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2023009226

National Health Care Institute
Care
Medicinal Products

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Our reference
2023009226

Date 17 April 2023
Subject Package advice on the lock procedure medicinal product brexucabtagene autoleucel (Tecartus®)

Dear Mr Kuipers,

The National Health Care Institute is advising you about brexucabtagene autoleucel (Tecartus®), hereinafter referred to as "brexu-cel", in the treatment of adult patients with recurrent or refractory mantle cell lymphoma (r/r MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (BTK inhibitor). The reason for this advice was brexu-cel being placed in the 'lock procedure' for expensive medicinal products.

The National Health Care Institute advised you in September 2022 not to include brexu-cel in the basic health care package. The cost-effectiveness analysis that the marketing authorisation holder had submitted was not of sufficiently high quality to let the National Health Care Institute give you a recommendation for any price negotiations.
The marketing authorisation holder has in the meantime submitted an amended cost-effectiveness analysis that the National Health Care Institute has assessed. Brexu-cel is in line with the established medical science and medical practice for the above indication and it has therapeutic added value compared to comparative treatment using chemotherapy or immunotherapy. The National Health Care Institute advises you to include brexu-cel in the health insurance package for the specified indication. Based on the most realistic incremental cost-effectiveness ratio (ICER), the National Health Care Institute believes that a discount of at least 80% would be appropriate. The National Health Care Institute thereby recommends organising structural funding for setting up indication committees and data collection in the context of cyclical package management of expensive medicines.

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

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General

At your request, the National Health Care Institute assesses whether new care should be part of the health insurance package. To be able to make a recommendation, the National Health Care Institute has assessed brexu-cel on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. We consider these criteria from the scientific perspective and in terms of public support. We also review the aspects of efficiency and transparency. The National Health Care Institute is advised about its package reviews by two independent committees:

- the Scientific Advisory Board (WAR) for the review of data according to the established medical science and medical practice, and for determining the cost-effectiveness; and
- the Package Advisory Committee (ACP) for the social deliberations.

We also consulted stakeholders during the assessment process.

Integral weighting of package criteria

Established medical science and medical practice

The effectiveness and safety of brexu-cel in adult patients with r/r MCL have been studied in a single-arm, open-label phase 2 study (ZUMA-2). To determine a difference in overall survival, a (weighted) indirect comparison was made between ZUMA-2 and a retrospective external control cohort (SCHOLAR-2).
Treatment with brexu-cel resulted in a clinically relevant extension of overall survival (at least 39 months versus 16 months on comparative treatment).
Whether the quality of life improves after treatment with brexu-cel compared to the comparative treatment cannot be assessed due to the lack of data.
There is uncertainty about the treatment effect on overall survival due to the lack of direct comparative evidence and the low number of patients included. However, given the size of the effect, it is unlikely that in practice, brexu-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 (a significant unmet medical need). Finally, better evidence in the form of a randomised study is difficult to achieve because of the rarity of the indication and the lack of effective treatment options into which patients can be randomised.

Treatment with brexu-cel is often accompanied by severe side effects. In view of the treatability by establishing risk mitigation measures, the National Health Care Institute considers the adverse effects of brexu-cel to be acceptable in relation to the severity of the disease (life-threatening) and the effect that is achieved with the treatment.

Brexu-cel meets the established medical science and medical practice in the treatment of adult patients with recurrent or refractory mantle cell lymphoma

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[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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(r/r MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (BTK inhibitor), and has therapeutic added value compared to the comparative treatment.

Budget impact analysis
Taking account of substitution, applying brexu-cel for the above indication will be associated with estimated costs of between €10.6 and €11.4 million in the third year. The National Health Care Institute estimates that 30 patients per year will be treated with brexu-cel for this indication in year 3 after inclusion in the package. The cost of a single administration of brexu-cel is €360,000. The total costs per one-off course of treatment amount to €391,115.67 (these costs include treatment with conditioning chemotherapy, bridging chemotherapy, treatment of side effects and possible re-treatment).
There is uncertainty about the number of patients with r/r MCL who will actually be treated with brexu-cel.

Cost-effectiveness analysis
After re-evaluating the cost-effectiveness analysis, the National Health Care Institute concludes that the pharmacoeconomic analysis is of sufficient methodological quality, and suitable for decision-making.
The marketing authorisation holder reports incremental cost-effectiveness ratios (ICERs) of €190,993 per QALY gained with respect to the standard treatment. At a reference value of €80,000 per QALY, brexu-cel is not cost-effective compared to the standard treatment.
In the base case analysis, the marketing authorisation holder adopted a price that was higher than the current list price (€375,882.25 versus €360,000). The base case also includes the costs of leukapheresis for patients who are not ultimately given brexu-cel. If the ICER outcome of €190,993 per QALY is adopted, as derived from the base case, the price of brexu-cel should be reduced by 75% to bring it below the maximum reference value of €80,000.

The National Health Care Institute believes that a more realistic ICER estimate would be obtained if, in addition to the population who received brexu-cel, the 6 patients who were included in the study but did not receive brexu-cel were also included. Based on this more realistic scenario, which includes the actual list price, the National Health Care Institute arrives at an ICER of €201,686 per QALY. Based on that calculation, the price of brexu-cel should be reduced by at least 80% to bring it under the maximum reference value of €80,000 per QALY.

Final conclusion

Brexucabtagene autoleucel (Tecartus®) meets the established medical science and medicalpractice in the treatment of adult patients with recurrent or refractory mantle cell lymphoma (r/r MCL) after two or more lines of systemic therapy, including a Bruton's tyrosine kinase inhibitor (BTK inhibitor). The medicinal product has therapeutic added value compared to the comparative treatment, given that it extends the overall survival. The exact size of the effect remains uncertain. The National Health Care Institute advises you to include brexucabtagene autoleucel in the health insurance package for the specified indication. Based on the most realistic incremental cost-effectiveness ratio (ICER), the National Health Care Institute believes that a discount of at least 80% would be appropriate. The National Health Care Institute thereby recommends organising structural funding for setting up indication committees and data

collection in the context of cyclical package management of expensive medicines. Concentration of the care delivery is indicated in the context of providing appropriate care.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

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