National Health Care Institute

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National Health Care Institute
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Our reference
2024024686

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Date 10 July 2024
Re: Package advice for lock procedure medicinal product teclistamab (Tecvayli®)

Dear Ms Agema,

The National Health Care Institute advises you on the assessment of teclistamab (Tecvayli®) for relapsed and refractory multiple myeloma (RRMM), after at least three previous treatments. The reason for this advice was the placement of teclistamab in the lock procedure for expensive medicinal products.

Registered indication
Teclistamab (Tecvayli®) is indicated 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.

Multiple myeloma (MM), also known as Kahler's disease, is a disorder that involves a malignant degeneration of plasma cells in multiple sites in the bone marrow. The proliferating plasma cells displace other bone marrow cells and cause lower levels of normal antibodies. MM is an incurable condition with a high degree of morbidity, especially bone lesions, renal failure and recurrent infections. There is a high degree of heterogeneity in disease progression because the disease depends on various factors such as the aggressiveness of the disease, patient age and comorbidity. The 5-year survival rate is 56%. The disease is diagnosed especially in the elderly. In 2021, 1,557 people were diagnosed with MM.

Claim by the marketing authorisation holder
Teclistamab (Tecvayli®) has an added value compared to the current standard treatments for the above indication.

Package advice
The National Health Care Institute recommends not to include teclistamab in the basic health care package for the above-mentioned indication.
The National Health Care Institute finds that teclistamab meets the legal criterion of 'established medical science and medical practice' and that there is an added value compared to the physician’s choice of treatment. However, the cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality. Therefore, its results cannot be used in the decision-making.

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This leaves the National Health Care Institute unable evaluate the cost-effectiveness and to advise on any price negotiations. This is essential for you and for the National Health Care Institute, because the reimbursement of teclistamab at the marketing authorisation holder's current asking price would possibly lead to a treatment that would not be cost-effective. In addition, the high price combined with the number of patients leads to a high budget impact that can only be socially responsible if the treatment is cost-effective. The National Health Care Institute is aware that the outcome of the National Health Care Institute's assessment will be disappointing both for patients and practitioners. The National Health Care Institute therefore invites the marketing authorisation holder to modify the pharmaco-economic analysis.

We explain the preparation 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 criteria[1]: effectiveness[2], cost-effectiveness[3], necessity[4] and feasibility[5]. The Scientific Advisory Board (WAR) has advised the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders were consulted during the process.

Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

The medical management of multiple myeloma (MM) consists of the combination of different classes of medicinal products with different mechanisms of action. Patients may be eligible for treatment with teclistamab monotherapy after 3 treatment lines. Teclistamab, a bispecific antibody, has a different mechanism of action from the already available treatments for RRMM.
The treatment in the 4th line and beyond is also determined by the previous treatments. There is therefore no standard treatment in the 4th line and beyond. In Dutch practice, several different regimes are applied in the 4th line and beyond. That is why teclistamab is compared with the physician's choice of treatment.

Teclistamab has only been studied in a single-arm study. A randomized clinical trial (RCT) is desirable, but has not been performed. A comparison has been made with an external control to enable a statement about the effectiveness relative to the physician's choice of treatment. Based on the indirect comparison, National

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

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

[3] Cost-effectiveness report (2015). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl.

[4] 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).

[5] 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 health care organisation, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

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Health Care Institute concludes that treatment with teclistamab results in a clinically relevant prolongation of relative overall survival (OS) (HR 0.64). The absolute weighted survival gain was 10.1 months. However, the quality of the evidence, partly because of having to make an indirect comparison with an observational study, is of very low quality. Therefore, progression free survival (PFS) was also considered as a surrogate outcome parameter for OS. The weighted relative PFS showed clinically relevant improvement after treatment with teclistamab, compared to the physician's choice of treatment (HR 0.48), but this evidence is also of very low quality.
The effect of teclistamab treatment on quality of life compared to the physician's choice of treatment is unknown due to the lack of quality of life data for the external control cohort. In the single-arm study, teclistamab appears to have a positive effect on the quality of life, especially on the specific domain of pain. The incidence of serious adverse effects showed a clinically relevant higher rate with teclistamab treatment than with the physician's choice of treatment. Similarly, the evidence for the adverse effects is of very low quality, due to the above-mentioned reasons.

It is not expected that higher quality evidence will become available for teclistamab monotherapy in the near future.

Based on the present evidence of the indirect comparison, a significant and clinically relevant survival gain is demonstrated. Despite the uncertainty resulting from the indirect comparison and a potentially more negative adverse event profile, the impact on survival and PFS weighs heavily in the final assessment. The professional and patient associations have indicated that they attach great importance to the PFS as a stand-alone outcome parameter in the present indication. In addition, in the case of RRMM, a correlation between PFS and OS has been demonstrated, although with some uncertainty.
Despite an increase in side effects, teclistamab also appears to have a positive effect on the quality of life. Overall, the National Health Care Institute concludes that there is sufficient confidence that treatment with teclistamab will lead to a clinically relevant improved survival rate, which makes a potentially more negative adverse event profile acceptable.

With that, teclistamab meets the criterion of established medical science and medical practice for 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.

Cost-effectiveness
The cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality. As a result, the National Health Care Institute cannot provide a methodologically reliable estimate of cost-effectiveness.
For example, there is a lot of uncertainty surrounding the indirect comparison, which is mainly aimed at matching the two cohorts and imputation of missing values. In addition, the switch to a lower dosing frequency and the costs for follow-up treatment are not sufficiently elaborated. Critical questions on this subject have not been adequately answered by the marketing authorisation holder. Also, several scenario analyses that were requested by the National Health Care Institute are missing. Given the immaturity of the OS data, this makes the

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results of the extrapolations too uncertain. The other criticisms include the lack of a comparison with the Dutch patient population and the inclusion of productivity losses.
Because of these points, the National Health Care Institute does not have sufficient confidence in the current pharmaco-economic analysis with the corresponding results. The National Health Care Institute concludes that the results of the analysis cannot be used in the decision-making.

Budget impact analysis
The National Health Care Institute estimates that 367 patients per year in the 4th line and 108 patients per year in the 5th line will be treated with teclistamab for this indication in year 3 after inclusion in the health insurance package. The total costs per patient per year are €231,672. When a switch to a dose once every two weeks is taken into account, the annual costs per patient are €210,796. This results in macro costs of between €50.2 and €55.1 million in the third year. When substitution is taken into account, the budget impact in year 3 ranges between €30.3 and €35.1 million.

Should you need any further information, please do not hesitate to contact us. The assessment reports have been added as annexes (pharmacotherapeutic report, budget impact analysis, pharmaco-economic report).

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board