SUMMARY

axicabtagene ciloleucel

YESCARTA 0.4 - 2 x 10^8 cells

dispersion for infusion

Reassessment at the request of the TC

Original French opinion adopted by the Transparency Committee on 6 September 2023

The legally binding text is the original French opinion version

Transparency Committee's conclusions

Clinical Benefit

- Large B-cell lymphomas, including diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMLBCL) are aggressive non-Hodgkin lymphomas with an unfavourable prognosis in the event of multiple relapses and disease refractory to at least two treatment lines, as reported by patient and user associations.
- YESCARTA (axicabtagene ciloleucel) is a curative treatment for relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy.
- The new data available are not of a nature to modify the Committee's previous conclusions. The efficacy/adverse effects ratio of YESCARTA (axicabtagene ciloleucel) remains high in the short and medium term and is still to be determined in the longer term, particularly in terms of maintenance of clinical remission and achievement of full recovery.
- There are therapeutic alternatives (see section 05 of this opinion).
- YESCARTA (axicabtagene ciloleucel) remains a third or later-line treatment, in relapsed or refractory patients, in good general condition, with a life expectancy and disease progression compatible with the waiting time before administration.

- **Public health benefit**

Considering:

- the seriousness of the disease, particularly in relapsed or refractory patients after two or more lines of systemic therapy, which is life-threatening in the short term, as reported by patient and user associations,
- its prevalence,
- the inadequately met medical need at this stage of the disease prior to the arrival of CAR-T cell-based medicinal products,
- the partial response to this need, due to:
  - the additional impact on morbidity and mortality in the short and medium term, but which remains to be determined in the long term, particularly in terms of full recoveries;
  - the lack of demonstrated impact on quality of life in the absence of relevant data;
  - the limitations of the indirect comparisons, making precise quantification of the clinical effect difficult, and the limitations of indirect comparisons with KYMRIAH (tisagenlecleucel);
  - the long time frame between eligibility of patients and reinjection of CAR-T cells, estimated to be a median of 50 days based on real-world data, and persistent uncertainties with respect to the clinical consequences, in particular in terms of efficacy, of the different phases in the procedure (from eligibility to administration);
- the absence of an improvement in the care pathway of patients due to:
  - hospitalisations, including in the ICU (particularly during the first 10 days following infusion or in the event of the onset of early signs or symptoms of cytokine release syndrome and/or neurological effects), whereas the third and later-line treatment of lymphoma can be administered in an outpatient context in a day hospital,
  - hospitalisation of patients far from their homes,
  - the need to remain close to this hospital for monitoring for at least 4 weeks following infusion,
- the impact on the organisation of care:
  - accreditation of hospitals based on precise criteria,
  - close coordination between the various departments of centres authorised to treat patients with CAR-T cells (laboratories, internal pharmacy, clinical departments, etc.),

YESCARTA (axicabtagene ciloleucel) is unlikely to have an impact on public health, on the basis of currently available data.

Considering all these elements, the Committee deems that the clinical benefit of YESCARTA 0.4 - 2 x 10^8 cells (axicabtagene ciloleucel) dispersion for infusion remains substantial in "the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy" and at the MA dosages.

The Committee issues a favourable opinion for maintenance of inclusion of YESCARTA 0.4 - 2 x 10^8 in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the "treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy" and at the MA dosages.

Clinical Added Value

Considering:

- the updated data from the ZUMA-1 study, following a median follow-up of 63.1 months, which confirms the previously analysed results, particularly in terms of complete response (58% of patients in the mITT population, of whom 30% still in complete response at the time of the analysis after 60 months), and overall survival (median overall survival of 25.8 months in the mITT population; 5-year survival probability estimated to be 42.6%), in life-threatening clinical situations in which the treatment options are limited and do not enable remission to be envisaged,
- the role of YESCARTA (axicabtagene ciloleucel) compared to KYMRIAH (tisagenlecleucel), which remains difficult to determine given the major methodological limitations of the indirect comparison provided,
- the safety profile marked by significant short-term toxicity,
- additional experience with respect to the real-world data for YESCARTA (axicabtagene ciloleucel) in the French DESCAR-T registry (27 activated centres, 756 treated patients, median follow-up of 15 months since eligibility), which are consistent with the clinical data (ZUMA-1),
- and the initial uncertainties identified, which persist despite the Transparency Committee's requests, particularly with respect to:
  - the exact effect size compared to historic management, in the absence of any robust comparison,
  - maintenance of the clinical efficacy in the long term, particularly concerning achievement of full recovery for patients in lasting remission,
  - and the absence of long-term safety data,

the Committee considers that its previous conclusions are not liable to be modified. On the basis of currently available data, the Committee deems that YESCARTA 0.4 - 2 x 10^8 cells (axicabtagene ciloleucel) dispersion for infusion provides a moderate clinical added value (CAV III) in terms of efficacy compared to the historic management of relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after two or more lines of systemic therapy, based on various chemotherapies.