Swiss Public Summary of the Risk Management Plan (RMP)

for

TECARTUS®

(autologous anti-CD19-transduced CD3+ cells)

Version 1.0 (October 2021)
Based on EU RMP version 1.0 (October 2020)

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1 SUMMARY OF RISK MANAGEMENT PLAN FOR TECARTUS® (AUTOLOGOUS ANTI-CD19-TRANSDUCED CD3+ CELLS)

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 minimize them.

The RMP summary of Tecartus 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 Tecartus in Switzerland is the „Arzneimittelinformation / Information sur le médicament“ (see www.swissmedic.ch) approved authorized by Swissmedic. Gilead Sciences Switzerland Sàrl is fully responsible for the accuracy and correctness of the content of the here published summary RMP of Tecartus.

1.1 The Medicine and What is it Used for

Tecartus is authorized for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton’s tyrosine kinase (BTK) inhibitor (see SmPC for full indication). It contains autologous anti-CD19-transduced CD3+ cells as the active substance and it is given as a single infusion product for autologous and intravenous use only.

Further information about the evaluation of Tecartus’s benefits can be found in Tecartus’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage link to the EPAR summary landing page:

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

1.2 Risks Associated with the Medicine and Activities to Minimise or Further Characterize the Risks

Important risks of Tecartus, together with measures to minimise such risks and the proposed studies for learning more about Tecartus’s risks, are outlined below.

Measures to minimise 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed (eg, 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 Tecartus is not yet available, it is listed under 'missing information' below.

1.2.1 List of important risks and missing information

Important risks of Tecartus are risks that need special risk management activities to further investigate or minimise 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 Tecartus. 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 1-1. List of Important Risks and Missing Information

Important Identified Risks	Serious neurologic events, including cerebral oedema
	CRS
	Cytopenias
	Infections
	Hypogammaglobulinaemia
Important Potential Risks	Secondary malignancy
	Immunogenicity
	RCR
	TLS
	Aggravation of GvHD
Missing Information	New occurrence or exacerbation of an autoimmune disorder
	Long-term safety

1.2.2 Summary of Important Risks

Tecartus has been assigned the legal status of a medicine subject to medical prescription in the European Union (EU), whereby therapy must be administered in a qualified clinical setting, and be initiated by a doctor experienced in the management of haematological malignancies (as described in section 4.2 of the SmPC).

Table 1-2. Summary of Important Risk(s) and Missing Information

Important Identified Risk	Serious Neurologic Events including Cerebral Oedema
Evidence for linking the risk to the medicine	Although neurologic toxicity is associated with KTE-X19, the mechanisms underlying the neurologic events remain unclear. Results of ZUMA-2 showed that 68% of the patients experienced neurologic events, with 33% of the patients experiencing grade 3 or higher neurologic events. No subject experienced a Grade 5 neurologic event.
Risk factors and risk groups	Multiple groups have found anti-CD19 CAR T and CD14+ myeloid cells in the cerebrospinal fluid (CSF) of patients, and elevated IL-6 levels in the CSF have been observed in patients experiencing neurotoxicity {Brudno 2016a}. Correlative analyses were performed for Cohort 1 only. The median peak anti-CD19 CAR T-cell level in blood was 8.27-fold higher in subjects with Grade 3 or higher neurologic events relative to the median peak level in subjects with Grade 2, Grade 1, or no neurologic events (361.50 versus 43.71 cells/μL; nominal p = 0.0001). Of the 17 key analytes statistically evaluated, the median peak serum levels for the following analytes were higher (nominal Wilcoxon rank-sum p value ≤ 0.05) among subjects who experienced Grade 3 or higher neurologic events versus Grade 2, Grade 1, or no neurologic events after infusion of KTE-X19: granzyme B, IFN-γ, IL-1RA, IL-2, IL-6, IL-10, TNF-α and GM-CSF. Compared with subjects ≥65 years of age, subjects <65 years of age had a similar incidence of neurologic events (70% vs 67%). Compared with males, females had a higher incidence of serious neurologic events (50% vs 28%). The majority of subjects were male (68 subjects, 83%), which limits the interpretation of these results. Compared with subjects who had a baseline ECOG performance status of 0, subjects who had a performance status of 1 had a ≥ 10% higher incidence of Grade 3 or higher neurologic events (45% vs 25%), and serious neurologic events (39% vs 27%).
Risk Minimization Measure(s)	Routine risk minimization measures: SmPC sections: 4.2, 4.4, 4.8 Patient Leaflet: 2, 4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimization measures: HCP educational material Patient Alert Card (PAC) Controlled distribution program
Additional Pharmacovigilance activities	Registry study, prescriber survey, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan

Important Identified Risk	**Cytokine Release Syndrome**
Evidence for linking the risk to the medicine	Cytokine release syndrome is induced by activated anti-CD19 CAR T cells after engagement with the CD19 target and may involve a generalised and reversible inflammatory process. In ZUMA-2, 91% of the patients experienced CRS; 15% had severe CRS. CRS is considered an important identified risk due to its frequency and seriousness and the potential for severe outcomes if left untreated.
Risk factors and risk groups	*Patient factors* In some reports, the severity of CRS and elevation of serum cytokines have been related to disease burden, with higher disease burden predicting more toxicity presumably because this leads to higher levels of T-cell activation {Almasbak 2016, Brudno 2016a}. Maude et al. reported that the baseline disease burden (the percentage of blast cells in bone marrow before infusion) correlated with the severity of the CRS; a higher disease burden was significantly associated with severe CRS (P =0.002) {Maude 2014}. CRS associated with adoptive T-cell therapies has been consistently associated with elevated IFN-γ, IL-6, and TNF-α levels, and increases in IL-2, GM-CSF, IL-10, IL-8, IL-5, and fractalkine {Davila 2014, Grupp 2013, Kalos 2011, Kochenderfer 2012}. Compared with subjects who were < 65 years old, subjects who were ≥ 65 years old had a higher incidence of Grade 3 or higher CRS (19% versus 8%). The majority of subjects were male (68 subjects, 83%), which limits interpretation of gender comparative analysis. However, compared to male subjects, females had a ≥ 10% higher incidence of KTE-X19 Grade 3 or higher CRS (43% versus 9%). Compared with subjects who had a baseline ECOG performance status of 0, subjects who had a performance status of 1 had a higher incidence of Grade 3 or higher CRS (16% versus 14%). CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, pulmonary). Worsening of underlying organ pathologies can occur in the setting of CRS. In addition, haemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLS/MAS) may occur in the setting of CRS.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC sections: 4.2, 4.4, 4.8 PL section: 2, 4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: HCP educational material PAC Controlled distribution program
Additional Pharmacovigilance activities	Registry study, prescriber survey, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan.

Important Identified Risk	**Cytopenias**
Evidence for linking the risk to the medicine	Cytopenias are consistent with the known toxicities of the conditioning regimen of chemotherapy. In addition KTE-X19 may cause myelosuppression by a cytokine mediated mechanism. In ZUMA-2, 85%, 66%, and 70% of the patients had neutropenia, anaemia and thrombocytopenia, respectively; 84%, 51% and 51% of these cases were Grade 3 or higher, respectively. There were no reported AEs of aplastic anaemia. Cytopenias are considered important identified risk due to their frequency, seriousness and severity which could lead to important clinical manifestations such as infection or bleeding.
Risk factors and risk groups	A systematic review of cancer patients receiving chemotherapy showed that older age, poor performance status, female gender, comorbidities, and low BMI are risk factors for the development of febrile neutropenia {Lyman 2014}. The risk of febrile neutropenia increases in direct proportion to the severity and duration of neutropenia {Lyman 2010}. Bone marrow involvement was found to be a risk factor for chemotherapy induced neutropenia and fever {Kitay-Cohen 1996}.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC sections: 4.4, 4.8 PL section: 2, 4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan
Important Identified Risk	**Infections**
Evidence for linking the risk to the medicine	Infections, especially serious infections, are consistent with the known toxicities of the conditioning regimen of chemotherapy. In addition KTE-X19 can cause depletion of B-cells. In ZUMA-2, 56% of the subjects had any infection. Infections are considered important identified risk due to their frequency, seriousness and severity if left untreated. Thus, further evaluation of frequency, severity, seriousness and outcome of this risk in the post-marketing period is warranted.
Risk factors and risk groups	Factors that predispose to infection are divided into those that are host associated and those that are treatment associated. *Patient factors* Host-associated factors include underlying immune deficiencies, medical comorbidities, past infections, poor nutritional status, and psychological stress. The type of malignancy and status of the malignancy (i.e., active or in remission) are important factors in determining infection risk. Patients with acute lymphoma who are neutropenic, either due to their underlying disease or due to cytotoxic chemotherapy, are at risk for a different set of infections than those who are not neutropenic {Zembower 2014}. *Additive or synergistic factors* Treatment-associated factors include surgery, radiation, immunosuppressant therapies, antimicrobial use, and invasive procedures are important factors in the risk of infections {Zembower 2014}.

Important Identified Risk	**Infections**
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC sections: 4.4, 4.8 PL section: 2, 4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan
Important Identified Risk	**Hypogammaglobulinaemia**
Evidence for linking the risk to the medicine	Hypogammaglobinemia is caused by B-cell aplasia. In ZUMA-2, 16% of the patients experienced hypogammaglobinemia. At Month 3, the first time point at which B cells were measured after KTE-X19 infusion in Cohort 1 subjects, median B-cell levels declined to 0.090% (range: 0.017% to 96.147%). Median B-cell levels demonstrated recovery by Month 18 in evaluable subjects (median: 10.624%, range: 3.967% to 15.992%). Hypogammaglobinemia is considered an important identified risk due to the risk of infections if left untreated.
Risk factors and risk groups	Prior treatment with rituximab and concomitant use of other drugs (e.g., steroids) that can induce hypogammaglobulinaemia.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC sections: 4.4, 4.8 PL section: 4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan
Important Potential Risk	**Secondary Malignancy**
Evidence for linking the risk to the medicine	Secondary malignancy is consistent with the known outcomes of immunosuppression and/or genotoxicity resulting from chemotherapy. Patients with NHL are known to be at risk for developing secondary malignancies {Smeland 2016, Tward 2006}. Secondary malignancy is serious, potentially life-threatening and would require medical intervention and hence it is an important potential risk.

Important Potential Risk	**Secondary Malignancy**
Risk factors and risk groups	*Patient factors* Age is a risk factor for secondary malignancy {Andre 2004, Moser 2006}. A meta-analysis showed that NHL patients experience a higher risk for secondary malignant neoplasms than the general population (pooled relative risk of 1.88 overall and 1.32 for solid tumors) {Pirani 2011}. *Additive or synergistic factors* Use of any type of chemotherapy alone was associated with higher risk for secondary malignant neoplasms. A similar result was observed in the sub-analysis on patients treated only with alkylating agents, while the pooled relative risk of secondary malignant neoplasms for patients who underwent treatment with CHOP or CHOP-like or radiotherapy alone was raised but not statistically significant. A combined modality of treatment was significantly associated with the risk for overall secondary malignant neoplasms but not for solid tumors {Pirani 2011}.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC section: 4.4 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan.
Important Potential Risk	**Immunogenicity**
Evidence for linking the risk to the medicine	Antibodies can reduce the efficacy of KTE-X19 and can cause safety issues like anaphylaxis, CRS, infusion reactions etc. that may require medical intervention and hence it is an important potential risk. Immunogenicity was identified by the development of antibodies that tested positive for reactivity against the murine monoclonal antibody FMC63 (parent antibody for the single-chain variable region fragment [scFv] used for production of the anti-CD19 CAR in KTE-X19) as measured by ELISA. No KTE-X19 related confirmed cases of immunogenicity were seen in ZUMA-2 in this cell based assay.
Risk factors and risk groups	Not known.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC section: 4.8 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan

Important Potential Risk	**Replication-competent Retrovirus (RCR)**
Evidence for linking the risk to the medicine	As a murine γ-retroviral vector is used in the production of KTE-X19, a potential risks exists for the presence of RCR. No subjects tested positive for presence of RCR, however RCR is considered an important potential risk due to the risk of genotoxicity that may lead to secondary malignancy. Thus further evaluation in the post-marketing period is warranted.
Risk factors and risk groups	Not applicable
Risk Minimization Measure(s)	Routine risk minimisation measures: Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan.
Important Potential Risk	**Tumour Lysis syndrome (TLS)**
Evidence for linking the risk to the medicine	Tumor lysis syndrome occurs as a result of massive tumour cell death and thus it is consistent with the potential effects of conditioning chemotherapy and KTE-X19 treatment. In ZUMA-2, 1 subject had Grade 3 tumor lysis syndrome that was assessed as non-serious and related to KTE-X19. TLS is considered an important potential risk due to the seriousness of the condition.
Risk factors and risk groups	Patients with bulky disease, baseline elevated uric acid and renal impairment.
Risk Minimization Measure(s)	Routine risk minimisation measures: SmPC section: 4.4 PL section: 2 Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan.

Important Potential Risk	**Aggravation of Graft versus Host Disease (GvHD)**
Evidence for linking the risk to the medicine	The evidence of GvHD or aggravation of GvHD after administration of engineered CAR T cells in patients with a previous allo-HSCT is limited. As noted previously, Kochenderfer et al reported results from a study using donor derived leukocytes (from prior allo-HSCT donor) expressing a CD19 CAR to patients with persistent B-cell malignancies following allo-HSCT {Kochenderfer 2013}; updated data presented by Brudno et al {Brudno 2016b} demonstrated that of 20 patients with either B-ALL, CLL or non-Hodgkin lymphoma (NHL), no patients developed acute GvHD and 2 patients developed chronic GvHD after CAR T-cell infusion. In another clinical study, however, 2 patients with relapsed or refractory B-ALL who received allogeneic CD19 CAR T cells developed GvHD 3 to 4 weeks after CAR T-cell infusion. One patient presented with grade 2 liver GvHD, whereas the other developed grade 2 skin and liver GvHD. One of these patients died of relapse 8 weeks after T-cell infusion, whereas the other developed a hematologic CR as well as partial regression of extramedullary leukemic disease {Dai 2015}. Maude et al {Maude 2014}, Lee et al {Lee 2015}, and Park et al {Park 2018} reported on the administration of recipient derived CAR T cells for patients with relapsed or refractory ALL or NHL and observed no GvHD following CD 19 CAR T infusion {Smith 2018}. It is important to note that patients with a history of allogeneic stem cell transplantation were excluded from the ZUMA-2 study. As GvHD can be life threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	Patients who had undergone a prior 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.
Risk Minimization Measure(s)	Routine risk communication: SmPC section: 4.4 PL section: 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan
Missing information	**New occurrence or exacerbation of an autoimmune disorder**
Risk Minimization Measures	Routine risk minimisation measures: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None

Missing information	**New occurrence or exacerbation of an autoimmune disorder**
Additional Pharmacovigilance activities	Registry, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan
Missing information	**Long term safety**
Risk Minimization Measures	Routine risk minimisation measures: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: Use restricted to physicians experienced in the treatment of hematological cancers Additional risk minimisation measures: None
Additional Pharmacovigilance activities	Registry study, and studies ZUMA-3 and ZUMA-8 See Part VI Section 1.2.3 of this summary for an overview of the post-authorisation development plan

1.2.3 Post-authorization Development Plan

1.2.3.1 Studies which are Conditions of the Marketing Authorization

Table 1-3. Studies as Condition of the Marketing Authorization

Short Study Name	**Purpose of the Study**
Non-interventional prospective long-term efficacy and safety study based on data from a registry	A prospective study to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or refractory MCL and the Benefit/Risk in subgroups: elderly, females, patients with severe disease. Further evaluation of efficacy, additional characterisation of the identified risks, further evaluation of potential risks and missing information. This study will be designed as an efficacy and safety long-term follow up study.
KTE-C19-102 (ZUMA-2) Phase 2, multicenter, open-label study	To confirm long term efficacy and safety in subjects treated with KTE-X19 in Cohort 1

1.2.3.2 Other Studies in Post-Authorization Development Plan

Table 1-4. Other Studies in Post-Authorization Development Plan

Short Study Name	Purpose of the Study
Planned Prescriber Survey	Evaluating the effectiveness of risk minimisation activities: HCP educational material and Patient Alert Card
KTE-C19-103 (ZUMA-3) Phase 1/2, multicenter, open-label study	To evaluate efficacy and safety of KTE-X19 in relapsed/refractory Adult ALL subjects
KTE-C19-108 (ZUMA-8) Phase 1, multicenter, open-label study	To evaluate the safety and tolerability of KTE-X19 in adult subjects with relapsed/refractory CLL and SLL