Zorginstituut Nederland

> Return address PO Box 320, 1110 AH Diemen

To the Minister of Health, Welfare and Sport
P.O. Box 20350
2500 EJ THE HAGUE

2025014721

National Health Care Institute
Research, Development and Medicinal Products
Medicinal Products Team

Willem Dudokhof 1
1112 ZA Diemen
PO Box 320
1110 AH Diemen
www.zorginstituutnederland.nl
info@zinl.nl

T +31 (0)20 797 85 55

Contact
Ms N. Stam
warcg@zinl.nl

Our reference
2025014721

Date 25 June 2025
Re: Advice on lock procedure medicinal product axicabtagene ciloleucel (Yescarta®) for follicular lymphoma

Dear Ms Jansen,

The National Health Care Institute advises you on the assessment of axicabtagene ciloleucel (axi-cel, Yescarta®) for the treatment of follicular lymphoma after three or more previous systemic treatments lines. The reason for this advice was the placement of axi-cel in the lock procedure for expensive medicinal products.

The National Health Care Institute advises you to not include axi-cel for the treatment of follicular lymphoma after three or more previous systemic treatments in the basic healthcare package.

Follicular lymphoma (FL) is a form of lymph node cancer. The disease typically develops in a lymph node, but can also occur in other parts of the lymphatic system, such as the spleen, liver, or bone marrow. FL usually develops slowly and patients often respond well to treatments. Sooner or later, there is often a recurrence of the disease. Patients may also not respond at all or not respond fully to treatment (refractory). In the Netherlands, approximately 550 people per year are diagnosed with FL. A small number of these could be considered for axi-cel treatment after receiving 3 or more prior treatment lines. The disease is most common in the elderly; the average age of diagnosis is 65 years. The 5-year survival rate of patients with FL is approximately 90%. In the Netherlands, patients are currently being treated with rituximab-based treatments and allogeneic stem cell transplantation (alloSCT).

Registered indication
Axi-cel (Yescarta®) is indicated for the treatment of adult patients with recurrent or refractory (r/r) FL after three or more lines of systemic therapy.

Axi-cel is also registered for use in certain patients with diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBL) and primary mediastinal large B-cell lymphoma (PMBCL). Axi-cel is already being reimbursed for these indications.

National Health Care Institute
Research, Development and Medicinal Products
Medicinal Products Team

Date
25 June 2025

Our reference
2025014721

Claim by the marketing authorisation holder
Axi-cel (Yescarta®) has added value over standard treatment in the registered FL indication, including rituximab monotherapy, rituximab combination therapy and alloSCT.

Package advice

The National Health Care Institute recommends that axi-cel for adult patients with r/r FL after three or more lines of systemic therapy should not be included in the basic healthcare package. The National Health Care Institute has established that axi-cel does not meet the legal criterion of 'established medical science and medical practice' for this indication.

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) advises the National Health Care Institute on the (scientific) basis and the conclusion of the assessment. Stakeholders are consulted during the process.

Since axi-cel does not meet the legal criterion of 'established medical science and medical practice' for the above indication, an integral weighting of the four package criteria and advice by the Package Advisory Committee (ACP) is not warranted.

Substantive assessment
Effectiveness
Established medical science and medical practice
In a subset of the single-arm, phase 2 ZUMA-5 study, researchers studied axi-cel after three or more prior treatment lines in patients with FL. Given the single-arm study design, an indirect comparison is required. A weighted indirect comparison was published with the SCHOLAR-5 cohort, in which retrospective data were available from patients treated with standard of care. Based on this published indirect comparison, no reliable statement can be made at present about the relative effectiveness of axi-cel compared to standard treatment. Although the results from the indirect comparison seem numerically convincing, it is very

[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] Healthcare cost-effectiveness report (2024) 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, the support base, ethical and legal aspects, budget impact, etc. See the report on real-world package management 4 (2023).

National Health Care Institute
Research, Development and Medicinal Products
Medicinal Products Team

Date
25 June 2025

Our reference
2025014721

uncertain whether axi-cel actually provides a survival benefit. This is due, in part, to the short follow-up of the studies (of both ZUMA-5 and SCHOLAR-5) and the high degree of uncertainty surrounding the validity of the chosen control cohort. SCHOLAR-5 has the shortest median OS compared to the available data of other control cohorts, possibly due to a short follow-up. The physicians' association has indicated that no control cohort is well-aligned with Dutch practice. Additionally, no statement can be made about the effect of axi-cel on quality of life, as this has not been measured in the study. However, it is clear that treatment with axi-cel is associated with serious adverse effects.

As it is unclear whether this treatment prolongs a patient's life, and measurements did not show that the quality of life is improved or deteriorated by the treatment, and it is clear that treatment is associated with serious adverse effects, the National Health Care Institute, as advised by the Scientific Advisory Board (WAR), concludes that axi-cel for this indication does not meet the established medical science and medical practice. Longer-term data of the ZUMA-5 study is expected to be published later this year. The National Health Care Institute invites the marketing authorisation holder to submit a new reimbursement file in the context of a reassessment at that time.

Should you need any further information, please do not hesitate to contact us. The pharmacotherapeutic report is attached.

Yours sincerely,

M.J. Janssen
Chairperson of the Executive Board