

## **SUMMARY OF RISK MANAGEMENT PLAN FOR YESCARTA (AXICABTAGENE CILOLEUCEL)**

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

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

This summary of the RMP for Yescarta 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 Yescarta's RMP.

### **I. The Medicine and What is it Used for**

Yescarta is authorized for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy. In addition, Yescarta is authorized for the treatment of adult patients with relapsed or refractory primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy; and adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy (see SmPC for the full indication). It contains axicabtagene ciloleucel as the active substance and it is a single infusion product for autologous and intravenous use only.

Further information about the evaluation of Yescarta's benefits can be found in Yescarta'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\\_002292.jsp&mid=WC0b01ac058001d124](http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/human_med_002292.jsp&mid=WC0b01ac058001d124).

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

Important risks of Yescarta, together with measures to minimize such risks and the proposed studies for learning more about Yescarta'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 public (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In the case of Yescarta, 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 (e.g., via the periodic safety update report [PSUR]) 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 Yescarta is not yet available, it is listed under ‘missing information’ below.

## **II.A. List of Important Risks and Missing Information**

Important risks of Yescarta 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 Yescarta. 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 Part VI.1. List of Important Risks and Missing Information**

<b>Important Identified Risks</b>	Serious neurologic adverse reactions including cerebral oedema
	Cytokine release syndrome (CRS)
	Cytopenias including aplastic anemia
	Infections
	Hypogammaglobulinemia
<b>Important Potential Risks</b>	Secondary malignancy
	Immunogenicity
	Replication-competent retrovirus (RCR)
	Tumor lysis syndrome (TLS)
	Aggravation of graft vs host disease (GvHD)
	Transmission of infectious agents via product
	Decrease in viability of the product due to inappropriate preparation of infusion
	CD19 negative relapse
	Chimeric antigen receptor T cells (CAR T) persistence in relapsed patients
	Failure to produce a viable CAR T cell product
<b>Missing Information</b>	Use in pregnancy and lactation
	Use in non-Caucasian patient populations
	New occurrence or exacerbation of an autoimmune disorder
	Long term safety

**II.B. Summary of Important Risks**

Yescarta haematological cancers

**Table Part VI.2. Summary of Important Risk(s) and Missing Information**

<b>Important Identified Risk</b>	<b>Serious Neurologic Adverse Reactions including Cerebral Oedema</b>
<b>Evidence for linking the risk to the medicine</b>	Serious neurologic adverse reactions were reported in clinical trials, post-marketing surveillance, and in patient treated with other CAR T therapies.

<b>Risk factors and risk groups</b>	<p><b>Patient factors:</b> Younger patients (&lt;65) and male patients had a lower incidence of neurologic events.</p> <p><b>Dose-related:</b> A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of neurologic events.</p>
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b> SmPC sections 4.2, 4.4, 4.7, and 4.8 PL sections: 2, 4 Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b> Healthcare professional (HCP) educational material Patient alert card (PAC) Controlled distribution program</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the post-authorisation development plan.</p>
<b>Important Identified Risk</b>	<b>CRS</b>
<b>Evidence for linking the risk to the medicine</b>	CRS was reported in clinical trials, post-marketing surveillance, and in patient treated with other CAR T therapies.
<b>Risk factors and risk groups</b>	<p><b>Patient factors:</b> A higher disease burden and organ dysfunction was associated with a higher rate of CRS. Subjects with cardiac atrial or cardiac ventricular lymphoma involvement or history of cardiovascular disease.</p> <p><b>Dose-related:</b> A higher dose of CAR T cells and/or potency of the cells was associated with a higher rate of CRS.</p> <p><b>Synergistic effects:</b> Treatment with systemic immunostimulatory agents.</p>
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b> SmPC sections 4.2, 4.4 and 4.8 PL sections: 2, 4</p>

	<p>Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b>  HCP educational material  PAC  Controlled distribution program</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040  ZUMA-1: 31 Oct 2032  ZUMA-5: 30 Apr 2036  ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the postauthorisation development plan.</p>
<b>Important Identified Risk</b>	<b>Cytopenias including Aplastic Anaemia</b>
<b>Evidence for linking the risk to the medicine</b>	Cytopenias were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
<b>Risk factors and risk groups</b>	Prior exposure to chemotherapy or radiation.
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b>  SmPC sections 4.4 and 4.8  PL sections: 2, 4  Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b>  None</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040  ZUMA-1: 31 Oct 2032  ZUMA-5: 30 Apr 2036  ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the postauthorization development plan.</p>
<b>Important Identified Risk</b>	<b>Infections</b>
<b>Evidence for linking the risk to the medicine</b>	Infections were reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.

<b>Risk factors and risk groups</b>	<p><b>Patient factors:</b> Underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress.</p> <p><b>Additive or synergistic factors:</b> Surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures.</p>
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b></p> <p>SmPC sections 4.2, 4.4 and 4.8</p> <p>PL sections: 2, 4</p> <p>Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b></p> <p>None</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040</p> <p>ZUMA-1: 31 Oct 2032</p> <p>ZUMA-5: 30 Apr 2036</p> <p>ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the postauthorization development plan</p>
<b>Important Identified Risk</b>	<b>Hypogammaglobulinemia</b>
<b>Evidence for linking the risk to the medicine</b>	Hypogammaglobulinaemia was reported in clinical trials, post-marketing surveillance, and in patients treated with other CAR T therapies.
<b>Risk factors and risk groups</b>	Prior treatment with rituximab and concomitant use of other drugs (e.g. steroids) that can induce hypogammaglobulinemia.
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b></p> <p>SmPC sections 4.4 and 4.8</p> <p>PL section: 4</p> <p>Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b></p> <p>None</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040</p> <p>ZUMA-1: 31 Oct 2032</p> <p>ZUMA-5: 30 Apr 2036</p> <p>ZUMA-6: 31 Aug 2033</p>

	See Section II.C of this summary for an overview of the postauthorization development plan.
<b>Important potential risk</b>	<b>Secondary Malignancy</b>
<b>Evidence for linking the risk to the medicine</b>	Secondary malignancies were not reported in clinical trials.
<b>Risk factors and risk groups</b>	<b>Patient factors:</b> Age. <b>Additive or synergistic factors:</b> Chemotherapy and immunosuppressive treatments.
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> SmPC sections 4.4 Use restricted to physicians experienced in the treatment of haematological cancers <b>Additional risk minimization measures:</b> Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorization development plan.
<b>Important potential risk</b>	<b>Immunogenicity</b>
<b>Evidence for linking the risk to the medicine</b>	There have been a few reports of immunogenicity in clinical trials and post-marketing.
<b>Risk factors and risk groups</b>	Not known
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> SmPC section 4.8 Use restricted to physicians experienced in the treatment of haematological cancers <b>Additional risk minimization measures:</b> None
<b>Additional pharmacovigilance activities</b>	ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036

	ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorization development plan.
<b>Important potential risk</b>	<b>RCR</b>
<b>Evidence for linking the risk to the medicine</b>	There is no evidence for the occurrence of RCR in patients treated with axicabtagene ciloleucel.
<b>Risk factors and risk groups</b>	Not applicable
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> Use restricted to physicians experienced in the treatment of haematological cancers  <b>Additional risk minimization measures:</b> None
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Part VI Section II.C of this summary for an overview of the postauthorization development plan.
<b>Important potential risk</b>	<b>TLS</b>
<b>Evidence for linking the risk to the medicine</b>	There have been a few reports of TLS in clinical trials and post-marketing.
<b>Risk factors and risk groups</b>	<b>Patient factors</b> Tumour size and presence of bulky tumour, wide metastatic dispersal, and organ and/or bone marrow involvement. Patients' health status, including presence of hypotension, dehydration, acidic urine, oliguria, pre-cancer nephropathy, and previous experience with nephrotoxic agents {McBride 2012}.  <b>Additive or synergistic factors:</b> Medications and other compounds that tend to increase uric acid levels
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> SmPC sections 4.4 PL section 2

	<p>Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b> None</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the postauthorization development plan.</p>
<b>Important potential risk</b>	<b>Aggravation of GvHD</b>
<b>Evidence for linking the risk to the medicine</b>	There have been a few reports of GvHD in patients treated with axicabtagene ciloleucel.
<b>Risk factors and risk groups</b>	Patients who had undergone a prior allogeneic haematopoietic stem-cell transplant (allo-HSCT) and then received donor derived CAR T cells (from prior allo-HSCT donor) appear to be at an increased risk of developing aggravation of GvHD or GvHD.
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b> SmPC section 4.4 PL section 2</p> <p>Use restricted to physicians experienced in the treatment of haematological cancers</p> <p><b>Additional risk minimization measures:</b> None</p>
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the post-authorization development plan.</p>
<b>Important potential risk</b>	<b>Transmission of Infectious Agents via Product</b>
<b>Evidence for linking the risk to the medicine</b>	There have been no reports of transmission of infectious agents via product.

<b>Risk factors and risk groups</b>	Needle stick or other means of exposure to axicabtagene ciloleucel (e.g. through broken skin) are the main risk factors. Risk groups are the manufacturing personnel and HCPs handling patient cells.
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b> SmPC Sections 4.2 PL Section 3</p> <p><b>Additional risk minimization measures:</b> None</p>
<b>Important potential risk</b>	<b>Decrease in Viability of the Product due to Inappropriate Preparation of Infusion</b>
<b>Evidence for linking the risk to the medicine</b>	There have been no reports linked to a decrease in viability of the product due to inappropriate preparation of cell infusion.
<b>Risk factors and risk groups</b>	Lack of adherence to the specifications for preparation of infusion.
<b>Risk minimization measure(s)</b>	<p><b>Routine risk minimization measures:</b> SmPC section 4.2</p> <p><b>Additional risk minimization measures:</b> Guide to Handling, Method of Administration and Sampling Recommendations for Secondary Malignancies.</p>
<b>Important potential risk</b>	<b>CD19 Negative Relapse</b>
<b>Evidence for linking the risk to the medicine</b>	Due to substantial research limitations, there is currently no clear evidence that axicabtagene ciloleucel treatment might lead to CD19negative relapse.
<b>Risk factors and risk groups</b>	No risk groups or risk factors can be identified.
<b>Risk minimization measure(s)</b>	None
<b>Additional pharmacovigilance activities</b>	<p>KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033</p> <p>See Section II.C of this summary for an overview of the postauthorisation development plan.</p>
<b>Important potential risk</b>	<b>CAR T persistence in relapsed patients</b>

<b>Evidence for linking the risk to the medicine</b>	There is no evidence that axicabtagene ciloleucel treatment might lead to loss of efficacy due to low CAR T persistence.
<b>Risk factors and risk groups</b>	T-cell exhaustion likely stems from patients undergoing several rounds of chemotherapy prior to transplant.
<b>Risk minimization measure(s)</b>	None
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorisation development plan.
<b>Important potential risk</b>	<b>Failure to produce a viable CAR T cell product</b>
<b>Evidence for linking the risk to the medicine</b>	The inability to generate final product from cells is an infrequent occurrence.
<b>Risk factors and risk groups</b>	The exhausted state of the patient's lymphocytes from prior lines of therapy may contribute to difficulty in manufacturing product.
<b>Risk minimization measure(s)</b>	None
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorisation development plan.
<b>Missing information</b>	<b>Use in pregnancy and lactation</b>
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> SmPC section 4.6 PL section: 2 Use restricted to physicians experienced in the treatment of haematological cancers <b>Additional risk minimization measures:</b> None

<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 See Section II.C of this summary for an overview of the postauthorisation development plan.
<b>Missing information</b>	<b>Use in Non-Caucasian Patient Populations</b>
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> None  <b>Additional risk minimization measures:</b> None
<b>Additional pharmacovigilance activities</b>	ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorisation development plan.
<b>Missing information</b>	<b>New Occurrence or Exacerbation of an Autoimmune Disorder</b>
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> SmPC section 5.1 Use restricted to physicians experienced in the treatment of haematological cancers <b>Additional risk minimization measures:</b> None
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 See Section II.C of this summary for an overview of the postauthorisation development plan.
<b>Missing information</b>	<b>Long Term Safety</b>
<b>Risk minimization measure(s)</b>	<b>Routine risk minimization measures:</b> Use restricted to physicians experienced in the treatment of haematological cancers  <b>Additional risk minimization measures:</b> None
<b>Additional pharmacovigilance activities</b>	KT-EU-471-0117: 14 Nov 2040 ZUMA-1: 31 Oct 2032 ZUMA-5: 30 Apr 2036 ZUMA-6: 31 Aug 2033 See Section II.C of this summary for an overview of the postauthorisation development plan.

## II.C. Post-authorization Development Plan

### II.C.1. Studies which are Conditions of the Marketing Authorization

**Table Part VI.3. Studies as Condition of the Marketing Authorization**

<b>Study Short Name</b>	<b>Purpose of the Study</b>
KT-EU-471-0117	<p><b>Primary objective:</b></p> <p>To evaluate the incidence rate and severity of adverse drug reactions (ADRs) in patients treated with Yescarta, including secondary malignancies, CRS, neurologic events, serious infections, prolonged cytopenias, hypogammaglobulinaemia, and pregnancy outcomes in female patients of childbearing potential.</p> <p><b>Secondary objectives:</b></p> <p>To determine the overall survival rate and causes of death after administration of Yescarta.</p> <p>To determine the time to next treatment after administration of Yescarta.</p> <p>To determine the time to relapse or progression of primary disease after administration of Yescarta.</p> <p>To assess the safety and effectiveness profile by gender, age, and in special populations (patients with prior autologous stem cell transplant, high risk comorbidity index, patients treated with out-of-specification product), and additional subgroups may also be explored.</p> <p>To assess the risk of TLS and aggravation of GvHD, and the detection of RCR in samples of patients with secondary malignancies.</p> <p><b>Other exploratory objectives:</b></p> <p>To determine the occurrence of loss of target antigen and of functional CAR T persistence in patients relapsing after Yescarta therapy.</p>

### II.C.2. Other Studies in Post-Authorization Development Plan

**Table Part VI.4. Other Studies in Post-Authorization Development Plan**

<b>Study Short Name</b>	<b>Purpose of the Study</b>
KTE-C19-101 (ZUMA-1)	To evaluate the safety and efficacy of axicabtagene ciloleucel.

<b>Study Short Name</b>	<b>Purpose of the Study</b>
KTE-C19-105 (ZUMA-5)	To evaluate the safety and efficacy of axicabtagene ciloleucel.
KTE-C19-106 (ZUMA-6)	To evaluate the safety and efficacy of axicabtagene ciloleucel.