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To the Minister of Health, Welfare and Sport
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2025001641

Date 18 February 2025
Re: Package advice lock procedure medicinal product ciltacabtagene autoleucel (Carvykti®) for multiple myeloma

National Health Care Institute

Care
Medicinal Products

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Contact

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Our reference
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Dear Ms Agema,

The National Health Care Institute advises you on the assessment of ciltacabtagene autoleucel (Carvykti®), hereinafter cilta-cel, for the treatment of adult patients with relapsed and refractory multiple myeloma, after at least three previous treatments. The reason for this advice was cilta-cel being placed in the 'lock procedure' for expensive medicinal products.

Disorder

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 is unknown. In the Netherlands, it is estimated that approximately 1400 patients are diagnosed each year. Most patients are 65 years or older, but there are also younger patients. The median survival is about 2-9 years after diagnosis. How long a patient survives depends on the patient's fitness and treatment options. Patients can undergo autologous stem cell transplantation and many new medicines are already available and being developed. At the moment there are 4 other ongoing (re)assessments of medicinal products for MM at the National Health Care Institute.

Registered indication

Cilta-cel is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least three prior treatments, including a proteasome inhibitor, an immunomodulating agent and an anti-CD38 antibody, and who have shown disease progression at or after the last therapy. Recurrent means that the cancer has come back, after having first partially or completely disappeared. And refractory means that the cancer has not responded to a previous treatment. This indication is related to the use of cilta-cel after at least three previous treatments.

Meanwhile, cilta-cel has already been registered for use from secondary healthcare, namely for the treatment of adult patients with relapsed and refractory MM who have received at least one prior treatment, with an immunomodulating agent and a proteasome inhibitor, who have shown disease progression during the last therapy and who are refractory to lenalidomide.

Claim by the marketing authorisation holder (MAH)

Cilta-cel has an added value compared to standard treatment in patients with relapsed and refractory MM who have received at least three prior treatments including a proteasome inhibitor, an immunomodulating agent and an anti-CD38 antibody and who have shown disease progression at or after the last therapy. Using cilta-cel as secondary healthcare is not part of this assessment.

Package advice

In 2022, the National Health Care Institute advised your predecessor not to include cilta-cel in the basic healthcare package for the above indication. At that time, the National Health Care Institute concluded that for the above indication, cilta-cel met the legal criterion of 'established medical science and medical practice' and that there was an added value compared to standard treatment, but that the cost-effectiveness analysis of the MAH was of insufficient quality. This did not allow the National Health Care Institute to provide recommendations for any price negotiation.

The National Health Care Institute now advises you, after reassessment of the modified cost-effectiveness analysis of the MAH, to include cilta-cel for the above indication in the basic healthcare package, provided that the price can be reduced by at least 35% after successful price negotiations. The cost-effectiveness is unfavourable on the basis of the available data. The National Health Care Institute recommends that the price negotiations should take into account the availability of any new information on long-term effects of cilta-cel, the extension of the indication of cilta-cel to secondary healthcare and the possible availability of other treatments for the relevant patient group.

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 health insurance package paid from joint premiums.

The National Health Care Institute assesses on the basis of the four package criteria¹: effectiveness², cost-effectiveness³, necessity⁴ and feasibility⁵. The Scientific Advisory Board (WAR) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. If there are risks regarding the accessibility and affordability, the assessment of the package criterion of effectiveness (established medical science and medical practice) will be placed in the wider societal context of the four package criteria. The Insured

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 healthcare package. It is therefore mainly a test of a number of implementation aspects such as the healthcare organisation, support, ethical and legal aspects, budget impact and so on. See the report on real-world package management 4 (2023).

Package Advisory Committee (ACP) advises the Executive Board of the National Health Care Institute in this regard. This societal weighting results in the package advice. Stakeholders are consulted during the process.

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Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

In 2022, after the advice of the WAR, the National Health Care Institute already ruled that cilta-cel meets the established medical science and medical practice for the aforementioned indication.⁶ The effectiveness and safety of cilta-cel was investigated in a single-arm, non-comparative phase 1b/2 study (CARTITUDE-1). The standard treatment for MM in 4th line treatment consists of a wide range of medicinal combinations.⁷ The results of the CARTITUDE-1 study were indirectly compared with a retrospective external control cohort (MAMMOTH). After 12 months, 81% of patients treated with cilta-cel were still alive versus 42% of patients treated with comparative treatment. The estimated survival gain was 28.5 months. The lack of comparative study data and the immaturity of the data used in the indirect comparison (12.4 months) make the scope of the effect very uncertain.

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Treatment with cilta-cel is often accompanied by severe side effects. Given the treatability of the adverse reactions and the risk mitigation measures already put in place by the treatment providers, the National Health Care Institute considers the adverse effects of cilta-cel acceptable in relation to the severity of the disease (life-threatening) and the effect on survival achieved with the treatment.

Cost-effectiveness

In 2022, following the advice of the WAR, the National Health Care Institute ruled that the cost-effectiveness analysis submitted by the MAH was of insufficient quality. The National Health Care Institute has now reassessed the cost-effectiveness analysis adjusted and updated by the MAH. The modified analysis includes newer data with longer follow-up (34.5 months) and a comparison has been made with another external control cohort (LocoMMotion instead of MAMMOTH), which is better suited to Dutch practice according to the professional association. At 34.5 months, 62.9% of patients treated with cilta-cel were still alive. At 2 years, 33.7% of patients treated with the comparative treatment were still alive. These results support the conclusion that cilta-cel meets the established medical science and medical practice, which the National Health Care Institute had already reached on the basis of data with a shorter follow-up (12.4 months).

The National Health Care Institute now concludes that the starting point of the new cost-effectiveness analysis as submitted by the MAH was too optimistic. The National Health Care Institute, after consulting the WAR, takes the view that the analysis is useful for decision-making if other crucial assumptions are made for estimating the effects and costs of cilta-cel. These include the assumptions about progression-free survival, the survival time of patients who are already showing disease progression, and the costs of follow-up treatment after progression. Due to the uncertainty surrounding the effect of cilta-cel on post-progression survival,

⁶ Package advice for the lock procedure medicinal product ciltacabtagene autoleucel (Carvykti®) for the treatment of multiple myeloma | Advice | National Health Care Institute (2022)

⁷ The most common treatment combinations in 4th line treatment are: 1.) pomalidomide + cyclophosphamide + dexamethasone, 2.) elotuzumab + pomalidomide + dexamethasone, and 3.) carfilzomib + dexamethasone.

the National Health Care Institute presents an ICER range with two different assumptions. Scenario A assumes that there is indeed a post-progression survival benefit of cilta-cel compared to standard treatment. Scenario B assumes that there is no post-progression survival benefit of cilta-cel compared to standard treatment. The ICER range runs from €109,806 per QALY in scenario A to €142,105 per QALY in scenario B. With a reference value of €80,000, the price of cilta-cel based on the ICER range would have to be reduced by 25% and 35% respectively to be cost effective.

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Budget impact analysis

The National Health Care Institute estimates that 140 patients per year will be treated with cilta-cel for this indication in year 3 after inclusion in the package. The total costs per patient per year are €420,000 (these costs do not include administration and monitoring costs). This results in a budget impact of €37.9 to €46.2 million in the third year, varying according to the number of patients starting treatment (i.e. undergoing apheresis) and ultimately actually receiving infusion with cilta-cel. This will take into account the complete substitution of the current standard treatments.

ACP advice (social weighting)

The ACP has weighed the value of cilta-cel from a social point of view. The committee considers it important that cilta-cel for the treatment of RRMM after at least 3 lines of therapy should be available in the short term, but only at a socially acceptable price. Due to the degree of uncertainty and the significant budget impact that make the risk of displacement of care significant, the ACP recommends a price reduction of at least 35%. In addition, a pay for performance arrangement can be explored. The committee recommends a limited duration of the price arrangement so that the long-term effects of cilta-cel and the possible initial results of a study on the CAR T-cell therapy produced at the point of care are known for any subsequent price negotiations⁸. In the short term, a reimbursement request for the extension of the indication of cilta-cel to secondary healthcare is expected, which should be taken into account. The National Health Care Institute will adopt this ACP advice.

Appropriate care

The Netherlands restricts the application of CAR-T treatment. There is a national registry and use is made of a nationwide CAR-T tumour board for patient selection. As a result, there is a lot of confidence in the appropriate use of the treatment. The professional association will deploy cilta-cel according to a protocol, according to which all patients will be discussed by the tumour board. The National Health Care Institute endorses this appropriate use.

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).

⁸ Promising care - CAR T cell therapy produced at the point of care for patients with relapsed multiple myeloma | Work agenda | National Health Care Institute

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board

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