

# **CARVYKTI® (ciltacabtagene autoleucel)**

## **Category:**

Best Biotechnology Product

## **Company Name:**

Johnson & Johnson Services, Inc.

## **Product/Solution Name:**

CARVYKTI® (ciltacabtagene autoleucel)

## **Compound/Tech Name:**

ciltacabtagene autoleucel

## **Trade Name:**

CARVYKTI®

## **Corporate Name:**

Johnson & Johnson

## **Date of Approval:**

2022-02-28

## **Indications:**

Ciltacabtagene autoleucel (cilta-cel; CARVYKTI) is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR)-T cell therapy approved in the United States for the treatment of adult patients with relapsed/refractory multiple myeloma (RRMM) who have received at least 1 prior line of therapy, including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD), and are refractory to lenalidomide.

In the European Union, CARVYKTI has marketing authorization for the treatment of adult patients with RRMM, who have received at least 1 prior therapy, including a PI and an IMiD, have demonstrated disease progression on the last therapy, and are refractory to lenalidomide.

In Brazil, CARVYKTI is approved for the treatment of adult patients with multiple myeloma (MM), who previously received a PI and are refractory to lenalidomide, as well

as adult patients with RRMM, who previously received a PI, an IMiD, and anti-CD38 antibody.

In Switzerland, CARVYKTI is indicated for the treatment of adult patients with RRMM who have received at least 3 prior therapies, with at least a PI, an IMiD, and an anti-CD38 antibody, and have demonstrated disease progression on last therapy.

## **Therapeutic Areas:**

Oncology: multiple myeloma (MM)

## **General Information File Document upload:**

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## **Background information and need for drug / device:**

Multiple myeloma (MM), a hematologic malignancy, accounts for 1.8% of all newly diagnosed cancers in the United States. Most patients with MM will suffer disease relapse after each line of therapy (LOT), and unfortunately, the post-relapse treatment landscape is challenging as the disease quickly becomes nonresponsive to the major drug classes. For patients with heavily pretreated relapsed/refractory MM (RRMM), previous studies reported median progression-free survival of <6 months and median overall survival of ~1 year. Ciltacabtagene autoleucel (cilta-cel; CARVYKTI), a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy, led to deep and durable responses in heavily pretreated patients ( $\geq 3$  previous LOT) with RRMM in the phase 1b/2 CARTITUDE-1 trial. Long-term follow-up (median follow-up, 61.3 months) of the pivotal CARTITUDE-1 study in heavily pretreated RRMM (97% daratumumab refractory) confirmed that one-third (33%) of patients remained in remission for  $\geq 5$  years after a single CARVYKTI infusion without maintenance or subsequent therapy. Of these progression-free patients, 12 from a single center with serial minimal residual disease (MRD) assessments were all MRD- and imaging-negative at year 5 or later after CARVYKTI without additional therapy, showing profound long-term remission. Additionally, the potential for long-term remission was not limited to patients with standard-risk disease; patients with high-risk cytogenetics and those with extramedullary plasmacytomas were equally likely to be progression free. These results, combined with the median overall survival of 5 years seen in CARTITUDE-1, are remarkable given the historically dismal prognosis for this population with a median overall survival of ~1 year. No therapies currently approved for the treatment of triple-class exposed/refractory RRMM achieved similar outcomes; moreover, existing regimens typically require ongoing therapy and are often associated with relapses. CARVYKTI showed high efficacy and a manageable safety profile in the phase 3 randomized CARTITUDE-4 trial in patients with lenalidomide-refractory relapsed MM who were at earlier stages of their treatment journey (1-3 prior LOT). CARTITUDE-4 demonstrated that CARVYKTI is superior to established standard-of-care (SOC)

regimens in prolonging overall survival and progression-free survival. CARVYKTI significantly improved overall survival compared with SOC, with a 45% reduction in risk of death (hazard ratio [HR], 0.55 [95% CI, 0.39-0.79]; P=0.0009). CARVYKTI showed consistent overall survival and progression-free survival benefits vs SOC across prespecified subgroup analyses, including patients with standard- and high-risk cytogenetics, extramedullary disease, and 1 prior LOT and beyond, suggesting that CARVYKTI may overcome the poor prognosis associated with these high-risk features. Notably, CARVYKTI is the first and only CAR-T cell therapy to significantly extend overall survival vs SOC for patients with MM as early as second-line. Despite advancements in the MM therapeutic landscape in the 2 decades preceding the introduction of CARVYKTI, including several in the immediate years prior, improvements in clinical outcomes for patients with heavily pretreated RRMM remain limited. For patients as early as after first relapse, CARVYKTI offers the potential to achieve and maintain complete response for years. To date, more than 6,500 patients have been treated with CARVYKTI, both in the clinical trial setting and with commercially available product in the real-world setting.

## **Background File Document upload:**

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## **History of the development of the solution/product:**

Ciltacabtagene autoleucel (cilta-cel; CARVYKTI) is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR)-T cell therapy. In contrast with the therapeutic targets of earlier multiple myeloma (MM) treatments, BCMA is selectively expressed by the B-cell lineage and overexpressed by MM cells - a characteristic that may help limit on-target, off-tumor toxicities. CAR-T therapies combine the effector functions of T cells with the ability of antibodies to bind predefined targets with high specificity without the major histocompatibility complex restriction of T cells. The CARVYKTI clinical development plan comprises studies spanning the MM treatment continuum, reflecting the goal of transforming the patient treatment journey from diagnosis. Data from the phase 1 LEGEND-2 study, the first clinical trial of LCAR-B38M CAR-T cells, which express the same CAR construct as CARVYKTI, showed significant rates, depths, and durability of treatment responses and long-term survival outcomes in patients with heavily pretreated RRMM. Based on results from LEGEND-2, the pivotal phase 1b/2 CARTITUDE-1 trial was initiated. CARTITUDE-1, in which median progression-free survival was 34.9 months and median overall survival had not been reached (median follow-up, 33.4 months), confirmed the efficacy and the safety profile observed in LEGEND-2 and was the basis for the approval of CARVYKTI in the United States and other regions. In the most recent analysis from CARTITUDE-1 (median follow-up of 61.3 months), the median overall survival was 60.7 months, and 33% of patients remained alive and progression free without further antimyeloma treatment for  $\geq 5$  years after a single CARVYKTI infusion. In patients with lenalidomide-refractory MM after 1-3 lines of therapy, the phase 3

CARTITUDE-4 trial-the basis for label expansions in the United States and the European Union-showed that, alongside a safety profile of manageable adverse events with appropriate supportive therapy, CARVYKTI (median follow-up, 15.9 months) led to more and deeper treatment responses and significantly prolonged progression-free survival (59% reduction in the risk of disease progression or death) compared with 2 effective standard-of-care (SOC) regimens (daratumumab, pomalidomide, and dexamethasone; and pomalidomide, bortezomib, and dexamethasone). At a median follow-up of 33.6 months, median overall survival was not reached. CARVYKTI showed consistent overall survival and progression-free survival benefits vs SOC across prespecified subgroup analyses.

In cohort D of the multicohort phase 2 CARTITUDE-2 trial, CARVYKTI showed promising efficacy and safety in patients who had suboptimal response (did not achieve complete response or better) to frontline autologous stem cell transplant. Adverse events were consistent with the known safety profile of CARVYKTI.

In the phase 3 CARTITUDE-5 study, CARVYKTI is being further evaluated vs SOC in patients with newly diagnosed MM for whom autologous stem cell transplant is not intended; and in the phase 3 CARTITUDE-6 study, CARVYKTI will be compared with autologous stem cell transplant in patients with newly diagnosed MM.

## **Development File Document upload:**

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## **Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:**

Ciltacabtagene autoleucel (cilta-cel; CARVYKTI) is structurally differentiated by its chimeric antigen receptor (CAR) with 2 B-cell maturation antigen (BCMA)-directed antigen-binding domains. The CAR also possesses 4-1BB costimulatory and CD3 $\zeta$  signaling domains for optimized T-cell activation and proliferation. 4-1BB may also stimulate CD8<sup>+</sup> central memory T-cell generation and proliferation; consistent with this hypothesis, data show enrichment of CD8<sup>+</sup> central memory T cells in the CARVYKTI drug product.

Further distinguishing CARVYKTI are high rates of deep and long-lasting treatment responses and prolonged progression-free survival after a single infusion in patients with heavily pretreated relapsed/refractory multiple myeloma (RRMM). The phase 1 LEGEND-2 and phase 1b/2 pivotal CARTITUDE-1 studies suggest the potential of CARVYKTI to improve outcomes in heavily pretreated patients ( $\geq 3$  previous LOT) who have limited benefit from standard-of-care (SOC) treatments. The registrational, randomized phase 3 CARTITUDE-4 study showed CARVYKTI has superior efficacy-including significantly prolonging progression-free survival-vs SOC regimens as early as after first relapse along with potentially better tolerability in earlier lines. Based on CARTITUDE-4, CARVYKTI became the first and only BCMA-directed CAR-T therapy approved in the United States for the treatment of adult patients with

lenalidomide-refractory relapsed multiple myeloma after 1 line of therapy including a proteasome inhibitor and an immunomodulatory agent.

CARVYKTI also improves quality of life in patients with heavily pretreated relapsed refractory RRMM and in patients at earlier lines. In patients with 1-3 prior lines of therapy, quality of life improvements were greater in magnitude and were observed in a greater proportion of patients with a clinically meaningful change with CARVYKTI vs SOC. The treatment-free period afforded by CARVYKTI, through administration in a single dose, unlike continuous dosed therapies, may also have contributed to improvements in quality of life.

Ongoing studies have shown that CARVYKTI can benefit patients at additional stages of the multiple myeloma (MM) treatment continuum. Data from CARTITUDE-2 (cohort D) showed promising efficacy and safety with CARVYKTI with or without lenalidomide maintenance in patients who had a suboptimal response (did not achieve complete response or better) after frontline autologous stem cell transplant, a patient population with historically poor clinical outcomes. CARTITUDE-5 and CARTITUDE-6 aim to transform patient treatment journeys starting at diagnosis by displacing SOC at the first line of therapy. In patients with newly diagnosed MM, CARTITUDE-5 is evaluating CARVYKTI vs SOC in patients for whom autologous stem cell transplant is not intended, and CARTITUDE-6 is comparing CARVYKTI with autologous stem cell transplant.

### **Innovation File Document upload:**

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