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National Health Care Institute
Care
Medicinal Products

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Our reference
2022038076

Date 20 October 2022
Subject Package advice ciltacabtagene autoleucel (Carvykti®)

Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of ciltacabtagene autoleucel (Carvykti®), hereinafter called cilta-cel, for the treatment of adult patients with relapsing and refractory multiple myeloma (RRMM), who have received at least three previous treatments, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 antibody, and in whom disease progression has been demonstrated during or after the last therapy. The reason for this advice was cilta-cel being placed in the 'lock procedure' for expensive medicinal products.

Cilta-cel meets the established medical science and medical practice for the above indication and has a therapeutic added value compared to comparative treatment. The cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality, despite the fact that the market authorisation holder has been given the opportunity to improve it. Unfortunately, this means that the National Health Care Institute cannot advise you regarding any price negotiations you might conduct. This is essential for you and for the National Health Care Institute, because the reimbursement of cilta-cel at the marketing authorisation holder's current asking price would lead to a substantial, socially unjustifiable budget impact.
The National Health Care Institute advises you not to include cilta-cel (Carvykti®) in the basic healthcare package for this indication. 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 and better substantiate the pharmaco-economic analysis.

We would like to explain our findings and final conclusion below.

General

At your request, the National Health Care Institute assesses whether new care should be part of the standard health insurance package from the perspective of the basic healthcare package paid from joint premiums. In this decision, we weigh the matter, both in a scientific sense and from a social basis, and we weigh the aspects of efficiency and transparency. The National Health Care Institute

assessed cilta-cel on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute is advised in this matter by the Scientific Advisory Board (WAR) for advice on established medical science and medical practice and on cost-effectiveness. We also consulted stakeholders during the assessment process.

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Integral weighting of package criteria

Established medical science and medical practice

The effectiveness and safety of cilta-cel in adult patients with RRMM who have had at least three previous treatments (i.e. treatment lines) has been studied in a single-arm, non-comparative phase 1b/2 study (CARTITUDE-1). To determine a difference in overall survival, a (weighted) indirect comparison was made between CARTITUDE-1 and 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 indirect comparison of the overall survival of these two cohorts results in a hazard ratio (HR) of 0.24 (95% confidence interval: 0.14; 0.41). This effect is clinically relevant. Since the data from the CARTITUDE-1 study have not yet matured, the absolute survival gain can only be estimated on the basis of the available data. Treatment with cilta-cel resulted in an estimate survival rate gain of at least 28.5 months (at least 37.5 months versus 9 months on comparative treatment). Whether the quality of life improves after treatment with cilta-cel compared to the comparative treatment cannot be assessed due to the lack of data about both the cilta-cel and the comparative treatment.
There is uncertainty about the treatment effect on overall survival due to the lack of direct comparative evidence and immaturity of the data. However, given the size of the effect, it is highly unlikely that in practice, cilta-cel is not superior to the comparative treatment. In addition, the setting plays an important role in the assessment: there is an aggressive disease course and patients have virtually no effective treatment options left from the fourth treatment line.

Treatment with cilta-cel is often accompanied by severe side effects. In view of the treatability and the establishment of risk mitigation measures, 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 that is achieved with the treatment.

In the treatment of adult patients with relapsing and refractory multiple myeloma (RRMM), who have received at least three previous treatments, including a proteasome inhibitor, immunomodulatory agent and anti-CD38 antibody, and in whom disease progression has been demonstrated on or after the last therapy, cilta-cel meets the established medical science and medical practice, and has a therapeutic added value compared to comparative treatment.

Budget impact analysis

The National Health Care Institute estimates that 140 patients per year will be

[1] Real-world package management 3 (2013). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl

[2] Established medical science and medical practice assessment: updated version (2015). National Health Care Institute,
Diemen. Via www.zorginstituutnederland.nl

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

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treated with cilta-cel for this indication in year 3 after inclusion in the package. The total cost of infusion with cilta-cel is €420,000 per patient (these costs include administration and monitoring costs).
In that case, the costs amount to between €37.9 and €46.2 million per year. There is uncertainty about the distribution of treatments in the fourth line. The impact of this on the costs was not investigated in the budget impact analysis.

Pharmaco-economic analysis
The cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality, despite the fact that the market authorisation holder has been given the opportunity to improve it.
It is the opinion of the National Health Care Institute that the cost-effectiveness analysis is not sufficiently transparent, that there is a bias in the assumptions and a lack of evidence to substantiate the assumptions made in the pharmaco-economic analysis. Crucial choices in the pharmaco-economic model are not sufficiently substantiated by the marketing authorisation holder and requested analyses have not been applied throughout the dossier. As a result, the National Health Care Institute cannot provide a methodologically reliable estimate of cost-effectiveness. Nor can it give you an indication of the price reduction required to get close to an acceptable level of cost-effectiveness.

Unfortunately, this means that the National Health Care Institute cannot advise you regarding any price negotiations. This is essential for you and for the National Health Care Institute, because the reimbursement of cilta-cel at the marketing authorisation holder's current asking price would lead to a substantial, socially unjustifiable budget impact.

Package advice
The National Health Care Institute therefore advises you not to include ciltacabtagene autoleucel (Carvykti®) in the basic healthcare package for this indication. 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 and better substantiate the pharmaco-economic analysis.

Yours sincerely,

Sjaak Wijma
Chairperson of the Executive Board