

**Division Director Memo**

**Division of Clinical Evaluation and Pharmacology/Toxicology  
Office of Tissues and Advanced Therapies**

<b>APPLICATION:</b> BLA 125746	<b>TRADE NAME:</b> CARVYKTI	
<b>APPLICANT/SPONSOR:</b> Janssen Biotech, Inc.	<b>ESTABLISHED NAME:</b> ciltacabtagene autoleucel	
<b>SUBMISSION RECEIPT DATE:</b> 3/31/2021		
<b>PDUFA DATE:</b> 2/28/22	<b>PRODUCT CLASS:</b> B-cell maturation antigen (BCMA)- directed, genetically modified autologous T cell immunotherapy	
<b>REVIEW DATE:</b> 2/25/22	<b>ROUTE:</b> Intravenous infusion	

**INDICATION:** for the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody

**Review Team** (for comprehensive review team members from other offices, please see SBRA)

**Clinical:** Drs. Kavita Natrajan, Megha Kaushal, and Bindu Kanapuru (OCE); **Statistical:** Dr. Tianjiao Dai; **Pharm/Tox:** Dr. Ernesto Moreira; **Clin Pharm:** Dr. Xiaofei Wang; **CMC:** Drs. Zhaohui Ye, Graeme Price, Tiffany Lucas and Maitreyi Chattopadhyay

**REVIEW SUMMARY:**

Janssen Biotech, Inc. submitted this original BLA to seek marketing approval for CARVYKTI, a BCMA- directed, genetically modified autologous T cell immunotherapy, for the treatment of adult patients with relapsed or refractory (R/R) multiple myeloma.

The primary evidence of effectiveness and safety to support this application is generated from Study CARTITUDE-1, a Phase 1b/2, single-arm, open-label multicenter study in adults with relapsed or refractory (R/R) multiple myeloma after three or more lines of prior therapy to include an immunomodulatory drug (IMiD), proteasome inhibitor and an anti-CD38 antibody. Of the 113 subjects who underwent leukapheresis, 97 received CARVYKTI. The pre-specified primary efficacy endpoint was objective response rate (ORR), which included stringent complete response (sCR), complete response (CR), very good partial response (VGPR) and partial response (PR) as determined by an Independent Response Committee (IRC). Key secondary efficacy endpoints included CR, duration of response (DOR) and minimal residual disease (MRD) negativity.

The IRC assessed the ORR as 97.9% (95% CI: 92.7%, 99.7%), sCR as 78.4%, VGPR as 16.5% and PR as 3%, with a median duration of response (DOR) of 21.8 months. Note that of the efficacy evaluable population, 83% had received 4 or more prior lines of therapy.

With respect to safety, serious adverse reactions associated with CARVYKTI included cytokine release syndrome, neurologic toxicity to include immune effector cell associated neurologic syndrome (ICANS), Guillain-Barré syndrome and parkinsonian type symptoms, hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS), prolonged cytopenias, infections, and hypogammaglobulinemia. The most commonly reported adverse reactions were pyrexia, cytokine release syndrome, hypogammaglobulinemia, musculoskeletal pain, fatigue, infections, diarrhea, nausea, encephalopathy, headache, coagulopathy, constipation, and vomiting.

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I conclude that the Applicant has provided substantial evidence of effectiveness and safety from an adequate and well controlled study as well as confirmatory evidence based on mechanistic evidence to support an indication for the treatment of adults with relapsed/refractory multiple myeloma after 4 or more prior lines of therapy (including an IMiD, proteasome inhibitor, and anti-CD 38 antibody). Although the Applicant proposed an indication in adults with R/R multiple myeloma after 3 or more prior lines of therapy, as 83% of the subjects had received 4 or more prior lines of therapy, the data support a regular approval in patients who received 4 or more prior lines of therapy. The benefit/risk profile is favorable in the indicated patient population with implementation of a REMS for the serious life-threatening risks of CRS and neurotoxicity. I concur with the review team's, to include OCE's, recommendation of Approval with a Risk Mitigation and Evaluation Strategy (REMS) and a PMR for a postmarketing observational study to assess long-term toxicities of CARVYKTI, particularly secondary malignancies.

**OUTSTANDING ISSUES:**

None

**RECOMMENDED REGULATORY ACTION**

<input checked="" type="checkbox"/> <b>APPROVAL</b>	<input type="checkbox"/> <b>COMPLETE RESPONSE</b>	<input type="checkbox"/>
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