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Our reference
2025015133

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Date 16 July 2025
Re: Package advice lock procedure medicinal products elranatamab (Elrexfio®) and talquetamab (Talvey®) for multiple myeloma

Dear Ms Jansen,

This is a corrected version of the letter already sent on 2 July 2025 (reference no. 2025015133). The costs and budget impact for talquetamab have been adjusted in the BIA and in this package advice; the other reports are unchanged.

The National Health Care Institute advises you on the assessment of elranatamab (Elrexfio®) and talquetamab (Talvey®) for the treatment of relapsed and refractory multiple myeloma. This advice was prompted by the placement of elranatamab and talquetamab in the lock procedure for expensive medicinal products.
Elranatamab and talquetamab are similar medicines that have been assessed over the same period. The National Health Care Institute therefore combines the package advice for these products in one letter.

The National Health Care Institute advises you to include elranatamab and talquetamab as monotherapy for the treatment of 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 who have demonstrated disease progression during the last therapy.

Condition
Multiple myeloma (MM) is an incurable form of bone marrow cancer, also known as Kahler's disease, in which plasma cells grow uncontrollably in the bone marrow. The cause of the disease is unknown. In the Netherlands, it is estimated that approximately 1400 patients are diagnosed with MM each year. Most patients are 65 years or older, but there are also younger patients. Life expectancy after diagnosis is about 2-9 years. How long a patient survives depends on the patient's fitness and treatment options. Patients can undergo stem cell transplantation and many new innovative medicines are already available and being developed. The medicinal products elranatamab and talquetamab can be used in patients who have experienced the return of the disease after three previous treatments (relapsed) and who are not responding to prior treatment (refractory).

Registered indication

Elranatamab (Elrexfio®) and talquetamab (Talvey®) have both been indicated as monotherapy for the treatment of 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 who have demonstrated disease progression during the last therapy.

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Marketing authorisation holder claim
Both marketing authorisation holders claim an added value for elranatamab (Elrexfio®) and talquetamab (Talvey®) compared to the current physician's choice (PC) treatments for adult patients with RRMM who have received at least three prior treatments, including an iMID, PI, and an anti-CD38 antibody, and who have shown disease progression during the last treatment. In addition, the marketing authorisation holder of elranatamab (Elrexfio®) claims a therapeutic value that is comparable with that of teclistamab for patients who are not eligible for chimeric antigen receptor T-cell (CAR-T) treatment.

Package advice
The National Health Care Institute advises you to include elranatamab (Elrexfio®) in the basic health care package for the registered indication, provided that the inclusion in the package does not lead to additional costs, as explained in this letter.

The National Health Care Institute advises you to include talquetamab (Talvey®) in the basic health care package for the registered indication, provided that the inclusion in the package does not lead to additional costs as explained in this letter.

The National Health Care Institute has determined that elranatamab and talquetamab for this indication meet the legal criterion of 'established medical science and medical practice' and that they are equivalent to standard teclistamab treatment. Teclistamab has been recently assessed by the National Health Care Institute, concluding that teclistamab meets the established medical science and medical practice and has added value compared to standard treatment (PC)[1]. Teclistamab, elranatamab and talquetamab are all three bispecific antibodies that activate specific immune cells and belong to a new class of medicinal products.

We explain the development of this package advice below.

General
At your request, the National Health Care Institute assesses whether care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums.
The National Health Care Institute assesses on the basis of the four package

[1] https://www.zorginstituutnederland.nl/publicaties/adviezen/2025/04/14/pakketadvies-teclistamab-tecvayli-voor-de-behandeling-van-multipel-myeloom-herbeoordeling

criteria[2]: effectiveness[3], cost-effectiveness[4], necessity[5] and feasibility[6]. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders are consulted during the process.

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Met opmerkingen [RA1]: Is de regel niet om t/m 10 voluit te schrijven?

Met opmerkingen [LS2R1]: Bij studie fases zou ik dat niet doen

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

Elranatamab and talquetamab were both studied in single-arm phase (1-)2 studies (MagnetisMM-3 and MonumenTal-1). These studies were similar in study design. Using various analysis methods, the results of the MagnetisMM-3 and MonumenTal-1 studies were indirectly compared with an external control cohort (LocoMMotion/MoMMent), in which patients received physician's choice (PC) treatments. The standard treatment (PC) in the control cohort corresponds to the regimes used in Dutch practice[7].

Based on the indirect comparisons, elranatamab and talquetamab both show improvement in survival compared to PC. For elranatamab, this was a clinically relevant improvement. For talquetamab, survival on the basis of the point estimate has also shown a clinically relevant improvement, but the absolute effect cannot be determined at this moment as the median survival has not been achieved yet, despite a relatively long follow-up time.
Both products show a clinically relevant improvement in progression-free survival compared to PC. For both outcome parameters, overall survival and progression-free survival, the quality of evidence was very low due to the non-randomised study design, the indirect comparison and the observational nature of the comparative treatment. The relative effects observed are therefore very uncertain.

No data were published of the relative effectiveness of elranatamab and talquetamab on the outcome quality of life compared to PC.
In the MagnetisM-3 study, no effect on quality of life was observed for elranatamab. A small improvement in the 'pain' ranking was observed, but this was not clinically relevant. Clinically relevant effects on quality of life were potentially observed in the MonumenTal-1 study. However, these results have not been published.

In addition, elranatamab and talquetamab were indirectly compared to teclistamab. For the comparison of elranatamab with teclistamab, a published

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[2] Real-world package management 4 (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[3] Assessment of the established medical science and medical practice (2023). National Health Care Institute. Via www.zorginstituutnederland.nl.

[4] Healthcare cost-effectiveness report (2024) National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[5] Necessity is related to both the medical need due to the severity of a disease for the patient (burden of disease) and the need to insure something. See the report on real-world package management 4 (2023).

[6] The package criterion of feasibility deals with whether it is feasible or sustainable to include a specific form of care in the basic health care package. It is therefore mainly a test of a number of implementation aspects, such as the healthcare organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

[7] In Dutch practice, the most common regimes used for these patients include pomalidomide-cyclophosphamide-dexamethasone; carfilzomib-dexamethasone; elotuzumab pomalidomide-dexamethasone

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matching adjusted indirect comparison (MAIC) is available. In both indirect comparisons, the quality of evidence in terms of relative effectiveness is very low for the same reasons as mentioned above. On this basis, only a similar effect on survival can be concluded. Confidence in this similar effects on overall survival is enhanced by the similar effects that were observed on progression-free survival.

Elranatamab and talquetamab, like teclistamab, appear to have a less favourable safety profile than standard treatment (PC). These products are associated with serious adverse events such as cytokine release syndrome (CRS), neurological side effects and infections. Elranatamab and talquetamab have a similar safety profile to teclistamab. The physicians' association indicates that the adverse events of bispecific antibodies can be treated efficiently.

All in all, the National Health Care Institute, advised by the Scientific Advisory Board (WAR), concluded that elranatamab and talquetamab comply with the established medical science and medical practice for this indication, have an added therapeutic value in comparison with standard treatment and a therapeutic value comparable with that of teclistamab.

In recent times, several treatments have been introduced for the treatment of multiple myeloma beyond the third line of treatment. In the past year, the National Health Care Institute assessed three bispecific antibodies and the CAR-T treatment cilta-cel[8]. The studies and assessments could only take these developments into account to a limited extent. However, after inclusion in the basic healthcare package, these four medicinal products will compete with each other after three lines of treatment. There is currently no evidence of an effective sequential use of these products. In addition, cilta-cel will be used for patients in good physical condition. Patients who are not in good physical condition will be eligible for treatment with the bispecific antibodies. The effects of selecting patients with a poor physical condition on the effectiveness of bispecific antibodies (teclistamab, elranatamab, talquetamab) are unclear.

Budget impact analysis
The marketing authorisation holders of the bispecific antibodies have both indicated during the evaluation process that they are willing to reduce the price of the three bispecific antibodies. In the attached budget impact analysis, the proposed price reduction of the list price was calculated.
The National Health Care Institute estimates that 147 patients for the above indication will be treated in year 3 after inclusion in the package, with the patients being distributed equally among the three bispecific antibodies. This assumes that teclistamab will be included in the basic health care package. The total cost per patient is €151,510 for elranatamab, €200,372 for talquetamab and between €147,581 and €162,196 for teclistamab. In year 3, the macro cost of elranatamab is €7.3 million, of which €5.6 million is in the fourth line and €1.6 million is in the fifth line. For talquetamab, this is €9.6 million in year 3, of which €7.4 million in the fourth line and €2.2 million in the fifth line. The guiding principle of the budget impact analysis is that teclistamab and cilta-cel are included in the basic healthcare package.
The budget impact of elranatamab compared to teclistamab is between -€0.5 million and €0.2 million in the same year. For talquetamab, this amounts to

8 https://www.zorginstituutnederland.nl/publicaties/adviezen/2025/02/18/pakketadvies-ciltacabtagene-autoleucel-carvykti-voor-de-behandeling-van-multipel-myeloom

between €1.8 million and €2.5 million. In practice, the uncertainty about the dosages causes the most uncertainty. A lower dosing frequency leads tolower macro-costs.

If teclistamab is not included in the base healthcare package, the budget impact of elranatamab and/or talquetamab will increase, as only the PC is substituted, and not the much more expensive treatment teclistamab. If cilta-cel is not included in the basic healthcare package, the budget impact will also be greater, as more patients will be eligible for treatment with the bispecific antibodies. According to the physicians' association, bispecific antibodies can also play a role after progression on cilta-cel. This is not included in this BIA because the average progression-free survival on cilta-cel is longer than the three-year horizon. There is therefore a risk that more patients will be eligible for bispecific antibodies after these three years, resulting in higher macro-costs in later years. There is also a risk that the bispecific antibodies will be used sequentially. In that case, the macro-costs of the bispecific antibodies will be higher.

Based on the conclusion that elranatamab and talquetamab have an equal value compared to teclistamab, the introduction of elranatamab or talquetamab should not lead to additional costs compared to teclistamab. In these calculations, the negotiated price of teclistamab is leading. As long as teclistamab is not included in the basic health care package, the theoretical price of teclistamab based on the minimum price discount recommended by the National Health Care Institute will be used as the reference for calculating the price reduction for elranatamab and talquetamab.
See the teclistamab package advice[1] and reports to support the recommended minimum discount rates for teclistamab.

Cost-effectiveness
As there is an equal value, an assessment of the cost-effectiveness of elranatamab and talquetamab is not required. The large number of therapeutic treatment options, many of which are expensive medicinal products, results in an accumulation of high costs for MM, which is not cost-effective for most treatment sequences in patients who are not eligible for autologous stem cell transplantation.[9]

Appropriate care
To promote the effective use of bispecific antibodies, the National Health Care Institute considers it important that appropriate use arrangements are made. The physicians' association has indicated that it wishes to research the effective use of bispecific antibodies. The National Health Care Institute endorses the importance of efficiency studies for these treatments. In addition, the National Health Care Institute advises that treatment with elranatamab and talquetamab, just as intended for teclistamab, will be discussed in an indication committee. The uncertainty about the effectiveness of bispecific antibodies in sequential use and after CAR-T treatments should be considered by the indication committee. An evaluation of the possible sequential deployment should also be part of the appropriate use agreements.

Should you need any further information, please do not hesitate to contact us.

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[9] https://www.zorginstituutnederland.nl/publicaties/adviezen/2025/01/27/pakketadvies-multipel-myeloom-2025

The assessment reports have been added as annexes (pharmacotherapeutic report, budget impact analysis).

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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