National Health Care Institute

> Return address PO Box 320, 1110 AH Diemen

Minister of Medical Care
PO Box 20350
2500 EJ THE HAGUE

2024020325

National Health Care Institute
Care
Medicinal Products

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 M. de Vries
warcg@zinl.nl

Our reference
2024020325

Date 29 May 2024
Subject Package advice for axicabtagene ciloleucel (Yescarta®) for the treatment of lymphoma

Dear Ms Dijkstra,

The National Health Care Institute is advising you about the evaluation of axicabtagene ciloleucel (Yescarta®; hereinafter also "axi-cel") for the treatment of lymphoma. The reason for this advice was axicabtagene ciloleucel being placed in 'the lock procedure for expensive medicinal products'.

Registered indication
Axi-cel is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

Claim by the marketing authorisation holder
Axi-cel has added therapeutic value when treating relatively fit adult patients (as per the inclusion criteria of the ZUMA-7 study) with DLBCL or HGBL that relapses within 12 months from completion of first-line chemoimmunotherapy or that is refractory to it.

Package advice
The National Health Care Institute recommends that you include axi-cel in the basic insured package for fit adults with DLBCL or HGBL, that relapses within 12 months of first-line chemoimmunotherapy or is refractory to it and who are eligible for autologous stem cell transplantation in the second line, provided the net price can be reduced by at least 20% after successful price negotiations. The National Health Care Institute has established that axi-cel meets the legal criterion of 'established medical science and medical practice' for the above indication and that there is added therapeutic value compared to the standard treatment, including autologous stem cell transplants.

We have explained 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.

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

Background

Axi-cel is one of the chimeric antigen receptor (CAR) T-cell therapies already reimbursable for treating adult patients with recurrent or refractory DLBCL or primary mediastinal large-cell B-cell lymphoma (PMBCL), after 2 or more lines of systemic therapy (third-line treatment). CAR-T comprises personalised immunotherapy aimed at stimulating patients' own immune systems in cases of haematological tumours, to let them recognise and eliminate cancer cells. It is a form of gene therapy (modification of the DNA of the T cells) and is in principle a one-time treatment.

Diffuse large-cell B lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) are aggressive non-Hodgkin lymphomas (lymph node cancers). They are malignant conditions that arise in the lymphatic system due to proliferation of mature B cells (white blood cells responsible for producing antibodies). DLBCL and HGBL are both subtypes of large B-cell lymphoma (LBCL). DLBCL is the most frequent form of LBCL (accounting for 80% of cases). The median age at diagnosis of DLBC is 70. Almost 65% of patients are aged 65-plus when diagnosed. With current treatments, the five-year survival at diagnosis is roughly 64%. The profession sees potential for axi-cel treatment in patients with refractory/recurrent DLBCL (recurring after ≤12 months). For patients who do not respond to the initial chemotherapy (are refractory) or in whom the cancer has returned within one year of treatment (recurring after <1 year), the prognosis is much poorer. According to the guideline, the median survival of patients with primary refractory disease in whom treatment is initiated in the second line is only 6.3 months.

In the Netherlands, the standard second line of treatment (standard of care) consists of salvage chemotherapy/chemoimmunotherapy and – in patients who achieve remission – high-dose chemotherapy (carmustine, etoposide, cytarabine, melphalan) followed by autologous stem cell transplantation.

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

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Comprehensive weighting of package criteria

Effectiveness

Established medical science and medical practice

A phase-3 randomised trial (ZUMA-7) was conducted in the second-line setting in patients with R/R DLBCL (≤12 months) who were eligible for autologous stem cell transplantation, in which axi-cel was compared directly against standard treatment (including stem cell therapy). This study shows that axi-cel has a clinically relevant benefit on the crucial endpoints of survival and quality of life (at day 100) compared to the standard treatment.

After a median follow-up of 47.2 months, 45.6% of patients treated with axi-cel had died compared to 53.1% in the group given the standard treatment. In the arm with axi-cel, the median survival had not been reached by 47.2 months (95% CI: 26.6, not achieved). In the arm with the standard treatment, the figure was 31.1 months (95% CI: 17.1, not achieved). Given that axi-cel is already a treatment option in the third line, patients from the standard treatment arm could still be given a CAR-T such as axi-cel after failure. After a median follow-up of 24.9 months, this was already the case for more than half the patients. This means that the ZUMA-7 study showed that using axi-cel in the second line compared to deferring treatment with axi-cel until the third line results in an absolute reduction in mortality of 7.5% after a median follow-up of 47.2 months.

It is unclear whether axi-cel results in more or fewer severe side effects (such as cytokine release syndrome or encephalopathy). Serious adverse effects occurred in 95 out of 170 patients (56%) treated with axi-cel and in 78 out of 168 patients (46%) treated in the control group. This difference is not statistically significant. Axi-cel additionally resulted *inter alia* in a clinically relevant beneficial effect on the quality of life at day 100. However, the evidence for this is low quality.

Based on the above, the National Health Care Institute concludes that axicabtagene ciloleucel (axi-cel) meets the criterion of established medical science and medical practice when used in fit adults with DLBCL or HGBL whose cancer recurs within 12 months of first-line chemoimmunotherapy or is refractory to it and who are eligible for autologous stem cell transplantation according to the inclusion criteria of the ZUMA-7 study. There is added value compared to the standard treatment, SOC (including ASCT).

The professional group has indicated that *all patients who are fit enough for CAR-T in the second line* should be eligible for axi-cel treatment. This therefore concerns a broader positioning than the marketing authorisation holder's reimbursement request/claim, which explicitly asks for reimbursement for *patients who meet the inclusion criteria of the ZUMA-7 trial* and are therefore eligible (fit enough) for stem-cell therapy. The National Health Care Institute has weighed up the arguments of the profession extensively but cannot reach the same opinion on the established medical science and medical practice for this group.

Cost-effectiveness

The National Health Care Institute concludes that the pharmacoeconomic analysis is of sufficient quality and that the outcomes of the analysis are sufficient for decision-making. The ICER calculated by the marketing authorisation holder is €60,844 per QALY. However, the National Health Care Institute’s opinion is that the ICER is closer to €65,910 per QALY, when the average age of the population (57.2) is adjusted to 60 years, which is more representative for the Dutch patient

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population. Assuming an ICER of €60,844 per QALY as calculated by the marketing authorisation holder, the price of axi-cel would have to be decreased by at least 15% to take it below the relevant reference value of €50,000. Assuming an ICER of €65,910 per QALY as calculated by the National Health Care Institute, the price would have to be decreased by at least 20% to take it below the relevant reference value of €50,000.

Budget impact analysis
The National Health Care Institute estimates that 65 patients will be treated with axi-cel annually for this indication by year 3 after inclusion in the benefit package. The asking price for the one-off axi-cel treatment is €327,000 per patient. The reimbursement of axi-cel will be associated with additional costs estimated at about €19.5 million in the third year. Taking account of substitution of autologous stem cell transplantation (which is not covered by the budget for medicinal products), the budget impact in the third year is €18.8 million.

Appropriate care
The Netherlands is restrictive in applying CAR-T treatment. There is a national registry and a national CAR-T tumour board is used for selecting patients. As a result, there is much confidence that the treatment is being applied appropriately. The profession will use axi-cel protocols in the third line, as it does now in the second line, with all patients being discussed in the tumour board. The National Health Care Institute endorses this appropriate use.

Conditional inclusion
Axi-cel has not been proved to be effective care for the broad positioning 'not fit for autologous stem cell transplantation but fit for CAR-T' and is therefore not appropriate care. For orphan drugs, *conditionals* and *exceptionals* that do not (yet) meet the legal criterion 'established medical science and medical practice' due to insufficient evidence, there is a conditional inclusion (CI) arrangement.[6] Axi-cel may meet the criteria for this CI scheme for the said indication. The stakeholders concerned can submit a request to the National Health Care Institute for an exploratory interview.

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).

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board

[6] Procedure for initiating conditional inclusion of orphan drugs, conditionals and exceptionals (2023). National Health Care Institute, Diemen. Via www.zorginstituutnederland.nl