SMC2669

elranatamab solution for injection (Elrexfio®)

Pfizer Limited

09 August 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life and orphan equivalent medicine process

elranatamab (Elrexfio®) is accepted for use within NHSScotland on an interim basis subject to ongoing evaluation and future reassessment.

Indication under review: as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

In a single-arm, phase II study, in patients with relapsed and refractory multiple myeloma, elranatamab was associated with an objective response rate of 61%.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Elranatamab is a bispecific antibody that targets the CD3 receptors expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. By binding to both sites, elranatamab draws the T cells closer to the BCMA-expressing cells, which leads to lysis of these cells. The recommended subcutaneous dose of elranatamab is step-up doses of 12 mg on day 1 and 32 mg on day 4, followed by a full treatment dose of 76 mg weekly from week 2 to week 24; thereafter if patients have achieved a response the dosing interval should change to every 2 weeks. Treatment should be continued until disease progression or unacceptable toxicity. For more information on elranatamab dosing, including information on pre-treatments, step-up dosing schedule, and dosing modifications, refer to the Summary of Product Characteristics.[1]

1.2. Disease background

Multiple myeloma is a rare and incurable haematological cancer which mostly affects people over 60 years of age. It is the second most common haematological cancer after non-Hodgkin's lymphoma; in Scotland there are an estimated 477 new cases diagnosed each year. Characteristics of multiple myeloma include osteolytic lesions, anaemia, increased susceptibility to infections, hypercalcaemia, renal insufficiency or failure and neurological complications. Patients typically experience periods of disease control after initial treatment followed by progression, with subsequently shorter disease control periods after each successive treatment. Drug resistance to prior regimens in patients with relapsed or refractory multiple myeloma is due to continuous changes in the disease biology, in which a higher proportion of malignant cells are expressing a more aggressive, highly proliferative phenotype over time. Patients with multiple myeloma have a poor prognosis; median overall survival in patients who have received at least three prior lines of therapy and are refractory to both an immunomodulatory agent and a proteasome inhibitor is 13 months.[2, 3]

1.3. Treatment pathway and relevant comparators

In recent years, several new medicines have become available for patients with relapsed and refractory multiple myeloma and the treatment pathway is evolving. Treatment choice is influenced by many factors such as patient preference, age, cytogenetic profile, comorbidities, performance status, and most importantly the type of therapies previously received and response to these.[3, 13, 14] There may also be geographical variation in prescribing patterns in Scotland. Patients earlier in the treatment pathway may receive combinations of immunomodulatory agents (such as lenalidomide or thalidomide), proteasome inhibitors (such as bortezomib) or anti-CD38 antibodies (such as daratumumab) in conjunction with dexamethasone. There are several potential treatment options for patients who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy. These include lenalidomide plus dexamethasone, pomalidomide plus dexamethasone, isatuximab plus pomalidomide plus dexamethasone, carfilzomib plus dexamethasone, panobinostat plus bortezomib plus dexamethasone, and daratumumab monotherapy. Clinical experts consulted by SMC identified

several potentially relevant comparators including isatuximab plus pomalidomide plus dexamethasone, pomalidomide plus dexamethasone, daratumumab monotherapy and bendamustine.

1.4. Category for decision-making process

Eligibility for interim acceptance decision option

Elranatamab received an Innovation Passport allowing entry into the Innovative Licensing and Access Pathway (ILAP) and has conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency (MHRA).

Eligibility for a PACE meeting

Elranatamab meets SMC end of life criteria and orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of elranatamab comes from cohort A of MagnetisMM-3. See Table 2.1 for details.

Table 2.1. Overview of relevant study.[3, 4]

Criteria	MagnetisMM-3
Study design	Open-label, multicentre, non-randomised, phase II study.
Eligible patients	• Age ≥18 years. • Prior diagnosis of multiple myeloma and measurable disease according to International Myeloma Working Group (IMWG) criteria.[17] • Eastern Cooperative Oncology Group (ECOG) performance status ≤2. • Refractory to at least one immunomodulatory agent, one proteasome inhibitor and one anti-CD38 antibody. • Relapsed or refractory to the last antimyeloma regimen. (Note: Refractory was defined as having disease progression while on therapy or within 60 days of last dose in any line, regardless of response). • Cohort A: Has not received prior BCMA-directed therapy.
Treatments	Elranatamab given via subcutaneous injection in 28-day cycles with two step-up priming doses of 12 mg and 32 mg given on day 1 and day 4 of cycle 1 followed by the first full dose (76 mg) on day 8 of cycle 1 and once weekly thereafter. After six cycles, persistent responders (defined as partial response or better lasting ≥2 months) switched to a dosing interval of once every 2 weeks. Treatment was continued until confirmed disease progression or unacceptable toxicity.
Randomisation	Not applicable.
Primary outcome	Objective response rate (ORR), defined as having a best overall response (BOR) of confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR) or partial response (PR) according to IMWG criteria.[17] ORR was assessed by blinded independent central review (BICR).
Secondary outcomes	ORR by BICR baseline extramedullary disease status, ORR by investigator, CR rate, time to response (TTR), duration of response (DOR), duration of CR or better (DOCR), minimal

	residual disease (MRD) negativity rate, progression-free survival (PFS), overall survival (OS).
Statistical analysis	Efficacy and safety analyses were performed in the safety analysis set, defined as all patients enrolled who received at least one dose of elranatamab. The primary efficacy analyses evaluated the null hypothesis that the ORR by BICR was ≤ 30% for Cohort A.

After a median follow-up of 17.6 months, the objective response rate was 61%.[3, 4] See Table 2.2 for more details.

Table 2.2. Key efficacy results from cohort A of MagnetisMM-3 (Safety analysis set).[4, 5, 16]

	Elranatamab (n=123)	
Data-cut	**March 2023**	**September 2023**
Primary outcome: objective response rate (BICR-assessed as per IMWG criteria)		
Median follow-up	14.7 months	17.6 months
ORR	61%	61%
Stringent CR	15%	*
CR	20%	*
Very good PR	21%	*
PR	4.9%	*
Secondary outcome: duration of response (BICR-assessed as per IMWG criteria)		
Median DOR**	NR	NR
Secondary outcome: progression-free survival (BICR-assessed as per IMWG criteria)		
Number of events	53	*
Median PFS	NR	17.2 months
15-month PFS rate	51%	*
Secondary outcome: overall survival		
Number of deaths	55	60
Median OS	NR	21.9 months
15-month OS rate	57%	*

** Among responders (n=75)

Abbreviations: BICR = blinded independent central review; CR = complete response; DOR = duration of response; IMWG = International Myeloma Working Group; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response

*Other data were also assessed but remain confidential.**

Data from a further data cut were provided by the company prior to SMC committee meeting but were not assessed.

2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed as an exploratory outcome using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), the EORTC Multiple Myeloma Quality of Life Questionnaire (QLQ-MY20) and the EQ-5D. Overall, the results suggest that elranatamab maintained or improved symptoms and general health status.[6]

2.3. Supportive studies

Cohort B of MagnetisMM-3 had the same inclusion/exclusion criteria as Cohort A except patients had received prior BCMA-directed treatment, either licensed or investigational (n=64). After a median follow-up of 13.4 months, the confirmed ORR was 34%; 33% achieved very good partial response or better and 11% achieved complete response or better. Median duration of response (DOR) had not yet been reached. Median progression-free survival (PFS) was 3.5 months, and median overall survival (OS) was 11.3 months.[3]

2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing elranatamab with relevant comparators, the submitting company presented an indirect treatment comparison. Details are presented in Table 2.3.

Table 2.3: Summary of indirect treatment comparison

Criteria	Overview
Design	Unanchored matching adjusted indirect comparison (MAIC) and adjusted direct comparison.
Population	Adult patients with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.
Comparators	Physician's choice of therapy. The most common treatment regimens featured in LocoMMotion were carfilzomib plus dexamethasone (14%), pomalidomide plus cyclophosphamide plus dexamethasone (13%), pomalidomide plus dexamethasone (11%), ixazomib plus lenalidomide plus dexamethasone (5.6%) and panobinostat plus bortezomib plus dexamethasone (4.4%).
Studies included	Cohort A in MagnetisMM-3 (used in both the MAIC and adjusted direct comparison)[3]; LocoMMotion, a prospective, non-interventional study, used in MAIC[7, 8]; external control arm (ECA) study used in adjusted direct comparison.[9]
Outcomes	Progression-free survival (PFS) and overall survival (OS).
Results	Elranatamab had superior efficacy versus physician's choice of therapy in terms of PFS in both analyses, and OS in the MAIC adjusted analysis only.

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

In the MagnetisMM-3 study at data cut-off 14 March 2023, the median duration of treatment in Cohort A was 5.6 months. All patients in Cohort A reported a treatment-emergent adverse event (AE). In Cohort A, patients reporting a grade 3 or 4 AE was 71%, and patients with a dose reduction or interruption due to an AE were 28% and 77% respectively. Among patients in Cohort A who switched to fortnightly dosing (n=58), the incidence of treatment-emergent AEs decreased from 95% to 90% and grade 3 or 4 AEs decreased from 59% to 47%. In Cohort A, the most frequently

reported treatment-emergent AEs of any grade with an incidence ≥20% were cytokine release syndrome (CRS) (58%), anaemia (49%), neutropenia (49%), diarrhoea (42%), fatigue (37%), decreased appetite (33%), thrombocytopenia (31%), pyrexia (30%), COVID-19 related (29%), lymphopenia (27%), injection site reaction (27%), nausea (27%), hypokalaemia (26%), cough (25%) and headache (24%). The most commonly reported grade 3 or 4 AEs with an incidence ≥20% were neutropenia (49%), anaemia (37%), lymphopenia (25%) and thrombocytopenia (24%). No patients in Cohort A reported grade 3 or higher CRS. Regulatory bodies consider CRS, neurological toxicity, and infections to be the key risks of elranatamab. Severe episodes of CRS can be mitigated through actions such as the administration of recommended premedications and step-up dosing. Infections were reported in a high proportion of patients, and aside from disease progression was the most common grade 5 treatment-emergent AE (5.7% of patients). Infections are common in patients with relapsed/refractory multiple myeloma due to underlying immunosuppression, however elranatamab causes neutropenia and hypogammaglobulinaemia and therefore increases the risk of infection. Immune effector cell-associated neurotoxicity syndrome (ICANS) was reported in 3.3% of patients that received the licensed dose of elranatamab, however these were resolved by standard supportive care. Although currently available data enable a reasonable characterisation of the safety profile of elranatamab, the lack of a control group in MagnetisMM-3 and long-term data is limiting. [3, 4, 10]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Elranatamab is a bispecific antibody that targets both CD3 and BCMA receptors. This class of medicine is distinct from other available multiple myeloma treatments and offers a new mechanism of action.
- In cohort A of MagnetisMM-3, elranatamab demonstrated a clinically relevant anti myeloma effect in a population with a history of several prior treatments and refractory disease. 61% of patients had a response to treatment, with 35% (37% at the latest data cut) having a complete response or better. The depth and duration of response (although median not estimable at present) were also considered supportive and clinically relevant.[4, 5]

4.2. Key uncertainties

- MagnetisMM-3 was a single-arm, open-label, phase II study, which are prone to various biases such as selection bias. The treatment effect of elranatamab relative to relevant comparators in clinical practice is therefore uncertain. The submitting company presented indirect treatment comparisons versus physician's choice of treatment, which included a basket of potential treatments. It is not clear if the proportions of treatment regimens are similar to those prescribed in Scottish clinical practice. There is an evolving treatment pathway, heterogeneity of treatment selection, and the potential for geographical variation within NHSScotland.

- ORR is an appropriate outcome in phase II studies that measures antitumour activity. However, it may be unclear to what degree this antitumour activity corresponds to more robust measures of clinical benefit, such as OS or PFS. It is difficult to interpret the OS and PFS data from MagnetisMM-3 due to the single-arm, non-randomised design of the study, and is further complicated by deaths caused by the COVID-19 pandemic.[3]
- There was a limited sample size (n=123) in the key study. However, this may be expected in an orphan equivalent condition such as relapsed and refractory multiple myeloma.[3]
- Follow-up was limited; median duration of follow-up is 17.6 months (September 2023 data-cut). Therefore, it is still not possible to fully characterise the duration of response. Longer-term safety data are also limited.[5]
- The HRQoL outcomes evaluated in MagnetisMM-3 should be interpreted cautiously given the open-label design of the study.
- There may be differences between the study population of MagnetisMM-3 and the relevant Scottish population. The number of patients in the study with triple-class refractory disease (approximately 97%) may be higher than that expected in the eligible Scottish patient population.
- The indirect treatment comparisons had the following limitations:
    - Unanchored indirect comparisons are inherently uncertain and susceptible to confounding bias due to differences in unobserved or observed characteristics that were not adjusted for.
    - Comparisons based on real-world data versus clinical study data may be prone to bias as patients may respond better to treatment in a trial setting than in clinical practice and the quality of data collection may be poorer in real-world studies and may introduce error.
    - Safety and HRQoL were not assessed.
    - There were differences between the study populations which may bias the results. MagnetisMM-3 included more triple-class refractory patients than LocoMMotion (97% versus 74%) with a median of five versus four prior treatments respectively. Cytogenetic risk was not adjusted for due to high levels of missing data in LocoMMotion. Median duration of follow-up differed.
    - Wide confidence intervals and inconsistency in the results between the adjusted and unadjusted analysis, and between the PFS and OS results, suggests uncertainty.
    - Some of the relevant comparators identified by clinical experts consulted by SMC were not featured in the ITCssuch as isatuximab plus pomalidomide plus dexamethasone and daratumumab monotherapy. Only 4 patients (1.6%) received bendamustine in combination with prednisone.[7]

  Due to these limitations, the results of the ITCs are uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

The MHRA specific obligations include the submission of the final study report of MagnetisMM-3 (due March 2025) and the submission of results for MagnetisMM-5, a randomised phase III study comparing elranatamab monotherapy versus elranatamab plus daratumumab versus daratumumab plus pomalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy and no more than three, including lenalidomide and a proteosome inhibitor (due June 2027). A later data-cut of MagnetisMM-3 will help to further characterise the duration of response and long-term safety of elranatamab but is unlikely to address some of the uncertainties identified in this assessment such as the interpretation of OS or PFS. The MagnetisMM-5 phase III study versus active comparators may help to address some uncertainties provided that a subgroup of recruited patients have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody and have demonstrated disease progression on the last therapy.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that elranatamab fills an unmet need in this setting and consider it to be a therapeutic advancement as it is a new class of medicine that has shown to be effective in heavily pretreated patients.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine will have substantial implications for the service. Extensive monitoring is required, and in-patient admission may be required to initiate treatment, due to the potential for CRS or ICANS. There may be an advantage for the service and patient once treatment is established as it is administered subcutaneously. Clinical experts consulted by SMC also considered that a high proportion of patients that receive a bispecific antibody may require concomitant IV immunoglobulin (IVIg) to prevent infection, which could also have important implications for the service.

5. Patient and Clinician Engagement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of elranatamab, as an **orphan-equivalent/end of life** medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Myeloma is a severe, incurable, relapse-remitting disease that can develop at any age but is more common in people over the age of 60. While myeloma is a highly individual and complex cancer, common symptoms include bone pain, bone destruction, back pain, fatigue, kidney damage, a depleted immune system, and generalised weakness. As patients progress through subsequent treatments in the relapsed/refractory setting, many patients will also experience intensified side effects, which have a higher physical and psychological burden. Myeloma has a marked impact on people's mental and physical health, as well as their quality of life. Fear of the unknown is often highlighted by patients and carers, and the constant possibility of relapse has a huge psychological impact on patients. The physical and

psychological impact increases with every relapse. Patients are aware that every time they relapse, their options and life expectancy decrease. Ongoing symptoms and its various manifestations also affect a patient's ability to work, which may lead to financial worries, and to function well at home. A weakened immune system can also prevent people from partaking in activities previously enjoyed, including exercising, socialising, and travelling. This, alongside the need for frequent hospital visits, can result in a significantly reduced quality of life.

- In the past decade a wide range of treatments have been made available for treating relapsed and refractory myeloma which offer significant improvements in survival. However, myeloma is incurable, and even if remission is achieved with current treatments, patients know that they will relapse at an unknown point in the future. Currently available treatments are seen to provide reasonable responses in a minority, however for many the responses are not durable or are only "partially successful". Currently available treatments also have side effects associated with them which can have a physical and psychological toll. Steroids are commonly prescribed as part of treatment regimens, and can cause mood swings, irritability, and mania which is challenging for patients and their families. Given that myeloma evolves over time and becomes resistant to treatment, patients can quickly cycle through and run out of treatments options despite still being fit to receive further treatment. Therefore, there is a clear unmet need for new, well-tolerated treatments for the treatment of relapsed and refractory multiple myeloma.
- There are numerous benefits to support the introduction of elranatamab to clinical practice in Scotland. Elranatamab has the potential to greatly improve quality of life and overall life expectancy. Study data shows that elranatamab offers high response rates compared to what has historically been reported with other treatments, durable responses, disease control, and promising life expectancies which are all highly valued by patients. This treatment could allow patients to enjoy a normal day-to-day life. Patients could continue in work or education, and quality of life could be greatly improved by improving symptoms such as fatigue. Elranatamab has a novel mechanism of action. If approved, it would be the first T-cell engager and the first B cell maturation antigen (BCMA) targeted treatment for myeloma. Therefore, it has much potential to overcome treatment resistance and fulfil an unmet need for relapsed/refractory multiple myeloma patients. If approved, there would be a psychological benefit of knowing that another treatment is available should patients relapse. The value of hope offered by elranatamab eases the emotional burden which patients with relapsed and refractory multiple myeloma and their families experience. Furthermore, having different choices for treatment is desirable for patients. Elranatamab is administered as a monotherapy. Patients welcome not having to take concomitant steroids alongside elranatamab, which have considerable side effects and have likely featured in past treatment regimens for multiple myeloma.
- Carers and family members play a critical role in patients' disease and treatment journey and caring for someone with relapsed and refractory multiple myeloma is often very challenging and burdensome. Elranatamab is expected to provide durable responses for patients, which should lead to a reduction in dependency on family members and carers. Elranatamab has the potential to give families longer, quality time together. The fear of relapse and the

uncertainty associated with limited treated options is experienced by patients and families/carers alike, and the availability of elranatamab should have a positive psychological benefit for people who are close to the person with myeloma. The absence of dexamethasone is also expected to have a huge impact on carers, partners, and families. The changing mood and fluctuating energy levels patients experience when taking dexamethasone has a significant impact on their relationships and family dynamics. There may be an additional benefit for carers to deliver elranatamab in a healthcare setting as carers can feel a lot of responsibility to support and monitor patients at home with alternative treatments.

- Elranatamab is an effective treatment option for those who have triple-class exposed relapsed and refractory multiple myeloma, however there are some side effects associated with the treatment including CRS, hypogammaglobulinaemia, and increased risk of infections which can be a cause for concern for patients and their loved ones. However, patients are aware that these side effects typically occur when starting treatment, and they felt there were similar risks associated with other treatments. PACE participants felt that the adverse events associated with elranatamab are manageable, and that the risk of severe CRS and ICANS toxicities was low. Toxicities such as CRS are not unique to elranatamab, and clinicians are experienced in the management of such adverse events.
- There may also be service implications associated with the introduction of elranatamab due to close monitoring of side effects, increased resource required from specialist centres (at least initially), and the high likelihood of patients requiring prophylactic antibiotics/antivirals and IV immunoglobulins to prevent infection.

Additional Patient and Carer Involvement

We received a patient group submission from Myeloma UK, which is a registered charity. Myeloma UK has received 5.65% pharmaceutical company funding in the past two years, including from the submitting company. A representative from Myeloma UK participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The economic case for elranatamab is summarised in Table 6.1 below.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	25 years, with an assumed starting age of 67.1 years
Population	Adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody and have demonstrated disease progression on the last therapy
Comparators	The comparator used was a basket comparator, based on the treatments included in the LocoMMotion study.[7, 8] This was described as physician's choice of treatment (PCT) within the submission. The proportions of components within PCT were based on feedback received by

	the company from Scottish clinicians. The specific proportions have been marked as academic in confidence (AiC) by the submitting company, but the main components were: • carfilzomib and dexamethasone • pomalidomide, cyclophosphamide and dexamethasone • pomalidomide and dexamethasone
Model description	The submission uses a 4-state partitioned survival model. The included states were progression-free (on treatment), progression-free (off treatment), progressed disease and death.
Clinical data	The main source of clinical data for elranatamab was the MagnetisMM-3 study.[4] This informed the progression free survival (PFS), overall survival (OS) and time to treatment discontinuation (TTD) data for elranatamab patients. The MagnetisMM-3 study was single arm, leading the company to conduct an unanchored MAIC to inform the comparison with PCT. The source of data on PCT was the LocoMMotion study.
Extrapolation	The company fitted generalised gamma parametric curves to study data to inform the projection of PFS and OS for elranatamab patients. In doing so, the company found that the curves would cross, suggesting the impossible outcome that more patients were progression free than alive at certain time points. To address this the company assumed that OS could not fall below PFS, noting that the PFS was more mature and so more reliable. TTD for elranatamab was estimated by applying a log-logistic curve to study data. The company also applied a limitation that the rate of progression, death and discontinuation must be equal to or greater than an externally estimated mortality rate. Mortality in the multiple myeloma population was estimated by applying a time varying standardised mortality rate, derived from Giri et al. (2021), to general population mortality rates.[11] The company generated hazard ratio from the MAIC, comparing elranatamab to PCT, for both PFS and OS. OS was estimated by applying that hazard ratio directly to the OS curve for elranatamab. The company found evidence that the proportional hazards assumption did not hold for PFS and so applied an estimation technique developed by Mol et al. (2023) to generate a PFS projection.[12] No TTD was available for PCT and this was modelled by applying the ratio of median discontinuation and median PFS reported in the LocoMMotion study to the PFS for PCT. In the PCT arm, the typical assumption that PFS cannot exceed OS was used. The external mortality restriction was only applied to OS in the PCT arm.
Quality of life	Health related quality of life data was collected using the EQ-5D instrument in the MagnetisMM-3 study. The estimated utility was higher in the pre-progressed state than the progressed state, with the specific values marked as confidential. Adverse event disutilities were included.
Costs and resource use	Medicine cost categories in the submission were acquisition cost, administration costs, adverse events costs and subsequent treatment costs. Wider NHS costs included were for disease monitoring, clinician visits and end-of-life costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price. The results presented do not take account of the PAS discounts for pomalidomide and carfilzomib but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS price for pomalidomide and carfilzomib due to commercial confidentiality and competition law issues.

6.2. Results

The base case analysis suggested that when elranatamab was compared with PCT, the resulting incremental cost-effectiveness ratio (ICER) was £106,996, when list prices were used for all medicines. Inclusion of the confidential PAS discounts had a large downward effect on the ICER.

Disaggregated results suggested that the difference in quality of life between treatment arms was driven by greater occupancy of the progression free state by elranatamab patients. The main difference in costs was through the higher acquisition cost of elranatamab.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

The company conducted deterministic sensitivity analysis, probabilistic sensitivity analysis and scenario analysis to explore areas of uncertainty. Selection of the scenarios is presented below.

Table 6.3: Scenario analysis results

	Parameter	Base case	Scenario	ICER (£/QALY)
	Base case			£106,996
1	Time horizon	25 years	10 years	£142,908
2			15 years	£124,168
3			20 years	£112,062
4	PFS and OS relationship	PFS supersedes OS	OS supersedes PFS	£109,228
5	RDI	Included	Excluded	£147,030
6	Elranatamab stopping rule	36 months	Less than 10% of patients on treatment	£117,371
7			No stopping rule	£122,235
8	Elranatamab TTD	Log-logistic curve	Gompertz	£126,544
9		SMR adjusted TTD	No SMR adjustment to TTD	£116,814
10	Elranatamab hospitalisation	5 days	7 days	£107,886
11			SMC expert value: 10 days	£109,220

Abbreviations: PCT = Physician's choice of treatment, LYG = life year gained, QALY = quality adjusted life year, ICER = incremental cost-effectiveness ratio, PFS = progression free survival, OS = overall survival, TTD = time to treatment discontinuation, SMR = standardised mortality rate, HR = hazard ratio, RDI = relative dose intensity

6.4. Key strengths

The key strengths of the analysis were assessed as being:

- The modelling approach used is well accepted within oncology submissions.
- The approach to fitting survival curves to the elranatamab PFS and OS data was appropriate and alternative curves only had a small impact upon the cost-effectiveness estimates.
- The categories of costs included in the model were comprehensive.
- The scenario analysis was felt adequate.

6.5. Key uncertainties

The key uncertainties of the analysis were assessed as being:

- MagnetisMM-3 was a single arm study and the unanchored MAIC suffered from several weaknesses. As a result, the estimated relative efficacy of elranatamab over PCT used in the economic model was uncertain.

- The MagnetisMM-3 study was ongoing, and the data cut used within the economics was at 15 months of follow up. This was significantly shorter than the modelled period (25 years), and neither PFS nor OS had reached their median values. Given that uncertainty, and the poor prognosis for RRMM patients, alternative time horizons were explored (Scenarios 1 to 3 in Table 6.2)
- The projected OS and PFS curves in the elranatamab arm crossed early in the modelled period. In response the company deviated from standard methodology by assuming that OS cannot fall below PFS, rather than the more classical assumption that PFS cannot exceed OS. Scenario analysis showed that the approach had minimal impact upon the ICER (see Scenario 4). However, the data and modelling approach resulted in the modelled situation where, after a certain point elranatamab patients could no longer progress. The clinical plausibility of that implication was uncertain.
- The restriction the rate of progression or death in the elranatamab arm must be equal to or greater to an externally estimated mortality rate became binding early in the modelled period, meaning that the majority of the projection of PFS and OS for elranatamab patients was the result of the standardized mortality ratio, not observed survival data. Removal of the SMR adjustment would lead to implausibly high survival lengths and alternative values for the SMR identified by the company would have increased the cost effectiveness of elranatamab. However, the standardised mortality ratio was assumed to fall to 1 at beyond 6 years. This led to a proportion of elranatamab patients effectively cured, where they were not at risk of progression and had the same mortality risk as the general population. Given the nature of RRMM, the clinical plausibility of that is uncertain.
- The company has applied a stopping rule for elranatamab at 36 months. However, the company also reported feedback from clinicians which suggested a proportion of patients would be on treatment at 5 years and beyond. Alternative stopping points increased the ICER (Scenarios 6 & 7).
- Alternative survival curves for the estimation of time to elranatamab discontinuation, which fitted the observed data well, increased the ICER substantially (Scenario 8). The company argued these led to an implausibly high proportion of patients on treatment over the long term, however, this scenario is conducted maintaining the base case assumption that a stopping rule is applied at 36 months. While the stopping rule is uncertain, as noted above, the company created a paradox by maintain support for a stopping rule while arguing that long-term projections invalidate some parametric curves. Overall, length of elranatamab treatment remained a source of uncertainty.
- Clinicians consulted by SMC noted the potentially high impact of the medicine on health service delivery, and these costs may have been underestimated in the modelling. Experts indicated that inpatient stays may be longer than modelled at initiation of elranatamab (Scenario 11). The same experts also expressed the opinion that the rate of IVIg use, which the company based on the observed rate in the MagnetisMM-3 study adjusted for Scottish clinical guidelines, was too low, at only 21.1%. Those experts expected the majority of patients receiving elranatamab to also receive IVIg, with the most common response being

around 75% of patients would also get IVIg. Increasing the proportion of patients receiving IVIg increased the ICER, although it was not possible to capture wider interactions such as impacts on the duration of treatment and the relative treatment efficacy of elranatamab.

7. Conclusion

The Committee considered the benefits of elranatamab in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as elranatamab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee accepted elranatamab for use in NHSScotland subject to ongoing evaluation and future reassessment.

8. Guidelines and Protocols

The British Society for Haematology (BSH) published "Guidelines on the diagnosis, investigation and initial treatment of myeloma: a British Society for Haematology/UK Myeloma Forum Guideline" in March 2021.[13]

The National Institute for Health and Care Excellence (NICE) published "Myeloma: diagnosis and management" (NG35) in February 2016, which was updated in October 2018.[14]

The European Society for Medical Oncology (ESMO) and the European Haematology Association (EHA) published "Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up" in February 2021.[15]

9. Additional Information

9.1. Product availability date

31 March 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
elranatamab	**Step-up subcutaneous doses of 12 mg on day 1 and 32 mg on day 4, followed by 76 mg weekly from week 2 to week 24. Patients who have received at least 24 weeks treatment and have achieved a response should be given 76 mg every 2 weeks.**	**£16,970 (not including step-up doses; weekly dosing)** **£8,485 (not including step-up doses; 2-weekly dosing)**

Costs from MIMS online on 03 May 2024. Costs calculated using the full cost of vials/ampoules assuming wastage. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 44 patients eligible for treatment with elranatamab in each year. The estimated uptake rate was 30% in year 1 and 100% in year 5. This resulted in 13 patients estimated to receive treatment in year 1 rising to 44 patients in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 21 June 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.