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2022000878

Our reference
2022000878

Date 25 January 2022
Subject Package advice for the lock procedure drug tisagenlecleucel (Kymriah®)

Dear Mr Kuipers,

The National Health Care Institute is hereby advising you about the lock procedure drug tisagenlecleucel (tisa-cel, Kymriah®) for the treatment of patients with relapsing or refractory (r/r) diffuse large B-cell lymphoma (DLBCL, a specific form of lymphoma) after two or more lines of systemic therapy. The reason for this opinion is a reassessment based on newly published data for the above-mentioned indication.

The National Health Care Institute has concluded that tisa-cel, an anti-CD19 CAR-T cell therapy, meets the legal criterion of 'established medical science and medical practice' in patients with r/r DLBCL. The National Health Care Institute has determined that the therapeutic value of this medicine is comparable to that of the medicine axicabtagene ciloleucel (axi-cel, Yescarta®), which is already reimbursed. Both treatment options have a clinically relevant effect on overall survival. A second anti-CD19 CAR-T drug, tisa-cel, offers flexibility and an option to choose the most rapidly available CAR-T cell therapy; this may be critical for the r/r DLBCL population in question, given the unfavourable prognosis.
We advise you to include tisa-cel in the basic health care package, provided that price negotiations with the marketing authorisation holder successfully deliver a net price that does not exceed that of axi-cel. We would like to point out that the Insured Package Advisory Committee has recommended that the price for a treatment should be reduced when several drugs are available for the same indication.

General

At your request, the National Health Care Institute assesses whether new care should be part of the basic health insurance package, and makes a decision based on the basic insured package paid from joint premiums. We take into consideration the degree of certainty that this will be achieved, both in the scientific sense, as well as in terms of public support, and we consider the efficiency and transparency aspects. The National Health Care Institute assessed

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tisa-cel on the basis of the four package criteria[1]: effectiveness[2], cost-effectiveness[3], necessity and feasibility. The National Health Care Institute takes advice on this from the Scientific Advisory Board (WAR) regarding the review of established medical science and medical practice and for cost-effectiveness, and by the Insured Package Advisory Committee for the social assessment. We also consulted stakeholders during the assessment process.

Integral weighting of package criteria

Established medical science and medical practice
Tisa-cel is indicated for the treatment of:

- paediatric and young adult patients up to age 25 with refractory B-cell acute lymphoblastic leukaemia (r/r B-cell ALL), with a recurrence after transplantation or with a second or later recurrence of B-cell ALL;
- adult patients with recurring or refractory diffuse large cell B-cell lymphoma (r/r DLBCL) after two or more lines of systemic therapy.

In 2018, the National Health Care Institute ruled that tisa-cel meets the criterion of established medical science and medical practice for the first indication, r/r B-cell ALL.
At the time, the National Health Care Institute also ruled that tisa-cel did not meet the criterion of established medical science and medical practice for the second indication, r/r DLBCL after two or more lines of systemic therapy. The National Health Care Institute deemed the effect of tisa-cel on survival gain too uncertain. Important points of criticism were the as yet immature data on overall survival, uncertainty about the standalone effect of tisa-cel compared to the effect of bridging therapy, and the large dropout rate among patients after inclusion in the study but before tisa-cel administration.

The above-mentioned criticisms have been refuted by newly published long-term data from the tisa-cel registration study (JULIET study; median follow-up of 40 months). That study concludes that administering tisa-cel results in a clinically relevant effect on overall survival, with a significant proportion of patients with r/r DLBCL after two or more lines of systemic therapy being cured. The chances of survival through to 12, 24 and 36 months after administering tisa-cel are 48, 40 and 36 per cent respectively.
Compared to the historical control cohorts (treatment with salvage chemotherapy followed if possible by stem cell transplantation) and over a median follow-up duration of 40 months, the risk of death after administering tisa-cel was reduced by 34% (HR [hazard ratio] 0.66; 95% CI [confidence interval]: 0.49 – 0.89) to 44% (HR 0.56; 95% CI: 0.43 – 0.74), with an increase in median survival of 5.8 months.
The conclusion based on the new data is that bridging therapy is widely used in practice and that it is unlikely that the use of bridging therapy alone is responsible for the observed long-term effect on overall survival. Moreover, the feasibility of administering tisa-cel appears to be better in practice than in the JULIET study:

[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

up to 87% were able to receive tisa-cel as opposed to just 67% in the JULIET study.

The standard treatment nowadays for patients with r/r DLBCL after two or more lines of systemic therapy consists of axicabtagene ciloleucel (axi-cel, Yescarta®), which is also an anti-CD19 CAR-T cell therapy. This is why an indirect comparison was made between tisa-cel and axi-cel in the reassessment.

After administration of axi-cel (the ZUMA-1 study), as with tisa-cel, a plateau is observed for overall survival (survival to 12 and 24 months after infusion is 59 and 51 per cent respectively). Both anti-CD19 CAR-T cell therapies, tisa-cel and axi-cel, therefore have a clinically relevant effect on overall survival.
Differences in study design make an accurate indirect comparison between the effects of tisa-cel and axi-cel on overall survival more awkward. The conclusion is that the study population in the JULIET study with tisa-cel seems to have been more representative of practice than the study population in the ZUMA-1 study with axi-cel.

The serious, intervention-related, adverse effects appear to be similar for the two drugs.

The moment of apheresis is different for the two anti-CD19 CAR-T cell therapies. A second anti-CD19 CAR-T drug, tisa-cel, offers flexibility and an option to choose the most rapidly available CAR-T cell therapy; this may be critical for the r/r DLBCL population in question, given the unfavourable prognosis.

Budget impact
It is expected that 64 patients will have been treated with tisa-cel 3 years after inclusion in the package. The total cost per patient of treatment with tisa-cel comes to €320,454.04 (list price €320,000 + conditioning chemotherapy €454.04). The cost per patient for treatment with axi-cel comes to €327,483.63 (list price €327,000 + conditioning chemotherapy €483,63).
Including tisa-cel in the Medicine Reimbursement System (GVS) comes with additional costs. The level of those additional costs cannot be determined by the National Health Care Institute because the net price is unknown. Financial arrangements have been made for axi-cel, the treatment being compared, so its actual price is lower than the list price used.

Cost-effectiveness
Because of the similarities in effectiveness (equal therapeutic value) of tisa-cel and axi-cel, the National Health Care Institute has not carried out a cost-effectiveness analysis.

Appropriateness
Patients with r/r DLBCL in the Netherlands are treated according to a national treatment protocol in treatment centres that are qualified for CAR-T cell treatment. Every patient who is eligible for treatment with axi-cel and tisa-cel is discussed by the Dutch CAR-T tumour board.
They are also registered in the EBMT database (of the European Group for Blood and Marrow Transplantation, as required by the EMA upon registration) and a national register.

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Final conclusion

The National Health Care Institute recommends that you should include tisagenlecleucel (tisa-cel, Kymriah®) in the health insurance package for treating adult patients with recurrent or refractory diffuse large-cell B-cell lymphoma (r/r DLBCL) after two or more lines of systemic therapy, provided that the net price does not exceed the net price of the existing treatment with axicabtagene ciloleucel after successful price negotiations with the marketing authorisation holder. As the value is equal when compared to axi-cel, which is already being reimbursed, and there are no indications that either product is preferable to the other, we advise you to take the existing discount on axicabtagene ciloleucel into account during the price negotiations. We would like to point out that the Insured Package Advisory Committee has recommended that the price for a treatment should be reduced when more resources are available.

Yours sincerely,

Sjaak Wijma
Chair of the Executive Board