Tisagenlecleucel-T(Kymriah®) for the treatment of ALL

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 18 December 2018

Zorginstituut Nederland carried out an assessment of the medicinal product tisagenlecleucel-T (Kymriah®), whereby they came to the following conclusion.

On 5 September 2018 the Minister of VWS asked the *Zorginstituut* to issue advice on the pharmaceutical product, tisagenlecleucel-T (Kymriah®), in connection with its being made subject to article 2.1 of the Health Insurance Regulation (also known as being placed in the 'waiting room' or 'sluice'), due to its expected high costs. Products can only be accepted into the insured package after the *Zorginstituut* has advised on their inclusion in the insured package and, where applicable, subject to Ministry negotiations to arrive at a financial arrangement with the supplier.

The Minister placed tisagenlecleucel in the waiting room for two indications:

1 Paediatric and young adult patients up to the age of 25 years with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or later relapse (hereafter referred to as r/r B cell ALL)
2 Adult patients with a relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

Zorginstituut Nederland has in the meantime completed its assessment of tisagenlecleucel for the first indication, r/r B cell ALL. Its advice on the second indication, DLBCL, will follow in the course of 2019.

This letter describes the *Zorginstituut*'s advice in relation to r/r/ B cell ALL. In making this assessment, advice was requested from the Scientific Advisory Board (WAR) of the *Zorginstituut*. Interested parties were also consulted during the assessment procedure.

***Zorginstituut*'s findings**

Nature of the treatment
Tisagenlecleucel is an autologous immunocellular cancer therapy. In order to produce tisagenlecleucel, patients' own T cells have to be obtained via leukapheresis. These cells are subsequently genetically modified, *ex vivo*, by using a lentiviral vector encoding an anti-CD19 chimeric antigen receptor (CAR). After the patient has undergone pre-treatment with lymphodepleting chemotherapy, his/her own (autologous) CAR-T cells (tisagenlecleucel) are returned to the patient via intravenous infusion.

Established medical science and medical practice?
Tisagenlecleucel fulfils the criterion established medical science and medical practice in relation to the treatment of paediatric and young adult patients up to the age of 25 years with r/r B cell ALL. A single infusion of tisagenlecleucel leads to an estimated median survival of 11.9 months in comparison with the usual treatment with blinatumomab. Uncertainty exists about the size of this effect because it is based on an indirect comparison and marginal comments were made about the study set-up. However, it is unlikely that the actual difference in

survival will be smaller than 3 months. We therefore regard the effect of tisagenlecleucel on survival as clinically relevant. Factors that help support this conclusion are:

- long median survival (at least 11.9 months longer than previously reported in the literature) during treatment with tisagenlecleucel in a population with a very unfavourable prognosis who received powerful pre-treatment;
- the observation that in 100% of the complete responses one could also speak of a complete 'minimal residual disease' (MRD) response (in comparison with 51% in the blinatumomab study). This is an important factor, because a complete MRD response is a strongly prognostic factor, associated with survival gains.

Both tisagenlecleucel and blinatumomab (possibly followed by a stem-cell transplant) are associated with a high risk of severe unintended effects. The unintended effects seem acceptable in view of the severity of the disorder, and the treatability of the severe unintended effects.

Cost aspects
The *Zorginstituut* estimates that annually ca. 9 patients will actually be treated with tisagenlecleucel if it is included in the insured package. The total costs per patient, per treatment with tisagenlecleucel, amount to €320,000. The costs for conditioning chemotherapy amount to €517.00.

The added costs of tisagenlecleucel (Kymriah®) tisagenlecleucel (Kymriah®) in comparison with the usual treatment with blinatumomab for treating r/r B cell ALL amount to about €1.8 million when only the costs of pharmaceutical products are taken into account, and €2.1 million if additional costs for administration and monitoring are also taken into account. This involves uncertainty about possible off-label use and the exact costs involved in administering the product and monitoring the patient.

If the costs of allogenic bone marrow transplant (SCT) are taken into account, the annual added costs of tisagenlecleucel amount to €1.8 million, because the medical professionals estimate that the percentage of patients that receives allogenic SCT after tisagenlecleucel will be lower than after the usual treatment with blinatumomab (10% versus 30%).

As the expected budget impact is low, and under the *Zorginstituut*'s lower limit for the obligatory pharmacoeconomic analysis, cost-effectiveness for this indication was not determined.

Appropriate use
The Minister also asked the *Zorginstituut* to discuss agreements on appropriate use. At a scoping meeting on 28 March 2018, the parties indicated that they would follow the use of CAR-T products, such as tisagenlecleucel, and register them via existing IKNL and EBMT registers. As the treatment costs per patient will be high, the *Zorginstituut* will conclude an orphan drug arrangement and an orphan drug arrangement and carefully monitor and evaluate its use.

***Zorginstituut*'s conclusion**
For the indication acute B cell lymphoblastic leukaemia, tisagenlecleucel complies with established medical science and medical practice. Including it in the package for this indication will have limited budget impact. As a result, it is eligible for inclusion in the standard health care benefit package. We will conclude an orphan drug arrangement and, due to the high treatment costs per patient, we will evaluate its use once it has been included in the insured package.

As already mentioned, we will send our assessment of the use of tisagenlecleucel for the indication DLBCL early in 2019. We also note that various studies are currently examining the effectiveness of tisagenlecleucel on other indications. In other words, future expectations are that tisagenlecleucel will be used more broadly. The budget impact of this product can therefore grow considerably in the future. When we determine the cost-effectiveness of tisagenlecleucel for one of the future indications, we will take the product to the Insured Package Advisory Committee (ACP) for complete package advice.

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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.