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Summary of the Risk Management Plan (RMP) for CARVYKTI® (Ciltacabtagene autoleucel)

Marketing Autorisation Holder (MAH): Janssen-Cilag AG

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Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of CARVYKTI® is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of CARVYKTI® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of CARVYKTI®.

Summary of Risk Management Plan for ciltacabtagene autoleucel

This is a summary of the risk management plan (RMP) for CARVYKTI. The RMP details important risks of CARVYKTI, how these risks can be minimized, and how more information will be obtained about CARVYKTI's risks and uncertainties (missing information).

CARVYKTI's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how CARVYKTI should be used.

This summary of the RMP for CARVYKTI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CARVYKTI's RMP.

I. The Medicine and What it is Used For

CARVYKTI is authorized for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least 3 prior therapies, including an immunomodulatory agent (IMiD), a proteasome inhibitor (PI), and an anti-CD38 antibody and have demonstrated disease progression on the last therapy (see SmPC for the full indication). It contains ciltacabtagene autoleucel as the active substance and is given via intravenous infusion.

Further information about the evaluation of CARVYKTI's benefits can be found in CARVYKTI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of CARVYKTI, together with measures to minimize such risks and the proposed studies for learning more about CARVYKTI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of CARVYKTI, these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CARVYKTI is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of CARVYKTI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CARVYKTI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Cytokine release syndrome (CRS) (including hemophagocytic lymphohistiocytosis [HLH]) Neurologic toxicities (including immune effector cell-associated neurotoxicity syndrome [ICANS] and other neurotoxicities) Prolonged or recurrent cytopenia (excluding anemia) Serious infections Hypogammaglobulinemia
Important potential risks	Second primary malignancy Decrease in cell viability due to inappropriate handling or preparation of the product Tumor lysis syndrome (TLS) Aggravation of Graft versus Host Disease (GvHD) Generation of replication competent lentivirus (RCL)
Missing information	Long-term safety

	Impact on pregnancy and lactation Use in patients with pre-existing autoimmune disease Use in patients with pre-existing neurodegenerative disorders Use in patients with active central nervous system (CNS) involvement by malignancy Use in patients with chronic controlled human immunodeficiency virus (HIV) and Hepatitis B virus (HBV)/Hepatitis C virus (HCV) infection

II.B. Summary of Important Risks

Important Identified Risk: Cytokine release syndrome (including HLH)	
Evidence for linking the risk to the medicine	CRS, including events that were fatal or life-threatening, has been reported in patients treated with CARVYKTI in clinical trials and CRS was identified as an adverse reaction. The risk for CRS and information regarding this adverse reaction are described in the SmPC for CARVYKTI. CAR-T-related CRS is commonly described in the literature, with several published guidelines for toxicity grading and management. For CARVYKTI clinical trials, CRS was graded using American Society for Transplantation and Cellular Therapy (ASTCT) 2019 criteria as predefined in the trial protocols. Hemophagocytic lymphohistiocytosis (HLH) occurring in the context of CAR-T cell therapies can be a potential manifestation of severe CRS. Based on the strength of evidence from the clinical trial data and information from the literature, CRS (including HLH) is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Risk factors for severe CRS include high pre-infusion tumor burden, active infection, and early onset of fever or persistent fever after 24 hours of symptomatic treatment. Active uncontrolled infection was an exclusionary criterion in clinical trials.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 6.6 • PL Section 2 • PL Section 3

	• PL Section 4 • Requirement to have tocilizumab (or suitable alternative measures if not available and listed in the EMA shortage catalogue) and emergency equipment available prior to infusion and during the recovery period is included in SmPC Sections 4.2 and 4.4. • Recommendation for monitoring patients daily for signs and symptoms of CRS for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Sections 4.4 and 6.6. • Recommendation for patients to remain within the proximity of a qualified clinical facility for at least 4 weeks following infusion is provided in SmPC Section 4.4 and in PL Section 3. • Recommendation to counsel patients to seek immediate medical attention if signs and symptoms of CRS occur, and recommendation to evaluate the patient for hospitalization and institute treatment at the first sign of CRS is provided in SmPC Section 4.4. • Recommendation to delay CARVYKTI infusion for patients with unresolved serious adverse reactions from preceding lymphodepleting or bridging chemotherapies (including cardiac toxicity and pulmonary toxicity), rapid disease progression, or clinically significant active infection is provided in SmPC Section 4.4. • Recommendations for the treatment of ongoing infections (which may increase the risk of a fatal CRS event) and recommendation to delay CARVYKTI infusion until any infections are resolved, are provided in SmPC Section 4.4. • Recommendation for potential early use of tocilizumab in patients with high tumor burden or early or persistent fever is provided in SmPC Section 4.4. • Recommendations for evaluation, treatment, and management of CRS are provided in SmPC Section 4.4. • Recommendations for treating high grade CRS that remains severe following use of tocilizumab and corticosteroids are provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly granulocyte-macrophage colony-stimulating factor [GM-CSF]) during CRS is provided in SmPC Section 4.4. • Recommendation to evaluate for HLH in patients with severe or unresponsive CRS, and a warning that patients

	who develop HLH may have an increased risk of severe bleeding, is provided in SmPC Section 4.4. • Recommendation for reducing baseline burden of disease with bridging therapy prior to infusion in patients with high tumor burden in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Information regarding the incidence of CRS and the specific signs and symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if CRS symptoms occur, as described in PL Section 2, and should seek medical help as described in PL Section 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • Controlled Distribution Program and Availability of Tocilizumab • HCP Educational Program • Patient Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Neurologic toxicities (including ICANS and other neurotoxicities)	
Evidence for linking the risk to the medicine	Cases of CAR-T cell neurologic toxicities have been reported for subjects treated with CARVYKTI in clinical trials, and have included both ICANS as well as other neurotoxicity determined by the investigator to be related to CAR-T therapy and occurring after recovery of CRS and/or ICANS. Specific types of neurotoxicity other than ICANS include movement and

	neurocognitive toxicity with signs and symptoms of Parkinsonism, GBS, peripheral neuropathy, and cranial nerve palsies. Note that ICANS and other neurotoxicities are not mutually exclusive as patients can experience both ICANS and other neurotoxicity. Neurologic toxicities (including ICANS and other neurotoxicities) were identified as an adverse reaction. The risk for neurologic toxicities and information regarding this adverse reaction are described in the SmPC for CARVYKTI. While ICANS and other neurotoxicities (occurring within 8 weeks of infusion) associated with CAR-T therapy are well described in the literature, information on late onset of neurological events (ie, onset >8 weeks after CAR T cell infusion) is still evolving. Based on the known risk associated with CAR-T therapies, as well as on the strength of evidence from clinical trials of CARVYKTI, neurologic toxicities (including ICANS and other neurotoxicities) is considered an important identified risk.
Risk factors and risk groups	A known risk factor for neurologic toxicity with the use of CAR-T therapy is concurrent or resolved CRS. The cluster of movement and neurocognitive events appears to be potentially associated with a combination of two or more factors such as high tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.7 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to consider reducing baseline disease burden with bridging therapy prior to infusion in patients with high tumor burden is included in SmPC Section 4.4. • Recommendation for monitoring patients daily for signs and symptoms of neurologic events for 14 days after dosing and periodically for an addition 2 weeks are included in SmPC Section 4.4. • Recommendations on monitoring patients for signs and symptoms of ICANS for 4 weeks after infusion and thereafter for other neurotoxicity are included in SmPC Section 4.4.

	• Recommendation to counsel patients on the signs and symptoms of neurologic toxicities and to seek immediate medical attention if signs and symptoms occur is provided in SmPC Section 4.4. • Recommendation to continue to monitor patients for signs and symptoms of neurotoxicity after recovery from CRS and/or ICANs and recommendation to consider neurologic evaluation at the first sign of CAR-T cell related neurotoxicity is provided in SmPC Section 4.4. • Recommendations on treating patients with symptoms of neurotoxicity, including intensive care supportive therapy (including steroids) for severe of life-threatening cases, are included in SmPC Section 4.4. • SmPC Section 4.4 provides information on a subset of patients with a cluster of movement and neurocognitive adverse reactions that progressed in some to an inability to work or care for oneself. These events were associated with 2 or more factors at baseline such as higher tumor burden, prior Grade 2 or higher CRS, prior ICANS, and high CAR-T cell expansion and persistence. Patients should be monitored for these symptoms and managed with supportive care measures. • Instruction that patients should be monitored for GBS and treatment with intravenous immunoglobulin (IVIG) and plasmapheresis should be considered is included in SmPC Section 4.4. • Instruction that patients should be monitored for signs and symptoms of peripheral neuropathies and cranial nerve palsies, and that management with short-course systemic corticosteroids should be considered, is included in SmPC Section 4.4. • Instructions for treatment of neurotoxicities with early and aggressive supportive care (including steroids) in patients presenting with higher grade CRS or any grade ICANS is included in SmPC Section 4.4. • Recommendations on treatment for concurrent CRS and neurologic toxicity, including the use of corticosteroids, tocilizumab, and anti-seizure medication, is provided in SmPC Section 4.4. • Recommendation to refrain from driving and engaging in hazardous occupations or activities in the 8 weeks following infusion is provided in SmPC Section 4.7. • Information regarding the incidence of neurologic toxicities (including ICANS and other neurotoxicities) and the specific

	symptoms seen in clinical trials is provided in SmPC Section 4.8. • Patients should inform their doctor or nurse immediately if symptoms of ICANS or other neurotoxicities occur, as described in PL Section 2, and should seek medical help for ICANS as described in PL Section 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures • Controlled Distribution Program and Availability of Tocilizumab • HCP Educational Program • Patient Educational Program
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Prolonged or recurrent cytopenia (excluding anemia)	
Evidence for linking the risk to the medicine	Cytopenia has been identified as one of the most common adverse reactions in patients after receiving CARVYKTI. Cases of prolonged cytopenia (not resolved by Day 30) have been reported for subjects treated with CARVYKTI in clinical trials and prolonged cytopenia has been identified as an adverse reaction. In addition, cases of cytopenia recurring after 60 days post-infusion have been reported in clinical trials of CARVYKTI. The risk for prolonged or recurrent cytopenia and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Evidence from clinical data with CARVYKTI suggests a drug association, including temporal association and persistence. Anemia begins to appear after lymphodepleting therapy but typically resolves within approximately 3 weeks post-infusion, and hemoglobin continues to rise thereafter, suggesting that bone marrow hematopoiesis improves following CAR-T therapy. Because of this, anemia is not considered an important risk of CARVYKTI. Some cases of neutropenia, thrombocytopenia, and lymphopenia continued for a longer period of time, with some recurrences of Grade 3 or 4 after Day 60. Based on the incidence, temporal association, and persistence of the events in clinical trials, prolonged or recurrent cytopenia (excluding anemia) is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Risk factors that may contribute to the development of cytopenia include the type of background therapy, bone marrow function, and disease progression. The use of bridging therapy and lymphodepletion prior to CARVYKTI administration is also a risk factor. Other factors include pre-existing neutropenia, or the concurrent use of antibiotics, corticosteroids, or symptomatic treatment medications. Additionally, age of ≥65 years old and female gender are known risk factors for leukopenia
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to monitor blood counts prior to and after CARVYKTI infusion is provided in SmPC Section 4.4. • Recommendation to consider supportive care with transfusions for treatment of thrombocytopenia is

	provided in SmPC Section 4.4. • Recommendation to avoid the use of myeloid growth factors (particularly GM-CSF) during CRS is provided in SmPC Section 4.4. • Information regarding the incidence of prolonged or recurrent cytopenia (excluding anemia) is provided in SmPC Section 4.8. • Patients should inform their doctor right away if they have any symptoms of prolonged or recurrent cytopenia, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Serious infections	
Evidence for linking the risk to the medicine	Serious infections, including life-threatening or fatal infections, have been reported with subjects treated with CARVYKTI in clinical trials and serious infection has been identified as an adverse reaction. The risk for serious infection and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Based on the strength of evidence from clinical trials, serious infections are considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Patients with multiple myeloma are at risk of infection due to the overproduction of ineffective monoclonal antibodies from the underlying disease, which causes immune dysfunction. Additionally, the use of chemotherapy (including bridging therapy and lymphodepletion prior to CARVYKTI administration) and immunosuppressive treatments may

	increase the risk of infection. Multiple myeloma patients have as much as a 15-fold increase in risk of infections, particularly pneumonia. Risk factors for fatal COVID-19 infection include comorbidities associated with severe/fatal COVID-19 such as diabetes and obesity, and concomitant use of immune-suppressant medications.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendation to delay lymphodepletion therapy if a patient has clinically significant active infection is provided in Section 4.2. • Recommendation that infection prophylaxis should follow local guidelines, and that infections are known to complicate the course and management of concurrent CRS, are provided in SmPC Section 4.4. • Recommendation to delay CARVYKTI infusion until any clinically significant active infection or inflammatory disorder is resolved is provided in SmPC Section 4.4. • Recommendation that patients should be counselled on the importance of prevention measures for COVID-19, as patients treated with ciltacabtagene autoleucel may be at increased risk of severe/fatal COVID-19 infections, is provided in SmPC Section 4.4. • Recommendation on monitoring patients for signs and symptoms of infection is provided in SmPC Section 4.4. • Recommendations for the management and treatment of febrile neutropenia are included in SmPC Section 4.4. • Recommendation to screen for HBV, HCV, and HIV prior to collection of cells for manufacturing is included in SmPC Section 4.4. • Recommendation to monitor immunoglobulin levels after treatment and treat according to standard guidelines, including administration of immunoglobulin replacement, antibiotic prophylaxis and monitoring for infection is included in SmPC Section 4.4. • Information regarding the incidence of serious infections is provided in SmPC Section 4.8.

	• Ciltacabtagene autoleucel may increase the risk of life-threatening infections that may lead to death. Patients should tell their doctor right away if they have any signs or symptoms of infection, as described in PL Sections 2 and 4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Identified Risk: Hypogammaglobulinemia	
Evidence for linking the risk to the medicine	Hypogammaglobulinemia has been reported with subjects treated with CARVYKTI in clinical trials and hypogammaglobulinemia has been identified as an adverse reaction. The risk for hypogammaglobulinemia and information regarding this adverse reaction are described in the SmPC for CARVYKTI. Based on the strength of evidence from clinical trials, including incidence and temporal association, hypogammaglobulinemia is considered an important identified risk for CARVYKTI.
Risk factors and risk groups	Patients with multiple myeloma are at risk of developing hypogammaglobulinemia and are prone to infection. Hypogammaglobulinemia can be intrinsic to the disease, occurring in 45% to 83% of patients with asymptomatic multiple myeloma (ie, SMM) at some point during the disease course (Patel 2019). The most common infections in these early-stage patients involve the respiratory tract and are predominantly caused by encapsulated bacteria such as H. influenzae or S. pneumonia, and viral reactivation, suggesting a role of hypogammaglobulinemia in their pathogenesis (Compagno 2014). It is also frequently associated with chemo immunotherapy regimens used to treat the disease, particularly those that either deplete B cells and plasma cells, or inhibit B

	cell survival, impair activation or interaction with T cells. Multiple prior lines of therapy and low IgG baseline values may increase the risk of developing hypogammaglobulinemia in patients with relapsed multiple myeloma. Finally, patients with co morbidities, such as chronic lung or heart disease and extra-articular rheumatoid arthritis, have also been reported to have higher instances of hypogammaglobulinemia (Patel 2019).
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • SmPC Section 4.6 • SmPC Section 4.8 • Recommendation that immunoglobulin levels should be monitored after treatment with CARVYKTI, IVIG should be administered for IgG <400 mg/dL, and patients should be managed according to standard guidelines, including antibiotic or antiviral prophylaxis and monitoring for infection, is described in SmPC Section 4.4. • Recommendation that assessment of immunoglobulin levels in newborns of mothers treated with CARVYKTI should be considered is provided in SmPC Section 4.6. • Information regarding the incidence of hypogammaglobulinemia infections is provided in SmPC Section 4.8. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Second primary malignancy	
Evidence for linking the risk to the medicine	Second primary malignancies have been reported in clinical trials with CARVYKTI. Based on the clinical trial data, as well as the theoretical risk from lentiviral vector DNA insertion and replication competent lentivirus (RCL), second primary malignancy is considered an important potential risk.
Risk factors and risk groups	Risk factors for secondary primary malignancies include previous exposure to high-dose alkylating therapy and use of lenalidomide maintenance therapy.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • Recommendation for life-long monitoring of patients for secondary malignancies is provided in SmPC Section 4.4. • Recommendation to contact the MAH for instructions on collecting patient samples for testing is provided in SmPC Section 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Decrease in cell viability due to inappropriate handling or preparation of the product	
Evidence for linking the risk to the medicine	While no evidence of decrease in cell viability due to inappropriate handling or preparation has been identified to date from Trial MMY2001, this is a potential risk with CAR-T products based on their distinct method of manufacturing and administration.

Risk factors and risk groups	The risk factor is lack of strict adherence to the specifications for preparation of CARVYKTI infusion. All patients receiving infusion are potentially at risk.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 6.3 • SmPC Section 6.4 • SmPC Section 6.6 • Instructions for preparation of CARVYKTI, including thawing, are provided in SmPC Section 4.2. • Shelf life and special precautions for storage of CARVYKTI are provided in SmPC Sections 6.3 and 6.4. • Special precautions for disposal and other handling are provided in SmPC Section 6.6. Additional risk minimization measures • Product Handling Training
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training See section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Tumor Lysis Syndrome	
Evidence for linking the risk to the medicine	The incidence of TLS was low in clinical trials of CARVYKTI, with only one confounded case of TLS reporting as of the data cutoff. However, a biological plausibility may exist for risk of developing TLS in multiple myeloma patients with extensive disease burden and/or plasmacytomas, considering the antimyeloma effects of CARVYKTI. Therefore, TLS is considered an important potential risk.
Risk factors and risk groups	Patients at high risk for TLS include those with a high tumor burden (≥60% plasma cell infiltrate on the bone marrow biopsy or aspirate [whichever is higher] or those with multiple extramedullary disease sites and/or plasmacytomas.
Risk minimization measures	Routine risk minimization measures • Use restricted to physicians experienced in the treatment of hematological cancers

	Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Aggravation of Graft versus Host Disease	
Evidence for linking the risk to the medicine	No cases of aggravated or de novo GvHD have been reported in clinical trials of CARVYKTI to date. However, a biological plausibility may exist for increased risk of aggravation of GvHD, particularly in patients receiving allogenic transplant prior to 6 months of CARVYKTI or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant who will not be restricted from receiving CARVYKTI. Therefore, aggravation of GvHD is considered a potential risk.
Risk factors and risk groups	Risk factors for developing GvHD in multiple myeloma patients after receiving allogenic transplant include the following: higher degree of human leukocyte antigen (HLA) mismatch, older age of the donor or recipient, sex disparity between donor and recipient, prior acute GvHD (aGvHD), a splenectomized recipient, CMV seropositivity in the donor or recipient, donor EBV seropositivity. The probability of developing a subsequent acute or chronic GVHD increases with increasing numbers of risk factors (Hill 2021). Patients receiving allogenic transplant prior to 6 months of CARVYKTI or still receiving immunosuppressants to control a prior event of GvHD after allogenic transplant may be at increased risk for aggravation of GvHD.
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 • Instruction that CARVYKTI infusion should be delayed if a patient has active GvHD is provided in SmPC Section 4.4. • Instruction for patients to tell their doctor prior to infusion of CARVYKTI if they have signs or symptoms of GvHD in provided in PL Section 2.

	• Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Generation of Replication Competent Lentivirus	
Evidence for linking the risk to the medicine	While no cases of generation of RCL have been reported to date in clinical trials of CARVYKTI, this is a potential risk due to potential viral insertion (DNA integration) of the lentiviral vector.
Risk factors and risk groups	All patients who receive CARVYKTI are theoretically at risk.
Risk minimization measures	Routine risk minimization measures • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

	See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Long-term safety	
Risk minimization measures	No risk minimization measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Impact on pregnancy and lactation	
Risk minimization measures	Routine risk minimization measure • SmPC Section 4.6 • PL Section 2 • Recommendations that pregnancy status for females of childbearing age should be verified prior to starting treatment is provide in SmPC Section 4.6. • Recommendation on the need for effective contraception in patients who receive the lymphodepleting chemotherapy according to the corresponding prescribing information is provided in SmPC Section 4.6. • Recommendation to advise pregnant or breastfeeding women that there may be risks to the fetus or the breast-fed infant is provided in SmPC Section 4.6. • Recommendation that for any pregnant woman who receives CARVYKTI, assessment of immunoglobulin levels in newborns of mothers should be considered is provided in SmPC Section 4.6. • Patients should notify their doctor immediately if they are pregnant or think they may be pregnant following treatment with CARVYKTI, as described in PL Section 2.

	• Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with pre-existing autoimmune disease	
Risk minimization measures	Routine risk minimization measures Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with pre-existing neurodegenerative disorders	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.4 • PL Section 2 • A warning indicating that patients with significant CNS disease are likely to be more vulnerable to the

	consequences of adverse reactions observed with CARVYKTI and may require special attention is provided in SmPC Section 4.4. • Patients should tell their doctor before treatment with CARVYKTI if they have current or past nervous system disorders, as described in PL Section 2. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with active CNS involvement by malignancy	
Risk minimization measures	Routine risk minimization measures Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with chronic controlled HIV and HBV/HCV infection	
Risk minimization measures	Routine risk minimization measures • SmPC Section 4.2 • SmPC Section 4.4 • Instructions for screening of HBV, HCV, and HIV are included in SmPC Sections 4.2 and 4.4. • Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: 68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel 68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel 68284528MMY4009: A Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization:

68284528MMY4002: Long-term Follow-up Study for Participants Previously Treated with Ciltacabtagene Autoleucel

Purpose of the study: CAR-T therapy, characterized as a cell-based gene therapy, may be associated with delayed adverse events. The primary objective is to collect long-term follow-up data on delayed adverse events after administration of CARVYKTI, and to characterize and understand the long-term safety profile of CARVYKTI. The secondary objectives are to collect additional long-term data on RCL, CARVYKTI persistence, efficacy, and OS.

68284528MMY4004: An Observational Post-authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

Purpose of the study: CAR-T therapy, characterized as a gene therapy, might be associated with different adverse event profile under real-world conditions than previously known from clinical trials. The primary objective is to evaluate the short- and long-term safety and the risk of subsequent malignancy of CARVYKTI in adult patients with multiple myeloma. The secondary objective is to evaluate the effectiveness of CARVYKTI in adult patients with multiple myeloma.

68284528MMY4009: A Post authorization Safety Study to Evaluate the Safety of Multiple Myeloma Patients Treated with Ciltacabtagene Autoleucel

Purpose of the study: The data from this study will be analyzed together with other independent prospective registries and other data sources as part of the global PASS study 68284528MMY4004. The primary objective is to evaluate the short- and long-term safety and the risk of subsequent malignancy of CARVYKTI in adult patients with multiple myeloma. The secondary objective is to evaluate the effectiveness of CARVYKTI in adult patients with multiple myeloma.

II.C.2. Other Studies in Postauthorization Development Plan

Survey to evaluate the effectiveness of the ciltacabtagene autoleucel HCP Educational Program and the Product Handling Training

Purpose of the study:

- To measure the effectiveness of the HCP Educational Program, an additional risk minimization measure intended to increase awareness about the risks of CRS (including HLH) and neurologic toxicity (including ICANS and other neurotoxicities). There will be a Guide for Health Care Professionals to advise of the risks of CRS (including HLH) and neurologic toxicity (including ICANS and other neurotoxicities) and how to minimize these.
- To measure information on awareness of the HCP of the existence of Patient Alert Card, as well as the intention and time of providing it to the patients.
- To measure the effectiveness of the Product Handling Training, an additional risk minimization measure intended to increase awareness of the potential risk of decrease in cell viability due to inappropriate handling or preparation of the product