Regulatory Affairs

Kymriah

Summary of the EU Safety Risk Management Plan

Active substance(s) (INN or common name):	Tisagenlecleucel
Product(s) concerned (brand name(s)):	Kymriah®
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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 Kymriah 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 Kymriah in Switzerland is the “Arzneimittelinformation/ Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Novartis Pharma Schweiz AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Kymriah.

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This is a summary of the Risk Management Plan (RMP) for Kymriah. The RMP details important risks of Kymriah, how these risks can be minimized, and how more information will be obtained about Kymriah's risks and uncertainties (missing information).

Kymriah's Summary of Product Characteristics (SmPC) and the SmPC Package leaflet give essential information to healthcare professionals and patients on how Kymriah should be used.

This summary of the RMP for Kymriah 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 to the Kymriah RMP.

I. The medicine and what it is used for

Kymriah is a CD19-directed autologous immunotherapy indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukemia (B-ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

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

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/human_med_002287.jsp&mid=WC0b01ac058001d124

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of Kymriah, together with measures to minimize such risks and the proposed studies for learning more about Kymriah'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 SmPC and SmPC Package leaflet addressed to healthcare professionals and patients
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks

Together, these measures constitute routine risk minimization measures.

In the case of Kymriah, 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 analysed including Periodic Safety Update Report (PSUR) 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 Kymriah is not yet available, it is listed under ‘missing information’ below.

II.A: List of important risks and missing information

Important risks of Kymriah 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 Kymriah. 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 (e.g., on the long-term use of the medicine).

Table 13-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Cytokine release syndrome • Serious neurological adverse reactions • Infections • Tumor lysis syndrome • Prolonged depletion of normal B-cells/Agammaglobulinemia • Hematological disorders including cytopenias
Important potential risks	• Cerebral edema • Generation of replication competent lentivirus • Secondary malignancies (including vector insertion site oligo/monoclonality) • New occurrence or exacerbation of an autoimmune disorder • Aggravation of graft-versus-host disease • Transmission of infectious agents • Decrease in cell viability due to inappropriate handling of the product
Missing information	• Use in pregnancy and lactation • Use in patients with HBV/HCV/HIV • Use in patients with active CNS involvement by malignancy • Long-term safety • Immunogenicity

II B: Summary of important risks

Table 13-2 Important identified risk: Cytokine release syndrome

Evidence for linking the risk to the medicine	Cytokine release syndrome (CRS) is a direct mechanism based toxicity that occurs as a result of high-level immune activation. It is a systemic inflammatory response caused when cytokines are released by activated T cells, which has been observed in other types of T-cell directed therapies. This syndrome has become increasingly important with the use of new and more potent immunotherapies. The level of immune activation with these newer therapies occurs at levels greater than that occurring in nature. The severity ranges from mild to severe with a fatal outcome sometimes. Life-threatening and fatal events have been observed in tisagenlecleucel clinical trials. In the Novartis tisagenlecleucel clinical study programs for the indications of pediatric and young adult r/r B-ALL, adult r/r DLBCL, and adult r/r FL, CRS was graded using criteria predefined in the study protocols (Penn CRS grading scale for Study B2202, Study B2205J, Study B2001X, and Study C2201; Lee grading criteria for Study E2202). In the majority of patients, CRS after tisagenlecleucel infusion occurred with a median time to onset of 3 days in both pediatric and young adult r/r B-ALL and adult r/r DLBCL patients, and 4 days in adult r/r FL. Symptoms of CRS may include high fever, hypotension, hypoxia, dyspnea, tachypnea, rigors, myalgia, arthralgia, nausea, vomiting, diarrhea, diaphoresis, rash, anorexia, fatigue, tachycardia, and headache. In addition, multiple organ dysfunction, including transient cardiac failure, renal impairment, and liver injury with elevated hepatic enzymes have been observed. Disseminated intravascular coagulation, with low fibrinogen levels, or capillary leak syndrome may also occur. In the setting of severe CRS following CAR T-cell therapies including tisagenlecleucel, patients may develop a clinical phenotype that shares signs and symptoms of hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), as further evidenced by similar laboratory findings. There is a significant overlap across CRS, MAS and HLH, reflecting a group of severe systemic immunological disorders characterized by hyperactivation of macrophages and lymphocytes, pro-inflammatory cytokine production, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure. In the majority of patients, MAS/HLH responds to CRS resolution. Given this overlap, MAS/HLH may be considered to reflect manifestations of CRS of higher severity. However, it should be distinguished from late-onset, tocilizumab-refractory HLH/MAS-like toxicity that may represent a distinct and separate pathology than conventional CRS and requires a different treatment approach.
Risk factors and risk groups	Risk factors for severe CRS in paediatric and young adult B-ALL patients are high pre-infusion tumour burden, uncontrolled or accelerating tumour burden following lymphodepleting chemotherapy, active infection and early onset of fever or CRS following tisagenlecleucel infusion. Risk factor for developing severe CRS in adult DLBCL patients is high tumor burden prior to tisagenlecleucel infusion. Infections may also occur during CRS and increase the risk of a fatal event.

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-3 Important identified risk: Serious neurological adverse reactions

Evidence for linking the risk to the medicine	Neurotoxic events, suggested to be named 'CAR-T-cell-related encephalopathy syndrome' and subsequently termed 'immune effector cell-associated neurotoxicity syndrome' (ICANS), is the second most-common adverse reaction associated with CAR T-cell therapies. Neurotoxicity typically manifests as a toxic encephalopathy with wide range of variable symptoms such as confusion, delirium, tremors, aphasia, speech disorders, motor findings, and seizures. For fatal cerebral edema that occurred with other CAR T-cell products differently constructed than tisagenlecleucel, see Table 13-8. Notably, the onset of neurological events can be concurrent with CRS, typically during high fever and at the time of maximal grade of CRS, following resolution of CRS or in the absence of CRS. Severe ICANS symptoms are more frequently observed in cases when CRS develops early, which may be due to a high dose of CAR T cells, or unusually robust and rapid CAR T cell proliferation. Encephalopathy typically occurred after peak CRS symptoms and tended to be self-limiting with some exceptions. Neurological events with seizures or episodes of confusion 3-4 weeks following CAR T-cell therapy have been reported to occur. The majority of neurological events following tisagenlecleucel infusion were observed within 8 weeks; there is currently limited evidence that CAR therapies are associated with a late onset of neurological events (i.e., onset > 8 weeks after infusion). Most neurological events observed within 8 weeks were transient or self-limiting in nature. Frequently, encephalopathy, confusional state and delirium were observed. Other manifestations include a multifarious set of signs and symptoms including seizures, aphasia, speech disorder, and tremor. Some of the events are severe and may have a life-threatening outcome.

	The causality assessment of neurological events in patients treated with tisagenlecleucel can be confounded, as CNS toxicity can be associated with chemotherapy used for lymphodepletion and the presence of co-morbid conditions such as CRS, fever and infections.
Risk factors and risk groups	Risk factors are not known but may include prior medical history of central nervous system (CNS) disease/injury or CNS leukemic involvement. In addition, higher grade CRS may predispose.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • Controlled distribution program • Educational program including the Healthcare Professional Training Material and the Patient Educational Leaflet
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-4 Important identified risk: Infections

Evidence for linking the risk to the medicine	Serious infections, which may occur late, were observed in patients after tisagenlecleucel infusion, some of which were life-threatening or fatal..
Risk factors and risk groups	Severity of underlying disease and longer, more intense immunosuppression following preceding chemotherapy, radiation and/or tisagenlecleucel infusion may lead to an increased risk, severity and seriousness of infection.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-5 Important identified risk: Tumor lysis syndrome

Evidence for linking the risk to the medicine	Tumor lysis syndrome was clinically observed in a timely relation to tisagenlecleucel T-cell expansion. In the clinical experience with tisagenlecleucel thus far, most cases of tumor lysis syndrome (TLS) had a grade 3 in CTCAE severity, however, the risk has been moderate to low with appropriate monitoring after lymphodepleting chemotherapy, prophylaxis and treatment as needed.
Risk factors and risk groups	All recipients are at risk for this concern. In general, TLS occurs more frequently in hematological malignancies than in solid tumors. The highest risk of developing TLS is observed in patients with lymphoproliferative disorders with high proliferative rate and high tumor sensitivity to chemotherapy, like B-ALL and Burkitt's lymphoma. Tumor burden, reflected by serum LDH level, initial WBC count, tumor size, and extensive bone marrow involvement are considered main predictors for the development of TLS in these patients.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-6 Important identified risk: Prolonged depletion of normal B-cells/ Agammaglobulinemia

Evidence for linking the risk to the medicine	Prolonged depletion of B cells is an expected on-target toxicity of CD19-directed CAR T-cell therapy. This may result in hypo- or agammaglobulinemia, potentially rendering the patients more susceptible to certain infections.
Risk factors and risk groups	Patients with B-cell aplasia are at increased risk for certain infections including but not limited to those caused by encapsulated bacteria and viruses.

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-7 Important identified risk: Hematological disorders including cytopenias

Evidence for linking the risk to the medicine	Hematological disorders including cytopenias are commonly seen in patients receiving tisagenlecleucel. Patients may continue to exhibit cytopenias for several weeks following tisagenlecleucel infusion. Prolonged neutropenia has been associated with increased risk of infection.
Risk factors and risk groups	All patients are at risk after tisagenlecleucel infusion. Extensive prior exposure to anti-cancer therapy, such as chemotherapy or radiation in addition to lymphodepleting chemotherapy in proximity to tisagenlecleucel infusion, enhance the risk.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-8 Important potential risk: Cerebral edema

Evidence for linking the risk to the medicine	No fatal cerebral edemas have been reported following tisagenlecleucel infusion in the clinical development program or the post-marketing setting to date that would resemble five fatal cases reported for JCAR015 (Juno). Importantly, the risk of fatal cerebral edema appears to be dependent of the anti-CD19 CAR construct used to engineer CAR T-cell therapies; JCAR015 presents a different construct of an anti-CD19 CAR than the CAR construct of tisagenlecleucel. These five fatal cases of cerebral edema occurred in the ROCKET study and were characterized by a rapid evolution soon after JCAR015 infusion, appeared to be resistant to anti-cytokine treatment, and ensued brain death within 1-2 days after diagnosis. Following a retrospective exploratory analysis, it is believed that the fatal cerebral edemas in these five patients emerged from rapid T-cell expansion associated with the specific CAR T-cell product construct that determines the kinetics of T-cell expansion after infusion together with other risk factors such as high baseline blood levels of interleukin 15 (JCAR015). Key findings of this retrospective analysis of the JCAR015 cases with fatal cerebral edema showed that all five patients experienced rapid, early expansion of their CAR T cells within a week of being infused (rather than the typical time frame of 12-14 days), high levels of the CD8+ subtype and, consequently, a sharp spike in cytokines such as interleukin 2 and TNFα. Autopsy results from two of the patients showed a breakdown of the blood-brain barrier and microvascular disruption, possibly due to inflammatory cytokine surge. Potential risk factors at baseline included age younger than 30 years, Philadelphia chromosome negativity, subset of disease (i.e., B-ALL), fewer prior regimens, higher levels of interleukin 15 and decreased levels of platelets. Since the five fatal cases after exposure to the JCAR015 product have become known, another patient with fatal cerebral edema was reported in the ZUMA-1 trial following axicabtagene ciloleucel treatment. This patient progressed to CRS grade 4 refractory to tocilizumab and dexamethasone on Day 4, developed cerebral edema refractory to siltuximab and mannitol on Day 9, and died on Day 11. The clinical course of this case treated with KTE-019 may not be comparable with those 5 cases treated with JCAR015, which is further supported by a retrospective analysis of baseline cytokine and chemokine levels in serum and cerebrospinal fluid suggesting significant pre-existing underlying inflammatory condition providing an alternate explanation. Another fatal cerebral edema case following axicabtagene ciloleucel was reported in the standard of care setting. Risk factors and risk groups are unknown.
Risk factors and risk groups Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.7 Effects on ability to drive and use machines • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given

	• SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-9 Important potential risk: Generation of replication competent lentivirus

Evidence for linking the risk to the medicine	Tisagenlecleucel uses third generation self-inactivating lentiviral vector. Generation of a replication-competent lentivirus (RCL) following infusion of the vector product remains a theoretical possibility. Replication-competent lentivirus will be detected by qPCR for vesicular stomatitis virus-G (VSV-G) of peripheral blood. Replication-competent lentivirus has not been described in the scientific literature for lentiviral vectors that use a production method similar to the tisagenlecleucel vectors. Furthermore, lentiviral vectors have been successfully used in conjunction with HIV infected patients, with no evidence of vector mobilization after 60 days or insertional mutagenesis observed up to 36 months. To date, no indication of RCL tisagenlecleucel batches was detected by using VSV-G DNA (specification ≤ 50 copies/µg) assay as a substitute. Furthermore, patients enrolled in interventional clinical trials have been screened for RCL with no RCL identified to date.
Risk factors and risk groups	The development of RCL could pose a risk to both the patient and their close contacts.
Risk minimization measures	**Routine risk minimization measures** • None **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-10 Important potential risk: Secondary malignancies (including vector insertion site oligo/monoclonality)

Evidence for linking the risk to the medicine	To date, no cases of secondary malignancy have been assessed to be causally related to tisagenlecleucel by Novartis. No suspected secondary malignancies following CAR T-cell therapies developed by other pharmaceutical companies have been reported in literature. Based on historic experience in patients with X-linked severe combined immunodeficiency, chronic granulomatous disease, and Wiskott-Aldrich syndrome, vector-mediated insertional mutagenesis and subsequent malignant cell transformation have been observed following gene correction via autologous human stem cell based gene therapy, where

	first-generation gamma-retroviral vectors harboring long terminal repeats with strong enhancer/promoter sequences has been used. The potential risk of insertional oncogenesis was addressed in two LISA studies where 12 batches of manufactured tisagenlecleucel product ready for administration in patients (6 patients each from study B2202 and C2201) and two batches of product manufactured from healthy donor cells were analyzed. The results indicate that there was no preferential integration near genes of concern, no preferential sites of integration (hot spots), and no preferential outgrowth of cells harboring integration sites of concern. Tisagenlecleucel is based on autologous, fully differentiated T cells and therefore the carcinogenicity risk is considered to be low in comparison to genetic modification or repair such as human stem cells. As discussed in a review of CAR T-cell therapies, no cases of malignant transformation have been reported for genetic modification of T cells to date and there is currently no evidence for vector-induced immortalization, clonal expansion, or enrichment for integration sites near genes implicated in growth control or transformation. This is supported by the results of the LISA studies performed during the development of tisagenlecleucel. Theoretically, CAR-positive viable T cells could proliferate without control of normal homeostatic mechanisms. In pre-clinical studies and clinical experience to date, CAR-positive viable T cells have only proliferated in response to physiologic signals or upon exposure to CD19 antigen. In the context of tisagenlecleucel therapy, it is expected that the T cells will proliferate in response to signals from the CD19 expressing malignant tumor and normal B cells. This could be either harmful depending on the extent of proliferation or beneficial, since clonal dominance of adoptively transferred T cells has been associated with tumor reduction in adoptive transfer trials.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 5.3 Preclinical safety data **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 (as feasible) • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-11 Important potential risk: New occurrence or exacerbation of an autoimmune disorder

Evidence for linking the risk to the medicine	Most autoimmune diseases are driven by a dysfunction in the immune network consisting of B cells, T cells, and other immune cells. Reciprocal roles of T-cell help for B cells during adaptive immune responses and B-cell help in $CD4^+$ T-cell activation are being increasingly recognized.

	An emerging number and variety of autoimmune diseases following after anti-cancer treatment including immunotherapy are reported, ranging from asymptomatic immunological alterations to life-threatening systemic autoimmune diseases. However, specific etiopathogenic mechanisms that could clearly link the induced autoimmune disorder with the immunological pathways altered by the anti-cancer treatments are not well understood. Persistent immune abnormalities after treatment with chemotherapy, development of auto-antibodies and neoantigens are proposed to be crucial in the pathogenesis of autoimmune diseases post anti-cancer treatment. Based on current knowledge, the risk of autoimmune reaction is considered low with tisagenlecleucel, since CD19 is not present on most normal tissue other than B cells. The occurrence or exacerbation of an autoimmune disorder has not been observed with tisagenlecleucel to date. Prior anti-cancer therapy, such as radiation and chemotherapy, lymphodepleting chemotherapy prior to treatment with tisagenlecleucel or concomitant treatment may present additional risk factors.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures** • None **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-12 Important potential risk: Aggravation of graft-versus-host disease

Evidence for linking the risk to the medicine	The chance of graft-versus-host-disease (GVHD) occurring in patients after tisagenlecleucel infusion per se is considered low, but there is a potential risk of aggravation of pre-existing GVHD in patients with donor chimerism from a prior allogeneic HSCT post-tisagenlecleucel due to the milieu provided by robust activation of the transduced viable T cells. A study of activated DLIs (ex vivo activated cells collected from the donor and grown in the same fashion as tisagenlecleucel but without the CAR introduction) did not show high rates of GVHD (2/18 patients with grade 3 GVHD and none with grade 4). Of 18 ALL patients treated with autologous tisagenlecleucel therapy who had relapsed after prior allogeneic HSCT with residual mixed chimerism, none have developed GVHD after autologous tisagenlecleucel infusion.
Risk factors and risk groups	Patients with the presence of active GVHD from prior HSCT.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 4.8 Undesirable effects

	• SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-13 Important potential risk: Transmission of infectious agents

Evidence for linking the risk to the medicine	Multiple steps are required to produce tisagenlecleucel CAR T cells, involving leukapheresis to obtain patient autologous starting material, enrichment and activation, gene transduction via lentiviral vector and expansion. Transmission of infectious material via product could potentially derive from the patient's own leukapheresis material prepared from autologous blood, other material including the tisagenlecleucel viral vector required to manufacture tisagenlecleucel, through contamination during the manufacturing process or inadequate storage. The risk associated with tisagenlecleucel is considered very low. Stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines. The starting material for producing tisagenlecleucel are the patient's autologous (i.e., donor and recipient are the same) non-mobilised peripheral blood mononuclear cells collected by leukapheresis. Tisagenlecleucel is composed of autologous CD4+ and CD8+ T cells genetically modified with a murine HIV-1 lentiviral vector encoding a CAR against CD19. The product is manufactured by expansion of patient T cells after transduction without any hold step. Due to the nature of the product (i.e., cells), there is no possibility to introduce terminal sterilization or dedicated viral removal and inactivation steps. Therefore, stringent precautions to prevent introduction of viral adventitious agents and to ensure microbial safety of tisagenlecleucel product are taken as detailed below. 1. Control of raw materials and of the tisagenlecleucel vector • Control of animal and human derived raw materials entering the manufacturing process through certificates of origin and suitability. For human derived materials such as human serum, viral inactivation steps in the manufacturing process of these materials are performed • Control of the production of tisagenlecleucel vector using HEK293T cells, which are not known to express endogenous viruses • Additional controls through filtration of raw materials (media) performed prior to use in manufacturing

	• Control of the tisagenlecleucel vector through testing for adventitious viral agents • Testing for relevant human viruses as part of the patient eligibility assessment 2. Process and environmental controls • Control of the tisagenlecleucel drug product manufacturing process (antibiotics free) through use of closed systems. Where there are open steps, the process is performed under environmentally controlled conditions • Environmental controls (e.g., evaluating the quality of air, temperature, surfaces, personnel in a cleanroom environment) • Cleaning and decontamination of work surfaces and equipment • Aseptic verification, simulating all process steps and interventions is conducted to verify that the process is capable of maintaining sterility 3. Control of tisagenlecleucel by microbial contaminants testing as part of drug product release testing • Testing for bacterial endotoxin • Testing for sterility • Testing for mycoplasma Details on shipping and storage conditions of tisagenlecleucel product and disposal are described in the SmPC.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. There is a potential risk of transmission of infectious agents to close contacts including personnel involved in the tisagenlecleucel manufacturing process or health care providers involved in leukapheresis and administering tisagenlecleucel in addition to patients treated with tisagenlecleucel.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B

See Section 13.2.3 of this summary for an overview of the post- authorization development plan.

Table 13-14 Important potential risk: Decrease in cell viability due to inappropriate handling of the product

Evidence for linking the risk to the medicine	Inconsistencies may arise due to product handling including subjective determination of the thaw endpoint and risk of water borne contamination.
Risk factors and risk groups	Since this is a potential risk, no attributable increase to tisagenlecleucel has been established. Therefore, by definition, no risk groups or risk factors can be identified.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration • SmPC Section 6.3 Shelf life • SmPC Section 6.4 Special precautions for storage • SmPC Section 6.5 Nature and contents of container and special equipment for use, administration or implantation • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Package leaflet, Section 5 How to store Kymriah • SmPC Section Other sources of information **Additional risk minimization measures** • Controlled distribution program • Educational program including the Pharmacy/Cell Lab/Infusion Center Training Material
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • None

Table 13-15 Missing information: Use in pregnancy and lactation

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.6 Fertility, pregnancy and lactation • SmPC Section 5.3 Preclinical safety data • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-16 Missing information: Use in patients with HBV/HCV/HIV

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 Posology and method of administration

	• SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 6.6 Special precautions for disposal and other handling • SmPC Package leaflet, Section 2 What you need to know before you are given Kymriah • SmPC Package leaflet, Section 3 How Kymriah is given • SmPC Section Other sources of information **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-17 Missing information: Use in patients with active CNS involvement by malignancy

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.4 Special warnings and precautions for use • SmPC Section 5.1 Pharmacodynamic properties – Patients with active CNS leukemia **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-18 Missing information: Long-term safety

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.8 Undesirable effects • SmPC Package leaflet, Section 4 Possible side effects **Additional risk minimization measures** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019B2401 • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

Table 13-19 Missing information: Immunogenicity

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 5.2 Pharmacokinetic properties **Additional risk minimization measures** • None

Additional pharmacovigilance activities	**Additional pharmacovigilance activities** • CCTL019A2205B See Section 13.2.3 of this summary for an overview of the post-authorization development plan.

II C: Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

Table 13-20 Studies which are condition of the marketing authorization

Study short name	Rationale and study objectives
CCTL019B2401 (PASS) Non-interventional study with secondary use of data from the registries conducted by CIBMTR and EBMT, respectively, to evaluate the long-term safety of patients with malignancies treated with CAR T-cell therapies.	This study will provide further information on long-term, real-world safety and effectiveness up to 15 years following treatment with tisagenlecleucel based on secondary use of tisagenlecleucel data prospectively collected through the CIBMTR and EBMT registries for cellular therapy. The primary objective is to evaluate the safety of patients with B-lymphocyte malignancies treated with tisagenlecleucel in a real-world setting. The main secondary objective is to evaluate the long-term effectiveness of tisagenlecleucel.
CCTL019B2401 Subgroup analysis of B-ALL patients < 3 years of age	Evaluate the efficacy and safety of tisagenlecleucel in B-ALL patients below the age of 3 years treated in the commercial setting within PASS B2401, including information on: • manufacturing, safety and efficacy • the manufacturing experience for batches for patients below 3 years of age.
CCTL019B2401 Subgroup analysis of DLBCL patients	Evaluate the efficacy of tisagenlecleucel with efficacy outcome measures in line with pivotal study C2201 and manufacturing experience in r/r DLBCL patients within PASS B2401.
CCTL019C2201	Phase 2 study to evaluate the efficacy and safety of tisagenlecleucel in adult patients with r/r DLBCL. In order to further characterize long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, Novartis submitted the 24-month follow-up and will submit the 5-year follow-up.
CCTL019H2301	Phase 3 study to evaluate the efficacy and safety of tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell aggressive NHL. To further characterize the long-term efficacy and safety in relapsed/refractory DLBCL, Novartis will submit the results of Study CCTL019H2301.

CCTL019C2201	Phase 2 study to evaluate the efficacy and safety of tisagenlecleucel in adult patients with r/r DLBCL. In order to further characterize long-term efficacy and safety of Kymriah in relapsed/refractory DLBCL, Novartis submitted the 24-month follow-up and will submit the 5-year follow-up.
CCTL019H2301	Phase 3 study to evaluate the efficacy and safety of tisagenlecleucel versus standard of care in adult patients with r/r aggressive B-cell aggressive NHL. To further characterize the long-term efficacy and safety in relapsed/refractory DLBCL, Novartis will submit the results of Study CCTL019H2301.

II.C.2. Other studies in post-authorization development plan

Table 13-21 Other studies in the post-authorization development plan

Study short name	Rationale and study objectives
CCTL019A2205B (PASS) Long-term follow-up study in patients exposed to lentiviral-based CD19 directed CAR T-cell therapy in preceding clinical trials	The purpose of this Novartis PASS is to monitor all patients exposed to lentiviral vector based CD19 CAR T-cell therapy for 15 years from the last CD19 CAR T-cell infusion, to assess the risk of delayed AEs suspected to be related to CD19 CAR T-cell therapy, monitor for vectors persistence and RCL, and record the status of the primary malignancy (efficacy). The primary objective of the study is to describe selected delayed AEs suspected to be related to previous CD19 CAR T-cell therapy as outlined in current Health Authority guidelines. The secondary objectives are to monitor the persistence of CD19 CAR T-cell transgene in peripheral blood, monitor the expression of RCL, assess the long-term efficacy of CD19 CAR-T, monitor lymphocyte levels and describe the growth, development, and female reproductive status for patients who were aged < 18 years at the time of the initial CD19 CAR T-cell infusion.