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National Health Care Institute
Care
Medicinal Products

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Our reference
2022034729

Date 9 September 2022
Subject Package advice on the package lock medicinal product brexucabtagene autoleucel (Tecartus®)

Dear Mr Kuipers,

The National Health Care Institute advises you on the assessment of brexucabtagene autoleucel (brexu-cel, Tecartus®) 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 Brutons-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 advises you not to include brexu-cel in the basic health care package.

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 basic health insurance package from the perspective of the basic health care 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 brexu-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.

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 has been

[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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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 (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 and the establishment of risk mitigation measures, the National Health Care Institute considers the adverse effects of brexu-cel 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 (r/r MCL) after two or more lines of systemic therapy, including a Brutons-tyrosine kinase inhibitor (BTK inhibitor), and has therapeutic added value compared to the comparative treatment.

Budget impact analysis
The National Health Care Institute estimates that 33 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 a brexu-cel is €360,000. The total costs per patient per year amount to €391,115.67 (these costs include treatment with conditioning chemotherapy, bridging chemotherapy, treatment of side effects and possible re-treatment).
This results in costs of between €10.6 and €11.4 million in the third year. There is uncertainty about the number of patients with r/r MCL who will actually be treated with brexu-cel.

Pharmaco-economic analysis
The cost-effectiveness analysis provided by the marketing authorisation holder is of insufficient quality, despite the fact that the marketing authorisation holder has been given the opportunity to improve it.
The National Health Care Institute is of the opinion that the methodology of the cost-effectiveness analysis does not match the reference framework (Economic Evaluations guideline), and that there is a bias in the assumptions and a lack of evidence to substantiate the assumptions made in the pharmaco-economic analysis. The cost-effectiveness model is based on cure. However, the National Health Care Institute has decided that with the data the cost-effectiveness model is based on (median follow-up of 26 months), recovery cannot be claimed. Proper implementation of new data with a longer follow-up duration (median 35.6

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months follow-up) in the model and the file is necessary for the assessment, but has not been carried out by the marketing authorisation holder.
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 you might conduct. This is essential for you and for the National Health Care Institute, because the reimbursement of brexucel 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 advises you not to include brexucabtagene autoleucel (Tecartus®) in the basic health care 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