OPINION ON MEDICINAL PRODUCTS

ciltacabtagene autoleucel CARVYKTI 3.2 x 10^6 – 1.0 × 10^8 cells,

dispersion for infusion

First assessment

Adopted by the Transparency Committee on 23 November 2022

SUMMARY

The legally binding text is the original French opinion version

- **Multiple myeloma**
- **Sectors: Hospital**

Key points

Approval of reimbursement for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment.

Therapeutic improvement?

No therapeutic improvement.

Role in therapeutic strategy?

The therapeutic arsenal available for the treatment of multiple myeloma is extensive, including in particular:

- Alkylating agents, particularly used in the case of autologous transplants,
- Proteasome inhibitors (PI): bortezomib, ixazomib, carfilzomib
- Immunomodulators (IMIDs): thalidomide, lenalidomide, pomalidomide
- Anti-CD38 antibodies: daratumumab, isatuxumab

For symptomatic patients, the first-line treatment is dependent on whether the patient is eligible for intensive chemotherapy associated with autologous peripheral blood stem cell transplantation (APBSCT).

The first treatment line is standardised and associates: DARZALEX (daratumumab, anti-CD38 antibody) + IMID +/- PI. Melphalan (alkylating agent) and autologous stem cell transplantation may subsequently be proposed for eligible patients.

In the event of relapse or progression after the first-line treatment, the therapeutic decision is dependent on age, previous treatments, duration of the first remission, and the circumstances of the relapse, PBC availability, the patient's general state of health and comorbidities. Second-line and subsequent treatments are based on regimens associating IMID +/- PI +/- anti-CD38 antibody and dexamethasone.

For heavily pre-treated patients, a number of treatment options are available:

- For relapsed and refractory patients who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment, ABECMA (idecabtagene vicleucel, CAR-T) has been granted a marketing authorisation.
- For relapsed and refractory patients, who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment, TECVAYLI (teclistamab) has been granted a marketing authorisation.
- For patients who have received at least 4 previous treatments and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and one anti-CD38 monoclonal antibody, and whose disease progressed during the most recent treatment, BLENREP (belantamab mafodotin) has been granted a marketing authorisation. The Transparency Committee deemed it to be a secondary treatment when all treatment options have been exhausted, following a multidisciplinary review meeting opinion.
- For patients who have received at least four previous treatments and whose disease is refractory to at least two proteasome inhibitors, two immunomodulatory agents, and one anti-CD38 monoclonal antibody, and whose disease progressed during the most recent treatment, NEXPOVIO (selinexor) has been granted a marketing authorisation.

Role of the medicinal product:

CARVYKTI (ciltacabtagene autoleucel) is a 4th-line or subsequent treatment for relapsed and refractory multiple myeloma, among patients who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment.

Given the lack of methodologically robust comparative data, it is not possible to specify the role of CARVYKTI (ciltacabtagene autoleucel) in relation to the other therapeutic alternatives available.

Due to the time needed to make the product available (including the time to determine whether the patient is eligible for CAR-T cell treatment, leukapheresis, genetically-modified cell production, lymphodepleting chemotherapy until the patient is presented for reinjection) and the significant short-term toxicity, the general state of health and life expectancy of patients eligible for CARVYKTI (ciltacabtagene autoleucel) must be compatible with these time-frames.

The Committee also points out that:

- **considering the high frequency of grade ≥ 3 adverse events (100% of patients), in particular with cytokine release syndrome, neurological adverse effects and potential admissions to intensive care, and the constraints associated with the need for long hospital stays and the possible distance from the qualified centre, it is crucial that patients receive information on these constraints and the risks involved,**
- **CARVYKTI (ciltacabtagene autoleucel) must be administered in a healthcare organisation specifically qualified for the use of CAR-T cells,**
- **the summary of product characteristics (SPC) and the risk management plan (RMP) must be adhered to, and special monitoring during and after treatment is required.**

Special recommendations

The use of CARVYKTI (ciltacabtagene autoleucel) is limited to a restricted number of centres qualified for the use of CAR-T cells, given the complexity of the procedure, as set out in the order of 19 May 2021. In this context, the Committee points out the importance of comprehensive care (particularly including travel and accommodation close to qualified healthcare organisation, where necessary) as reported by patient and user associations.

The Committee points out the importance, for patients and their caregivers where applicable, of having information tailored to the complexity of the CAR-T procedure, the constraints associated with long hospital stays, and the risks involved for the patient.

The Committee calls for commitment from all stakeholders to ensure that the uncertainties in this dossier are addressed by the time of its reassessment. In this aim, the Committee calls for the participation of all qualified centres of the required category in order to obtain high-quality and exhaustive observational data.

Committee's conclusions

Actual Clinical Benefit

- Multiple myeloma is severe, life-threatening haemopathy.
- The proprietary medicinal product CARVYKTI (ciltacabtagene autoleucel) is a curative medicinal product.
- The efficacy/adverse effect ratio is significant.
- Therapeutic alternatives are available (see Section 05 of this opinion)
- CARVYKTI (ciltacabtagene autoleucel) is a fourth-line or subsequent treatment for relapsed and refractory multiple myeloma, among patients who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment.

Public health benefit

Considering:

- the severity of the disease and its incidence,
- the partially met medical need,
- the lack of response to the identified need,
- the lack of elements supporting a lack of deterioration of the care and/or life pathway, particularly considering the systematic hospitalisation for the first 14 days following infusion and the need for patients to remain close to the qualified healthcare organisation for at least 4 weeks post-infusion,
- the lack of data making it possible to assess its impact on the delivery of care, particularly considering the accreditation requirement for the healthcare organisations according to specific criteria and increased coordination between the different departments of centres authorised to administer CAR-T cells (laboratories, in-house pharmacy, clinical departments, etc.)

CARVYKTI (ciltacabtagene autoleucel) is not likely to have an impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of CARVYKTI (ciltacabtagene autoleucel) is significant in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and dosages.

Clinical Added Value

Considering:

- the efficacy data from a non-comparative phase 1/2 study, with an overall response rate of 83% [95%CI: 75-90] on the ITT population, in a life-threatening scenario,
- the uncertainties around the clinical relevance of the primary outcome measure selected (overall response rate) and its transposability to overall survival or improvement in quality of life,
- the uncertainties around the specific effect size of this treatment, considering the methodological weaknesses of indirect comparisons,
- the safety profile marked by significant short- and medium-term toxicity,
- the uncertainties around clinical efficacy and safety in the longer term,
- and despite the benefit of availing of a medicinal product that has been assessed after failure to respond to a previous treatment including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody,

the Transparency Committee deems that, based on the current data, and pending the findings of the CARTITUDE-4 randomised phase III study in particular, CARVYKTI (ciltacabtagene autoleucel), like ABECMA (idecabtagene vicleucel), provides no clinical added value (CAV V) for the treatment of adult patients with relapsed and refractory multiple myeloma, who have received at least three previous treatments, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody, and whose disease progressed during the most recent treatment.

HAS
HAUTE AUTORITÉ DE SANTÉ
Développer la qualité dans le champ sanitaire, social et médico-social