RSA) would be required.
- 7.2 The PBAC was satisfied that elranatamab provides, for some patients, a significant improvement in efficacy over standard of care, represented by Cd, Pd and Sd.
- 7.3 The PBAC acknowledged the input received from individuals, health care professionals and organisations for both this resubmission and the July 2024 submission. The PBAC noted that this input highlighted the need for new, effective, and well tolerated therapies for patients with RRMM. The PBAC also noted the input from Myeloma Australia's Medical and Scientific Advisory Group which supported use of elranatamab in the fourth line of therapy and advised that elranatamab could provide an alternative to CAR-T therapies.
- 7.4 The PBAC noted that the resubmission positioned elranatamab as a fourth-line therapy for use in patients who have progressed on at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The PBAC considered that this was appropriate and better aligned with the clinical evidence (compared to the July 2024 submission which positioned elranatamab as a third-line therapy).

- 7.5 The PBAC noted that although the resubmission was based on patients receiving 76 mg of elranatamab subcutaneously every 4 weeks from Week 49, this dosing regimen was not yet approved by the TGA (see paragraph 2.2). Thus, the PBAC based its consideration of elranatamab on the currently TGA approved dosing regimen, in which patients received 2-weekly dosing from Week 24, with no change to the dosing schedule at Week 49.
- 7.6 The PBAC considered that as elranatamab is a subcutaneous injection, it should have a dual listing on both the General Schedule and the Section 100 Program (Efficient Funding of Chemotherapy) – Related Benefits. In addition, the PBAC advised that the restrictions should:
- stipulate that treatment with elranatamab should be as monotherapy to align with the clinical evidence presented;
 - include a criterion stating the patients must have a WHO performance status of 2 or less to align with the clinical trial;
 - state that the patient must have relapsed after, or be refractory to, at least 3 prior lines of therapy including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody;
 - prevent use in patients who have received a prior BCMA-directed therapy; and
 - state that treatment is not PBS-subsidised if it is administered to an inpatient in a public hospital setting.
 - for induction (step-up) treatment, be listed as 1 vial with 1 repeat; and
 - for continuing treatment, be listed as 1 vial with 5 repeats. A Prescriber Instruction should be included to allow prescribers to increase the quantity of vials required to provide for 4-weeks of treatment in line with the dosing requirements for each stage of treatment, as specified in TGA Product Information. The intention is to provide 24-weeks of treatment (inclusive of repeats) and reduce extra co-payments for patients.
- 7.7 The PBAC considered that the comparator, standard of care, represented by Cd (51%), Pd (46.5%) and Sd (2.5%) was appropriate and reflected clinical practice. The PBAC considered that the estimated weighting for each therapy was reasonable.
- 7.8 The PBAC noted that the resubmission presented updated elranatamab data from Cohort A (patients who were naïve to BCMA-directed therapies) of the single arm study, MagnetisMM-3 trial, (N = 123). Treatment with elranatamab was associated with an overall response rate of 61.0% and a complete response rate of 37.4% after a median follow-up of 28.4 months. The PBAC noted that the resubmission also included evidence from Cohort B, which included patients who had received prior BCMA-directed therapies. The PBAC noted that these patients experienced poorer outcomes with elranatamab.
- 7.9 The PBAC noted that the resubmission presented a series of indirect comparisons for

each of the standard of care components based on the ENDEAVOR trial (Cd), the MM-003 trial (Pd) and the STORM trial (Sd).

- 7.10 The resubmission presented an unanchored indirect comparison of elranatamab versus Cd. The PBAC noted that the comparison was uncertain due to the small number of patients in the elranatamab subgroup and other limitations outlined in paragraph 6.29. The PBAC noted that although not statistically significant, the hazard ratios for progression free survival (HR = 0.66; 95% CI: 0.30, 1.42) and overall survival (HR = 0.67; 95% CI: 0.31, 1.48) favoured elranatamab.
- 7.11 The resubmission presented unanchored indirect comparisons and unanchored matching adjusted indirect comparisons (MAICs) between elranatamab and Pd and elranatamab and Sd. Results of all comparisons were nominally statistically significant in favour of elranatamab in terms of progression free and overall survival.
- 7.12 Overall, the PBAC considered that elranatamab was superior in terms of efficacy compared to Pd and Sd, and that elranatamab was likely superior compared to Cd.
- 7.13 In terms of safety, the PBAC recalled that it had previously considered that elranatamab was inferior compared to standard of care due to the high rates of cytokine release syndrome and immune-effector cell-associated neurotoxicity syndrome associated with elranatamab. Although the PBAC noted that the majority of these events were low grade and occurred within the first week of treatment whilst the patient was in hospital the PBAC again considered that elranatamab was inferior to standard of care in terms of safety. Further, the PBAC noted that the comparison of adverse events between elranatamab and Cd, Pd and Sd was limited by the reporting of events in the comparator studies and differences in the patient populations.
- 7.14 The PBAC noted that the resubmission presented a revised economic analysis versus standard of care which addressed a number of the issues raised in the July 2024 consideration. The PBAC noted that some issues with the economic model remained, including:
- The relative treatment effects of elranatamab versus the standard of care therapies were uncertain as they were based on unanchored indirect comparisons; and
 - The progression free survival curves were capped to ensure that they did not exceed the overall survival curves.
- 7.15 The PBAC noted the base case model included a time horizon of 7 years and that the model potentially overestimated the proportion of patients alive and progression free at the end of this period; however, the PBAC also noted that this overestimation was likely the case for both the elranatamab and standard of care arms. The PBAC noted testing alternative relative treatment effects and extrapolation functions was constrained by the model structure. On balance, the PBAC considered that a time horizon of 7 years was reasonable in the context of other RRMM considerations.

- 7.16 The PBAC noted that the economic analysis was based on 4-weekly dosing of elranatamab after Week 49. The PBAC noted that applying 2-weekly dosing from Week 24, with no change at Week 49, increased the base case incremental cost-effectiveness ratio (ICER) by $\frac{1}{2}$ % (using the published price of comparators).
- 7.17 The PBAC considered that elranatamab would be cost effective at an ICER of less than \$75,000 to < \$95,000 per quality adjusted life year, when applying the effective prices of carfilzomib, pomalidomide and selinexor. The PBAC advised that consideration of cost effectiveness should be based on the current approved TGA Product Information. The PBAC noted there is an application with the TGA for 4-weekly dosing and advised if that dosing regimen is approved, the sponsor can update its economic model on that basis.
- 7.18 The PBAC noted that the utilisation estimates were based on DUSC Secretariat analyses of the 100% PBS data sample as recommended in July 2024 (paragraph 7.17, elranatamab PSD, July 2024). The PBAC noted some uncertainties remained with the financial estimates (see paragraph 6.86) and considered that a RSA, with a $\frac{1}{2}$ % rebate over the expenditure caps, would be required. The PBAC also noted that the estimated utilisation would be higher when based on the current TGA Product Information i.e., 2-weekly dosing from Week 24 (with no change at Week 49).
- 7.19 The PBAC noted the large number of treatments listed on the PBS for the treatment of multiple myeloma. The PBAC recommended that the Department undertake a utilisation analysis to understand the treatment pathways and duration of treatment for PBS-listed therapies for multiple myeloma.
- 7.20 The PBAC recommended that elranatamab should not be treated as interchangeable with any other drugs.
- 7.21 The PBAC advised that elranatamab is not suitable for prescribing by nurse practitioners.
- 7.22 The PBAC advised that elranatamab should not be exempt from the Early Supply Rule.
- 7.23 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for elranatamab:
- a) The treatment is expected to provide a clinically relevant improvement in efficacy over standard of care, but the magnitude of benefit is uncertain.
 - b) The treatment is not expected to address a high and urgent unmet clinical need because there are alternative treatment options for patients with RRRM.
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.24 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
ELRANATAMAB					
elranatamab 44 mg/1.1 mL injection, 1.1 mL vial	NEW (CT)	1	1	1	Elrexio
elranatamab 44 mg/1.1 mL injection, 1.1 mL vial	NEW (GE)	1	1	1	Elrexio
Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) <input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy – Related Benefits (Code CT)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required – Immediate assessment (Telephone/Online)					
Authority type: <input checked="" type="checkbox"/> Non-complex Authority Required (non-CAR)					
Restrictions Summary / Treatment of Concept:					
Episodicity: [Blank]					
Severity: Relapsed or refractory					
Condition: Multiple myeloma					
Indication: Relapsed or refractory multiple myeloma					
Treatment Phase: Induction treatment (step-up dosing)					
Clinical criteria:					
The condition must be confirmed by a histological diagnosis					
AND					
Clinical criteria:					
Patient must have progressive disease after receiving at least 3 prior lines of therapy, including each of the following therapies: (i) a proteasome inhibitor, (ii) an immunomodulatory agent, and (iii) an anti-CD38 monoclonal antibody; or					
Patient must be refractory to, at least 3 prior lines of therapy, including each of the following therapies: (i) a proteasome inhibitor, (ii) an immunomodulatory agent, (iii) an anti-CD38 monoclonal antibody					
AND					
Clinical criteria:					
Patient must have a WHO performance status of 2 or less					
AND					
Clinical criteria:					
Patient must not have previously received treatment with another B-cell maturation antigen (BCMA) directed therapy for this condition.					
AND					
Clinical criteria:					
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition					
Prescribing instruction: According to the TGA-approved Product Information, hospitalisation is recommended at minimum for the first 2 doses (on Days 1 and 4) and for at least 48 hours after each administration is completed.					
Prescribing instruction: Patients who require restarting therapy due to dose delays may access step-up dosing through this induction treatment restriction.					
Prescribing instruction: This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.					

	<p>Prescriber Instructions: Progressive disease is defined as at least 1 of the following: (a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or (b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or (c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or (d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or (e) an increase in the size or number of lytic bone lesions (not including compression fractures); or (f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or (g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p> <p>Oligo-secretory and non-secretory patients are defined as having active disease with less than 10 g per L serum M protein. Details of: the histological diagnosis of multiple myeloma; prior treatments including name(s) of drug(s) and date of most recent treatment cycle; the basis of the diagnosis of progressive disease or failure to respond; and which disease activity parameters will be used to assess response, must be documented in the patient's medical records.</p> <p>Confirmation of eligibility for treatment with current diagnostic reports of at least one of the following must be documented in the patient's medical records:</p> <p>(a) the level of serum monoclonal protein; or (b) Bence-Jones proteinuria - the results of 24-hour urinary light chain M protein excretion; or (c) the serum level of free kappa and lambda light chains; or (d) bone marrow aspirate or trephine; or (e) if present, the size and location of lytic bone lesions (not including compression fractures); or (f) if present, the size and location of all soft tissue plasmacytomas by clinical or radiographic examination i.e. MRI or CT-scan; or (g) if present, the level of hypercalcaemia, corrected for albumin concentration.</p> <p>As these parameters must be used to determine response, results for either (a) or (b) or (c) should be documented for all patients. Where the patient has oligo-secretory or non-secretory multiple myeloma, either (c) or (d) or if relevant (e), (f) or (g) must be documented in the patient's medical records. Where the prescriber plans to assess response in patients with oligo-secretory or non-secretory multiple myeloma with free light chain assays, evidence of the oligo-secretory or non-secretory nature of the multiple myeloma (current serum M protein less than 10 g per L) must be documented in the patient's medical records.</p> <p>Refractory disease is defined as less than or equal to a 25% response to therapy, or progression during or within 60 days after completion of therapy</p>
	<p>Administrative advice: No increase in the maximum quantity or number of units may be authorised</p>
	<p>Administrative advice: No increase in the maximum number of repeats may be authorised</p>
	<p>Administrative advice: Special pricing arrangements apply</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
ELRANATAMAB					
elranatamab 76 mg/1.9 mL injection, 1.9 mL vial	NEW (CT)	1	1	5	Elrexio
elranatamab 76 mg/1.9 mL injection, 1.9 mL vial	NEW (GE)	1	1	5	Elrexio
Restrictions Summary / Treatment of Concept:					
	Episodicity: [Blank]				
	Severity: Relapsed or refractory				
	Condition: Multiple myeloma				
	Indication: Relapsed or refractory multiple myeloma				
	Treatment Phase: Continuing treatment				
	Clinical criteria:				
	Patient must have previously received treatment with this drug for this condition,				
	AND				
	Clinical criteria:				
	Patient must have had progressive disease after receiving at least 3 prior lines of therapy, including each of the following therapies: (i) a proteasome inhibitor, (ii) an immunomodulatory agent, and (iii) an anti-CD38 monoclonal antibody; or				
	Patient must have been refractory to, at least 3 prior lines of therapy, including each of the following therapies: (i) a proteasome inhibitor, (ii) an immunomodulatory agent, (iii) an anti-CD38 monoclonal antibody				
	AND				
	Clinical criteria:				
	Patient must not have previously received treatment with another B-cell maturation antigen (BCMA) directed therapy for this condition.				
	AND				
	Clinical criteria:				
	Patient must have a WHO performance status of 2 or less prior to initiating treatment with this drug for this condition				
	AND				
	Clinical criteria:				
	Patient must not have developed disease progression while receiving treatment with this drug for this condition.				
	AND				
	Clinical criteria:				
	The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition				

	<p>Prescribing Instructions: Progressive disease is defined as at least 1 of the following:</p> <p>(a) at least a 25% increase and an absolute increase of at least 5 g per L in serum M protein (monoclonal protein); or</p> <p>(b) at least a 25% increase in 24-hour urinary light chain M protein excretion, and an absolute increase of at least 200 mg per 24 hours; or</p> <p>(c) in oligo-secretory and non-secretory myeloma patients only, at least a 50% increase in the difference between involved free light chain and uninvolved free light chain; or</p> <p>(d) at least a 25% relative increase and at least a 10% absolute increase in plasma cells in a bone marrow aspirate or on biopsy; or</p> <p>(e) an increase in the size or number of lytic bone lesions (not including compression fractures); or</p> <p>(f) at least a 25% increase in the size of an existing or the development of a new soft tissue plasmacytoma (determined by clinical examination or diagnostic imaging); or</p> <p>(g) development of hypercalcaemia (corrected serum calcium greater than 2.65 mmol per L not attributable to any other cause).</p>
	<p>Prescribing Instructions: Prescribers may request the number of vials in line with the dosing requirement for each stage of treatment with the intention of providing the number of vials for each 4-weeks of treatment (24-weeks of treatment including repeats). Up to 4 vials with 5 repeats may be requested for a patient undergoing treatment in weeks 2-26. Up to 2 vials with 5 repeats may be requested for a patient undergoing treatment from week 27 onwards. Requests beyond what is listed in the TGA approved product information will not be approved.</p>
	<p>Prescribing instruction: This drug is not PBS-subsidised if it is administered to an in-patient in a public hospital setting.</p>
	<p>Administrative advice: No increase in the maximum number of repeats may be authorised</p>
	<p>Administrative advice: Special pricing arrangements apply</p>
	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</p>

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.