NCPE Assessment

Technical Summary

Elranatamab (Elrexfio®)

HTA ID: 23066

01 July 2025

Applicant: Pfizer Healthcare Ireland

Elranatamab 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.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of elranatamab (Elrexfio®).

Following assessment of the Applicant's submission, the NCPE recommends that elranatamab (Elrexfio®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments.*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Pfizer Healthcare Ireland) Health Technology Assessment of elranatamab (Elrexfio®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In May 2024, Pfizer Healthcare Ireland submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of elranatamab (Elrexfio®). The licensed population are adult patients with relapsed and refractory multiple myeloma (RRMM), who have received at least three prior therapies including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 monoclonal antibody (mAb), and who have demonstrated disease progression on the last therapy. Individuals who have received prior treatment with one IMiD, one PI and one anti-CD38 mAB are described as being triple-class exposed (TCE). The Applicant is seeking reimbursement of elranatamab on the Oncology Drugs Management Scheme.

Elranatamab is a bispecific monoclonal antibody which targets CD3 on T-cells and B-cell maturation antigen (BCMA) on multiple myeloma cells. This results in proinflammatory cytokine release and subsequent lysis of multiple myeloma cells. Other BCMA-directed therapies include ciltacabtagene autoleucel and teclistamab.

Elranatamab is formulated as a 40 mg/ml solution for subcutaneous injection. It is available in vials containing either 44mg or 76mg of elranatamab. The recommended dosing schedule, for treatment initiation, is 12mg once on Day One and 32mg on Day Four. From Day Eight, patients should receive a maintenance dose of 76mg once every week. From Week 25 onwards, patients who have achieved a response should transition to a dose of 76mg once every two weeks. From Week 49, patients who have received at least 24 weeks of treatment at once every two-week dosing, and who maintained the response, should transition to a dose of 76mg once every four weeks. In all patients, treatment should be continued until disease progression or unacceptable toxicity.

For the majority of patients with RRMM who are TCE, elranatamab will most likely be prescribed as a third- or subsequent line treatment option. This place in therapy is supported by clinical evidence, clinical guidelines, and clinical opinion. However, a technical detail in the product licence for elranatamab permits use in an earlier treatment setting. The product licence for elranatamab does not stipulate that a person must have received three prior lines of therapy in the course of becoming TCE. Clinical Opinion to the Review Group indicated that a small number of patients will be treated with an IMiD, a PI, and an anti-CD38 mAb in the first-line setting. These patients would be eligible for elranatamab in the second-line setting.

There is no universal standard of care for management of patients with RRMM in Ireland. Physician's Choice of Treatment (PCT), defined as a basket of drug regimens most commonly used to treat RRMM in Ireland, was identified as a comparator. Teclistamab was also included as a comparator.

1. Comparative effectiveness of elranatamab

The clinical efficacy of elranatamab was informed by outcomes from MagnetisMM-3, which is an ongoing, phase II, single-arm trial. Eligible participants were adults with RRMM who were TCE and whose disease progressed on the last therapy. Participants (n=187) were assigned to either Cohort A (BCMA-naïve; n=123) or Cohort B (BCMA-exposed; n=64). The Applicant considered Cohort A to be most relevant to the assessment as, at the time of submission, no BCMA-directed therapies were approved for reimbursement in Ireland. However, teclistamab was approved by the HSE for reimbursement in March 2025. More BMCA-directed therapies may be reimbursed in the future. Therefore, the Review Group considered that Cohort B was also relevant to the assessment. However, these were not included in the indirect treatment comparisons (ITCs) or in the cost-effectiveness model (CEM). The relative effectiveness of elranatamab in this subpopulation has not been investigated. This was considered a limitation of the assessment.

The primary efficacy endpoint in MagnetisMM-3 was objective response rate (ORR) as assessed by blinded independent central review. Key secondary endpoints included overall survival (OS) and progression-free survival (PFS). The most recent data cut was March 2024; median follow up was approximately 28 months. Results demonstrated that, for all endpoints, more favourable outcomes were observed for participants in Cohort A compared to those in Cohort B. For Cohort A, ORR was 61% (95% confidence interval (CI), 51.8% to 69.6%). Median OS was 24.6 months (95% CI, 13.4 to not estimable) and median PFS was 17.2 months (95% CI, 9.8 to not estimable). For Cohort B, ORR was 34.4% (95%CI, 22.9% to 47.3%). Median OS was 11.3 months (95% CI 6.5 to 22.2) and median PFS was 4.4 months (95% CI 1.9 to 7.4). Additional limitations of the clinical evidence included the single-arm design of MagnetisMM-3, the lack of direct comparative efficacy evidence for elranatamab versus other treatments for RRMM, the small number of participants recruited, and uncertainty regarding the validity of ORR as a surrogate endpoint to predict OS.

In the absence of direct comparative evidence, unanchored ITCs were performed to evaluate the comparative effectiveness of elranatamab versus each of the comparators. Data from Cohort A in MagnetisMM-3 informed efficacy for elranatamab. Efficacy of PCT and teclistamab was

informed by data from the LocoMMotion and MajesTEC-1 studies, respectively. To control for confounding, the matching-adjusted indirect comparison (MAIC) method was used, in which individual participant data from MagnetisMM-3 were reweighted using propensity-score methods, in order to align with comparator trial populations (based on published summary data) in terms of a number of prognostic and/or effect-modifying variables. Relative treatment effects for OS and PFS were estimated as hazard ratios. Results from the ITCs suggested that elranatamab was associated with increases in OS and PFS compared with PCT and teclistamab.

A key limitation of the comparative effectiveness analysis was the absence of randomised comparative data and the corresponding use of unanchored ITCs. Unanchored ITCs are associated with a substantially higher risk of bias and corresponding lower certainty of evidence than randomised controlled trials. In particular, validity of the unanchored MAIC approach relies on the assumption that all prognostic and effect-modifying variables have been adjusted for. While the Applicant adjusted for a number of relevant variables, others could not be included (e.g., cytogenetic risk, triple class refractory status), leading to a risk of confounding bias. Other limitations noted by the Review Group included the low effective sample sizes, leading to wide confidence intervals for the relative treatment effects, and the immaturity of the data (particularly for OS), leading to uncertainty in the long-term treatment effectiveness.

2. Safety of elranatamab

Clinical safety of elranatamab was informed by data from the MagnetisMM-3 trial. All participants treated with elranatamab (n=187) were included in the safety analysis. The majority of participants (91.4%) experienced at least one treatment-related adverse event (AE) (91.1% participants in Cohort A; 92.2% of participants in Cohort B). The most frequently reported treatment-related AEs included cytokine release syndrome (58.8%), neutropenia (36.9%), and anaemia (26.2%). AEs of special interest were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS); both are potentially fatal. To reduce the risk of CRS and ICANS, elranatamab should be initiated according to the step-up dosing schedule. Patients should be premedicated with paracetamol, a corticosteroid and an antihistamine prior to administration of the first three doses of elranatamab. Patients must remain within proximity of a healthcare facility for 48 hours following administration of each step-up dose administered on Day One and Day Four.

3. Cost effectiveness of elranatamab

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a partitioned survival model developed in Microsoft Excel®. The population considered in the CEM was adult patients with RRMM, who were TCE, who had demonstrated disease progression on the last therapy, and who had not previously received a BCMA-directed therapy. The intervention was elranatamab. For the base case, comparators were PCT and teclistamab.

The CEM comprised three mutually exclusive health states: progression Free [PF], Progressed Disease [PD] and Death. All patients entered the model in the PF health state and were assigned to treatment with either elranatamab, PCT, or teclistamab. During each model cycle, patients could either remain in their current state, transition to the PD state, or transition from the PF or PD states to the Death state. Transitions to improved health states were not permitted. Model cycle length was one week. A lifetime horizon was assumed. A half-cycle correction was not applied.

OS and PFS were modelled independently. Outcomes from the Applicant's unanchored ITCs were used to inform treatment effectiveness. OS curves were capped by mortality risk for the general population, informed by data from the Central Statistics Office, and adjusted in order to capture mortality risk experienced by patients with RRMM. To implement this adjustment, the Applicant applied a time-varying standardised mortality ratio (SMR), which was informed by a US-based, prospective cohort study. However, this predicted sharp decreases in mortality over time, which the Review Group considered implausible. Functionality was included in the CEM to use a time-constant SMR, also derived from the US-based, prospective cohort study. The Review Group considered this to produce more plausible long-term mortality predictions.

The Applicant selected a lognormal distribution to extrapolate OS over the lifetime horizon of the CEM. However, the Review Group considered that the gamma distribution generated more plausible extrapolations of OS.

The Applicant selected a Weibull distribution to model elranatamab time to treatment discontinuation (TTD). The Review Group considered that the log-normal distribution generated more plausible long-term predictions of TTD.

A systematic literature review identified health related quality of life data, collected from the MagnetisMM-3 trial, as the most appropriate to inform health state utility values. Data collected using the EQ-5D-5L instrument was converted to EQ-5D-3L using the Hernandez-Alva algorithm. A limitation of the data collected in MagnetisMM-3 is that each participant likely contributed, at most, one post-disease progression observation. Therefore, there is uncertainty that the data

collected accurately represents the health related quality of life of patients in the PD state.

Costs and resources included were drug costs, drug administration costs, subsequent treatment costs, AE costs and disease management costs. A once-off, end-of-life cost was also included.

Results

All cost-effectiveness analyses presented here are based on the publicly available price to wholesaler for each drug. However, teclistamab, and several drugs included as part of PCT, were approved for reimbursement subject to confidential price negotiations. These confidential pricing arrangements are not captured in the cost-effectiveness analyses presented below.

Results of the Applicant base case deterministic cost-effectiveness analysis are presented in Table 1.

Table 1: Applicant base case incremental cost-effectiveness results (pairwise ICERs) [a, b, c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Base case analyses					
PCT	92,759	1.12	-	-	-
Elranatamab	165,416	2.51	72,657	1.39	52,361
Teclistamab	206,417	1.46	-	-	-
Elranatamab	165,416	2.51	-41,001	1.05	Dominant

CIC: commercial in confidence; **ICER:** incremental cost-effectiveness ratio; **PAS:** Patient Access Scheme**; PCT:** Physician's Choice of Treatment; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations: elranatamab versus PCT = €58,963/QALY, elranatamab is dominant versus teclistamab (i.e elranatamab is (less costly, more effective).
[b] A CIC PAS has been proposed for elranatamab, not included in this table
[c] CIC PASs are in place for teclistamab, and drugs included in PCT (carfilzomib, daratumumab, ixazomib), not included in this table

Total costs and QALYs presented are discounted (4%).
Figures in the table are rounded; calculations may not be directly replicable.

Several changes were made to inform the NCPE adjusted base case. These included changing the time-varying SMR to the time-constant SMR, selecting the gamma distribution for extrapolation of OS, and selecting the lognormal distribution for extrapolation of TTD for elranatamab. Results of the NCPE adjusted base case are presented in Table 2.

Table 2: NCPE adjusted base case incremental cost-effectiveness results (pairwise ICERs) [a, b, c]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	Pairwise ICER (€/QALY)
Base case analyses					
PCT	92,003	0.94	-	-	-
Elranatamab	182,311	2.03	90,308	1.09	83,224
Teclistamab	196,599	1.18	-	-	-
Elranatamab	182,311	2.03	- 14,288	0.85	Dominant

CIC: commercial in confidence; **ICER:** incremental cost-effectiveness ratio; **PAS:** Patient Access Scheme**; PCT:** Physician's Choice of Treatment; **QALY:** quality-adjusted life year

[a] Corresponding probabilistic ICERs using 1,000 iterations: elranatamab versus PCT = €93,556 per QALY; elranatamab is dominant versus

teclistamab (i.e elranatamab is less costly, more effective).
[b] A CIC PAS has been proposed for elranatamab, not included in this table
[c] A CIC PAS is in place for teclistamab, and for drugs included in PCT (carfilzomib, daratumumab, ixazomib), which are not included in this table
Total costs and QALYs presented are discounted (4%).
Figures in the table are rounded; calculations may not be directly replicable.

Sensitivity analysis

Deterministic one-way sensitivity analysis (DSA) indicated that the most influential parameters in the CEM, for both the Applicant and the NCPE adjusted base case, were relative dose intensity for elranatamab, percentage of patients transitioning from a once weekly to less frequent dosing schedule for elranatamab, and utilities for the PD health state.

Under NCPE adjusted base case assumptions, the probability of cost-effectiveness of elranatamab versus PCT at the €45,000 per quality adjusted life year (QALY) and €20,000 per QALY thresholds was 0.3% and 0%, respectively. The probability of cost-effectiveness of elranatamab versus teclistamab was 0% at both the €45,000 per QALY and €20,000 per QALY thresholds. A price-ICER analysis, using NCPE-adjusted base case assumptions, indicated that reductions of 35% and 52% (including the Framework Agreement rebate) would be required to meet the €45,000 per QALY and €20,000 per QALY cost-effectiveness thresholds, respectively.

4. Budget impact of elranatamab

The price to wholesaler of elranatamab is €2,913 for one 44mg vial and €5,032 for one 76mg vial. Cost per patient per treatment course is highly variable and very sensitive to parameters including TTD, relative dose intensity, and switching from once weekly to less frequent dosing schedules. Applicant and NCPE estimates of cost per patient per treatment course of elranatamab (incorporating mark-up, Framework Agreement rebate and VAT) were €255,669 and €305,707, respectively. The difference in cost estimates arises from different assumptions regarding TTD (Applicant 1.34 years; NCPE 1.77 years).

Eligible patients were those with RRMM, who are TCE, and who would receive elranatamab as a third- or subsequent-line option. Eligible patient numbers were estimated to be 151 in Year One, rising to 157 in Year Five. The Applicant assumed that elranatamab would displace PCT and teclistamab in Years One and Two, but only displace teclistamab from Year Three onwards. Market share values for elranatamab and teclistamab were considered to be highly uncertain. Net budget impact estimates were sensitive to assumptions regarding TTD and percentage of patients switching from once weekly to less frequent dosing schedules for both elranatamab and teclistamab. These parameters are all uncertain. The Applicant estimated five-year cumulative gross and net drug-budget impacts for elranatamab were €41.7 million and - €1.25 million,

including VAT. The NCPE estimated five-year cumulative gross and net drug-budget impacts were €51.7 million and €8 million, respectively. The budget impact analyses presented here do not capture the commercial pricing arrangements negotiated for teclistamab and other drugs included as part of PCT.

5. Patient Organisation Submission

A patient organisation submission was received from Multiple Myeloma Ireland.

6. Conclusion

The NCPE recommends that elranatamab (Elrexfio®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*. This recommendation takes into account the confidential pricing arrangements negotiated for teclistamab and other drugs included as part of PCT, which are not reflected in the cost-effectiveness and budget impact estimates shown in this summary report.

* This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.