Axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with recurring or refractory diffuse large-cell B-cell lymphoma (DLBCL) and primary mediastinal large-cell B-cell lymphoma (PMBCL)

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 7 March 2019

Zorginstituut Nederland carried out an assessment of the medicinal product axicabtagene ciloleucel (Yescarta®), whereby the conclusion was as follows.

Zorginstituut Nederland has completed its assessment of axicabtagene ciloleucel (Yescarta®) for the treatment of adult patients with recurring or refractory diffuse large-cell B-cell lymphoma (DLBCL) and primary mediastinal large-cell B-cell lymphoma (PMBCL). The Minister of Health Welfare and Sport (VWS) has placed axicabtagene ciloleucel (axi-cel) for this indication in the "waiting room" or "sluice" for expensive drugs.

The *Zorginstituut* has assessed axi-cel based on the four package criteria[1] effectiveness,[2] cost-effectiveness,[3] necessity and feasibility. This letter is to inform the Minister about the results of our integral assessment of these package criteria. Assessing from the perspective of the basic package which is paid from collective premiums, the *Zorginstituut* looks at whether new care is better than what is currently available. In doing this we look at the degree of certainty that this will be achieved, both from a scientific perspective, and in terms of societal support. The *Zorginstituut* was advised by two independent committees: the Scientific Advisory Board (WAR) which examines the data on established medical science and medical practice and determines the cost-effectiveness, and the Insured Package Advisory Committee (ACP) which considers the societal assessment. Interested parties are also consulted during the process.

Integral consideration of the package criteria and package advice

Axi-cel fulfils the statutory criterion 'established medical science and medical practice' for the above-mentioned indication.

Axi-cel is a personalised immunotherapy whose purpose is to stimulate the immune system of patients with haematological tumours to recognise and eliminate cancer cells. It is a gene-therapeutic treatment (changing the DNA of the body's own T-cells), in principle a one-off treatment. The therapy is intended for a sub-group of cancer patients with a high burden of disease (0.83 on a scale of 0-1), partly because no further effective treatment is available for this sub-group of patients and as a result only 17% will still be alive after one year.

A single infusion of axi-cel leads to an estimated median survival of 11.1 months in comparison with the usual treatment. Although this estimated survival gain is uncertain due to the indirect comparison, the estimated effect of axi-cel is well within the norms for clinical relevance. As a result, it seems very unlikely that the actual difference in survival is smaller than what is regarded as clinically relevant. This conclusion is also supported by a recent publication showing that about 50% of the patients are still alive after two years.

[1] Package Management in Practice 3 (2013). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[2] Assessment of Established Medical Science and Medical Practice: updated version (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

[3] Cost-effectiveness report (2015). Zorginstituut Nederland, Diemen. Via www.zorginstituutnederland.nl

The administration of axi-cel is associated with a high risk of severe unintended effects. These seem acceptable, however, in view of the severity of the disorder and the fact that it is treatable.

A single infusion of axi-cel costs €327,000 (including conditioning chemotherapy). As the estimated number of patients varies, the *Zorginstituut* has calculated a 'low' and a 'high' scenario (in the event of rapid certification of treatment centres) for budget impact. With the low scenario (with 90 patients), the additional costs 3 years after its introduction are €29.3 million compared with treatment using existing products. With the high scenario (with 135 patients), this is €43.9 million. Uncertainty exists about several aspects, such as: numbers of patients, the spread of patients over various lines of treatment and market penetration (based on, e.g. certification procedures and capacity of treatment centres).

We note that various studies are currently examining the effectiveness of axi-cel for new indications. This means the budget impact could increase considerably in the future. Two of the studies are examining use in an earlier line of treatment for DLBCL, i.e., after first-line systemic therapy, instead of second-line.

The *Zorginstituut* concluded that the methodological quality of the analysis of cost-effectiveness supplied by the manufacturer is inadequate. The model used is less suitable due to the lack of sufficient data on survival in the long term. What we can say is that when using standard methods for survival analyses, the ICER is very uncertain and varies from €46,048/QALY to as much as €600,262/QALY (or even dominance of the standard treatment, i.e., the standard treatment is cheaper and more effective).

As there is currently a lack of sufficient data on survival in the longer term, cost-effectiveness cannot be estimated reliably. However, it is highly likely that the actual ICER of axi-cel will exceed the relevant reference value that applies to this severe disease, i.e. €80,000/QALY. For this reason we advise the Minister not to include axi-cel in the insured package unless a price reduction can be agreed. We cannot say, however, by what percentage the price should fall in order to facilitate cost-effective deployment. Due to uncertainty about the long-term effect, and because it involves a one-off treatment, a pay-for-performance agreement would seem a good option. Particularly because the medical specialists have indicated that they will set up a national tumour board and follow patients via existing registers of the IKNL and the EBMT in the event of acceptance into the insured package. We suggest that the Minister considers coupling the level of the reimbursement to certainty about the effect in the long term. We also advise the Minister, when making agreements about the duration of a price arrangement, to take into account the possible arrival of competing drugs, so that health care insurers can take this into account in their purchasing policy.

Having listened to the ACP, the *Zorginstituut* emphasises that axi-cel should already become available during the negotiation period. After all, it is an effective therapy, that may even be curative for some patients.

Evaluation

If axi-cel is accepted into the insured package based on the outcome of price negotiations, the *Zorginstituut* will actively monitor its use. The *Zorginstituut* plans to inform the Minister in 2022 about the results of these measurements. We will do that based on data maintained by the medical professional group in a(n)

(international) register, whereby *Zorginstituut Nederland* will pay attention to the following points:

- The extent to which the originally estimated number of patients agrees with the number of patients actually treated;
- Cost developments relative to the original estimation, part of which is formed by monitoring the actual price of axi-cel;
- Care consumption with a view to assessing the points of departure for appropriate use.

If this monitoring indicates strong discrepancies from the current estimates, this can form a reason for the *Zorginstituut* to reassess axi-cel's position.

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The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.