**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

**Elranatamab for treating relapsed or refractory multiple myeloma after 3 therapies [ID4026]**

**Response to stakeholder organisation comments on the draft remit and draft scope**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit and proposed process**

| Section | Stakeholder | Comments [sic] | Action |
| --- | --- | --- | --- |
| Appropriateness of an evaluation and proposed evaluation route | Pfizer | No comment. | Thank you for your comment. No action needed. |
| Takeda UK | The topic and evaluation route are appropriate. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum**)** | Myeloma remains an incurable cancer. BCMA targeted therapies show significant promise in inducing remissions in previously treated myeloma patients. Targeting myeloma cells using bispecific antibodies which are off the shelf treatment options, enables wide deliverability for myeloma patients. The proposed technology appraisal is appropriate | Thank you for your comment.No action needed. |
| Myeloma UK | No comments. | Thank you for your comment. No action needed. |
| Wording | Pfizer | The wording of the remit is appropriate. | Thank you for your comment. No action needed. |
| Takeda UK | No changes suggested. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | Elranatamab is a novel bispecific T cell engager under investigation for relapsed multiple myeloma and has a novel mechanism of action compared to approved treatments. | Thank you for your comment. The appraisal committee will consider the innovative nature of the technology. No action needed. |
| Myeloma UK | Myeloma UK considers the remit to reflect the issues of clinical and cost effectiveness. | Thank you for your comment. No action needed. |
| Timing Issues | Pfizer | There is a significant urgency to provide access to elranatamab in patients with relapsed or refractory multiple myeloma who have already received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD) and an anti-CD38 monoclonal antibody (CD38 mAb) as there is a lack of effective and quality of life-preserving treatment options once patients have exhausted these three class options. In addition, these patients often become frailer, suffer cumulative toxicities from prior treatments, and thus become unsuitable to receive further therapies which might be efficacious but aggressive1,2. The expected median survival for a patient with relapsed/refractory multiple myeloma who has been exposed to a CD38 mAb, a PI and an IMiD is 12.4 months3.  A NICE appraisal closely aligned with the regulatory timings provided below will ensure timely access to elranatamab.  1. Bahlis NJ, Corso A, Mugge LO, Shen ZX, Desjardins P, Stoppa AM, et al. Benefit of continuous treatment for responders with newly diagnosed multiple myeloma in the randomized FIRST trial. Leukemia. 2017;31(11):2435-42.  2. Minnema M, Gavriatopoulou M. Optimising Treatment in Relapsed, Refractory Multiple Myeloma. European Oncology & Haematology. 2018;14:96.  3. Mateos, MV., Weisel, K., De Stefano, V. et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia 2022; 36, 1371–1376. | Thank you for your  comment. This topic  has been scheduled  into the technology  appraisal work  programme with the aim  of providing timely  guidance as soon as  possible after the  company receives the  marketing authorisation  and introduces the  technology in the UK. |
| Takeda UK | No comments. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | Myeloma is a life limiting cancer. Salvage therapies with clinical efficacy are urgently needed to improve clinical outcomes for this patient population.  Effective treatments for those that have received the main 3 classes of myeloma therapies is a priority. | Thank you for your  comment. This topic  has been scheduled  into the technology  appraisal work  programme with the aim  of providing timely  guidance as soon as  possible after the  company receives the  marketing authorisation  and introduces the  technology in the UK. |
| Myeloma UK | No comments. | Thank you for your comment. No action needed. |
| Additional comments on the draft remit | Pfizer | No comments. | No action needed. |
| Takeda UK | None. | No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | None. | No action needed. |
| Myeloma UK | None. | No action needed. |

Comment 2: the draft scope

| Section | Consultee/ Commentator | Comments [sic] | Action |
| --- | --- | --- | --- |
| Background information | Pfizer | The background information on multiple myeloma is accurate.  We suggest the following information on the technology is included for completeness:  “Elranatamab is a heterodimeric, humanised full-length bispecific IgG2 kappa antibody directed against both BCMA and CD34.”  4. Pfizer Inc. Investigator's Brochure - PF-06863135 (Elranatamab). June 2021. Version 6.0, 2021. | Thank you for your comment. This section  of the scope aims to  provide a brief overview  of the marketing authorisation and studied populations for the technology. No action needed. |
| Takeda UK | No comments. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | The background is correct, although including approved treatments for patients that have had at least 2 prior therapies is not relevant to the scope. | Thank you for your comment.Comparators within scope documents are kept broad and comprehensive. NICE  guidance for  lenalidomide plus dexamethasone (TA171) and for panobinostat plus bortezomib and dexamethasone (TA380)  do not restrict use to  people who have received 2 prior therapies and so  they have been included  as comparators. No action  needed. |
| Myeloma UK | We consider this information to be complete and accurate. | Thank you for your comment. No action needed. |
| Population | Pfizer | The population is defined appropriately. | Thank you for your comment. No action needed. |
| Takeda UK | *Is the population defined appropriately?*  Yes. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | The MagnetisMM-3 trial did not stipulate number of prior therapies and is for those that have been exposed to a proteasome inhibitor, immunomodulatory agent and CD38 monoclonal antibody. Within the current treatment pathway this may be achieved after 2 prior lines. | Thank you for your comment. The wording of the population in the scope includes the number of prior therapies and does not restrict use to people with a specified number of prior lines. The technology will be  appraised in line with  the marketing  authorisation and  company’s positioning. |
| Myeloma UK | We consider the population to be appropriately defined.  We welcome that it has not been restricted and is in line with likely marketing authorisation.  Despite approvals for treating myeloma in recent years given the heterogeneity of the disease an unmet need remains and there is a need for flexibility at each stage of the pathway.  It is common in myeloma appraisals that final company submissions are narrower than full marketing authorisation.  If the company seeks to pursue NICE approval for a narrower patient population than the final marketing authorisation it is vital that this reflects unmet need, current and likely future gaps in the pathway, and is not just driven by commercial considerations. | Thank you for your comment. The  technology will be  appraised in line with  the marketing  authorisation and  company’s positioning.No action needed. |
| Subgroups | Pfizer | The pivotal clinical trial for this appraisal, MagnetisMM-3 includes the following cohorts: patients with no prior BCMA-directed treatment and patients who have previously received BCMA-directed treatment. Clinical effectiveness will be examined separately for these cohorts. | Thank you for your comment. No action needed.  If a subgroup of the  population eligible for  treatment within the  marketing authorisation  needs separate  consideration this  should be detailed in  the company  submission. Any  evidence and analysis  to support this would be  welcomed. |
| Takeda UK | No subgroups suggested. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | *Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?*  No | Thank you for your comment. No action needed. |
| Myeloma UK | No comments. | Thank you for your comment. No action needed. |
| Comparators | Pfizer | **Pomalidomide plus low-dose dexamethasone (**TA427) was included in the draft scope and is a relevant comparator for elranatamab in patients who have received 3 prior therapies, including a PI, an IMiD, and a CD38 mAb. Pomalidomide plus low-dose dexamethasone has been accepted as a relevant comparator in prior NICE multiple myeloma appraisals (TA783, TA658).  While **daratumumab monotherapy** (TA783) is recommended in patients with relapsed or refractory multiple myeloma after 3 prior therapies, patients eligible for elranatamab will have likely received daratumumab (in combination with bortezomib and dexamethasone, TA573) in earlier lines of therapy. Patients are not routinely re-challenged with daratumumab in later lines of therapy. In addition, during TA783 the CDF clinical lead stated that the use of daratumumab monotherapy in the 4th line setting had fallen following NICE’s recommendation of isatuximab with pomalidomide and dexamethasone.  **Lenalidomide plus dexamethasone** (TA171) is not a relevant comparator for elranatamab in this setting. Clinical experts in TA505 stated that lenalidomide plus dexamethasone is mainly used after 2 prior therapies.  **Panobinostat plus bortezomib and dexamethasone** (TA380) is no longer a relevant comparator in this setting in the UK, as confirmed through committee conclusions in TA658 and TA783.  **Ixazomib plus lenalidomide and dexamethasone** (TA505) is currently undergoing a CDF review, with an expected publication date of February 2023 (ID1635). It is unlikely that ixazomib in combination with lenalidomide and dexamethasone will be part of UK clinical practice at the time of submission. Furthermore, this therapy is mostly used in the 3rd line setting, based on expert clinical opinion and in line with the final scope for ID1635 which only lists comparators for patients who have had at least 1 (2nd line) or 2 therapies (3rd line).  **Belantamab mafodotin** is being evaluated by NICE in two separate appraisals:  1. ID5108: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 2 therapies.  a. This appraisal was suspended on 16th November 2022 and therefore this treatment option will not be part of UK clinical practice at the time of submission.  2. ID270: Belantamab mafodotin for treating relapsed or refractory multiple myeloma after 4 or more therapies. Publication expected June 2023.  a. This treatment option is indicated for patients who have received 4 or more prior therapies (5th line setting), which is in a later setting than elranatamab in ID4026. In addition, it will not be part of UK clinical practice at the time of submission for ID4026. | Thank you for your comment. No action required.  Thank you for your comment. The comparators listed  in the scope aims to be  inclusive. A rationale  should be provided for  excluding any  comparators from the  evidence submission,  which can be  considered by the  appraisal committee. No action needed.  Comparators within scope documents are kept broad and comprehensive. NICE  guidance for  lenalidomide plus dexamethasone (TA171)  does not restrict use to  people who have received 2 prior therapies and so  this has been included  as a potential  comparator. No action  needed.  Thank you for your comment. The comparators listed  in the scope aim to be  inclusive. A rationale  should be provided for  excluding any  comparators from the  evidence submission,  which can be  considered by the  appraisal committee. No action needed.  Thank you for your comment. A positive recommendation for ixazomib plus lenalidomide and dexamethasone was published in February 2023 (TA780). Ixazomib plus lenalidomide and dexamethasone is therefore included  as a comparator.  Thank you for your comment. Elranatamab has been studied in a clinical trial in people with relapsed or refractory multiple myeloma after at least 3 prior therapies. The final guidance for ID2701 (belantamab mafodotin for patients who have received 4 or more prior therapies) is expected to be published in late August 2023. It has been included as a comparator with the caveat that this is subject to the outcome of the NICE evaluation. A rationale should be provided for  excluding any  comparators from the  evidence submission,  which can be  considered by the  appraisal committee. |
| Takeda UK | *Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?*  Yes and Yes.  Isatuximab with pomalidomide and dexamethasone may be used in clinical practice at 4th line, but it is currently only included within the CDF and therefore should not be a comparator here. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | Lenalidomide, Bortezomib and Daratumumab based combinations are not appropriate comparators as patients are refractory to these agents after 3 prior therapies  Appropriate current comparator is Pomalidomide and dexamethasone | Thank you for your comment. The comparators listed  in the scope aim to be  inclusive. The company will have the opportunity during the full appraisal to outline which  comparators it  considers to be most relevant. |
| Myeloma UK | We agree that these are treatments available to this patient population.  However, Myeloma UK believes that pomalidomide and dexamethasone should be the current standard comparator.  In current clinical practice it is our understanding that patients, after at least 3 prior therapies, will receive:   * Pomalidomide plus low-dose dexamethasone * Cyclophosphamide and dexamethasone OR alternative alkylating chemotherapy and corticosteroid (when pomalidomide plus low-dose dexamethasone is not suitable) * Daratumumab monotherapy (use limited by previous exposure to daratumumab at earlier lines) * Ixazomib plus lenalidomide and dexamethasone (use may be limited by previous exposure to lenalidomide at earlier lines and is subject to NICE evaluation) * Isatuximab plus pomalidomide and dexamethasone (use limited by previous exposure to daratumumab at earlier lines and is subject to NICE evaluation) * Clinical trial * Compassionate use / Early access scheme   The combination of panobinostat plus bortezomib and dexamethasone is not widely used in clinical practice and should not be used as a comparator in this NICE appraisal.  The combination lenalidomide plus dexamethasone is not widely used at fourth line and beyond as majority of patients will have received lenalidomide at previous lines of treatment.  Bendamustine is not considered a relevant comparator | Thank you for your comment. The comparators listed  in the scope aim to be  inclusive. Cyclophosphamide plus dexamethasone has been added to the comparators in the scope. The company will have the opportunity during the full appraisal to outline which  comparators it  considers to be most relevant.    Regarding isatuximab with pomalidomide and dexamethasone; although a CDF review is currently underway for this technology, it will not be in routine use by the time of the submission for this appraisal (even if the outcome is a positive recommendation). It is therefore not included as a comparator. |
| Outcomes | Pfizer | The outcomes listed are appropriate. | Thank you for your comment. No action needed. |
| Takeda UK | *Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?*  Yes and Yes. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | *Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?*  Yes | Thank you for your comment. No action needed. |
| Myeloma UK | *Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?*  Yes | Thank you for your comment. No action needed. |
| Equality | Pfizer | No equality issues have been identified. | Thank you for your comment. No action needed. |
| Takeda UK | No equality issues identified. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | Nil | Thank you for your comment. No action needed. |
| Myeloma UK | No comments | Thank you for your comment. No action needed. |
| Other considerations | Pfizer | No comment. | Thank you for your comment. No action needed. |
| Takeda UK | No comments. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | Use of inpatient treatment facility for first few treatment doses, management of cytokine release syndrome and Immune effector cell-associated neurotoxicity syndrome should be noted as part of the appraisal. | Thank you for your comment. Where  relevant and  appropriate, all  available data are  welcomed and will be  considered by the  committee. Management of cytokine release syndrome and **i**mmune effector cell-associated neurotoxicity syndrome are assumed to be captured in the adverse effects of treatmentoutcome. |
| Myeloma UK | No additional suggestions. | Thank you for your comment. No action needed. |
| Questions for consultation | Pfizer | Is bendamustine a relevant comparator for people with multiple myeloma after 3 therapies in the NHS?  Recent prior NICE technology appraisals (TA658, TA783) have determined that bendamustine does not reflect established NHS practice in England for 4th and later-line treatment of relapsed or refractory multiple myeloma.  Where do you consider elranatamab will fit into the existing care pathway for refractory multiple myeloma? In line with its proposed marketing authorisation, XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XX. XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX  Would elranatamab be a candidate for managed access?  Elranatamab is an appropriate candidate for managed access as XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX XXX  Have all the appropriate outcomes been captured?  All the appropriate outcomes that capture the health-related benefits of elranatamab have been included in the draft scope.  NICE intends to evaluate this technology through its Single Technology Appraisal process. We welcome comments on the appropriateness of appraising this topic through this process.  The STA process is appropriate for this appraisal as it will result in timely guidance to the NHS. Due to the significant unmet need in this patient population, we recommend the appraisal timelines are closely aligned with the regulatory timings provided below to ensure timely access to elranatamab.  Would it be appropriate to use the cost-comparison methodology for this topic?  The cost-comparison method is not appropriate for this appraisal as the clinical efficacy and resource use between elranatamab and its comparators are not similar. | Thank you for your comment. No action needed.  Thank you for your comment. No action needed.  Thank you for your comment. No action needed.  Thank you for your comment. No action needed.  Thank you for your  comment. This topic  has been scheduled  into the technology  appraisal work  programme with the aim  of providing timely  guidance as soon as  possible after the  company receives the  marketing authorisation  and introduces the  technology in the UK.  Thank you for your comment. No action needed. |
| Takeda UK | **What treatments are established clinical management in the NHS for people with multiple myeloma after 3 therapies?**  As per the comparators listed.  **Is bendamustine a relevant comparator for people with multiple myeloma after 3 therapies in the NHS?**  We believe bendamustine is not commissioned by NHS England for the treatment of relapsed or refractory myeloma; therefore, it is not an appropriate comparator.  **Where do you consider elranatamab will fit into the existing care pathway for refractory multiple myeloma?**  Within its proposed marketing authorisation for patients who have received 3 prior lines of therapy (4th Line.  **Have all the relevant comparators for elranatamab been included in the scope?**  We believe so yes.  **Are there any subgroups of people in whom elranatamab is expected to be more clinically effective and cost effective, or other groups that should be examined separately?**  We do not know.  **Would elranatamab be a candidate for managed access?**  No comments.  **Have all the appropriate outcomes been captured?**  We believe so yes  **Do you consider that the use of elranatamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**  No.  **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.**  N/A  **Questions re potential equality issues:**  We see no equality issues.  **NICE intends to evaluate this technology through its Single Technology Appraisal process:**  This seems appropriate to us.  **Questions re the appraisal methodology:**  • **Would it be appropriate to use the cost-comparison methodology for this topic?**  No.  • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?**  Unknown, seems unlikely to be similar in its clinical efficacy.  • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?**  We do not know.  • **Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?**  We do not know. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | **What treatments are established clinical management in the NHS for people with multiple myeloma after 3 therapies?**  Patients receive pomalidomide dexamethasone or Isatuximab Pomalidomide dexamethasone if they are not refractory to Daratumumab  **Is bendamustine a relevant comparator for people with multiple myeloma after 3 therapies in the NHS?**  Bendamustine Is not available to treat myeloma patients after 3 prior therapies and therefore not an appropriate comparator  **Where do you consider elranatamab will fit into the existing care pathway for refractory multiple myeloma?**  After 3 prior anti myeloma therapies  **Have all the relevant comparators for elranatamab been included in the scope?**  Yes  **Are there any subgroups of people in whom elranatamab is expected to be more clinically effective and cost effective, or other groups that should be examined separately?**  No  **Would elranatamab be a candidate for managed access?**  Yes  **Have all the appropriate outcomes been captured?**  Yes  **Do you consider that the use of elranatamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?**  No  **Would it be appropriate to use the cost-comparison methodology for this topic?**  Yes  **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?**  There are no randomised comparative trials. But as patients who have received all available antimyeloma therapies still benefit from use of this technology demonstrates that the new technology provides significant clinical benefit  **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?**  Yes  **Is there any substantial new evidence for the comparator technology/ies that has not been considered?**  No  **Are there any important ongoing trials reporting in the next year?**  No | Thank you for your comment. No action needed. |
| Myeloma UK | ***Would elranatamab be a candidate for managed access?***  We believe that elranatamab would be a candidate for managed access.  ***Do you consider that the use of elranatamab can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?***  Myeloma remains incurable and even after successful treatment, almost all patients eventually become resistant to existing treatments. New drugs and treatment approaches are urgently needed to overcome treatment resistance.  Elranatamab is a new type of myeloma drug. It works in a completely different way to the myeloma drugs routinely commissioned for use in the UK.  As a B cell maturation antigen (BCMA) targeted T-cell engager it would introduce a novel treatment approach into the pathway. | Thank you for your comment. No action needed. |
| Additional comments on the draft scope | Pfizer | There are no additional comments. | No action needed. |
| Takeda UK | None. | Thank you for your comment. No action needed. |
| UK Myeloma Society (previously called UK Myeloma Forum) | None. | No action needed. |
| Myeloma UK | None. | Thank you for your comment. No action needed. |

**The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope**

GlaxoSmithKline (GSK)