swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Tecartus®

International non-proprietary name: brexucaptagene autoleucel

Pharmaceutical form: dispersion for infusion

Dosage strength(s): a single dose of Tecartus contains 2×10^6 CAR-positive viable T cells per kg of body weight (range: $1 \times 10^6 – 2 \times 10^6$ cells/kg), or a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above in approximately 68 mL dispersion in an infusion bag

Route(s) of administration: for autologous and intravenous use only

Marketing authorisation holder: Gilead Sciences Switzerland Sàrl

Marketing authorisation no.: 67884

Decision and decision date: approved on 25.08.2021

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BTK	Bruton's tyrosine kinase
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete remission
CRS	Cytokine release syndrome
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
ESMO	European Society for Medical Oncology
EVA	Ethylene vinyl acetate
FAS	Full analysis set
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IAS	Inferential analysis set
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
IRC	Independent review committee
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MCL	Mantle cell lymphoma
Min	Minimum
mITT	Modified intention to treat
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics

PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PPQ	Process performance qualification
PR	Partial response
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SD	Stable disease
SwissPAR	Swiss Public Assessment Report
TBI	Total body irradiation
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VIS	Vector integration site

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for brexucaptagene autoleucel.

Fast-track authorisation procedure
The applicant requested a fast-track authorisation procedure in accordance with Article 7 TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. Orphan drug status was granted on 14 May 2020.

2.2 Indication and dosage

2.2.1 Requested indication

Tecartus is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).

2.2.2 Approved indication

Tecartus is a genetically modified autologous T-cell immunotherapy directed against CD19 and is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after 2 or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

2.2.3 Requested dosage

Summary of the requested standard dosage:
A single dose of Tecartus contains 2 × 10^6 CAR-positive viable T cells per kg of body weight (or a maximum of 2 × 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

Each patient-specific single infusion bag of Tecartus contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 × 10^6 CAR T cells per kg body weight (range: 1 × 10^6 – 2 × 10^6 cells/kg), with a maximum of 2 × 10^8 anti-CD19 CAR T cells.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 July 2020
Formal control completed	22 July 2020
List of Questions (LoQ)	25 September 2020
Response to LoQ	14 December 2020
Preliminary decision	23 June 2021
Response to preliminary decision	5 August 2021
Final decision	25 August 2021
Decision	approval

3 Medical context

Mantle cell lymphoma (MCL) is an aggressive subtype of non-Hodgkin lymphoma (NHL) with distinctive clinical, biological, and molecular characteristics. It is more likely to affect men than women, and the median age at diagnosis is 68 years.

Mantle cell lymphoma belongs to the group of mature B-cell neoplasms. The lymphoma cells in MCL are thought to originate from antigen-naive pre-germinal centre B cells within the mantle zone of the lymph node and typically express the surface markers CD19, CD20, CD22, CD43, CD79a, FMC7, CD5, surface immunoglobulin (Ig) M, and surface IgD, but not CD11c and CD10. The molecular hallmark of more than 95% of MCLs is the chromosomal translocation t(11;14)(q13;q32), which results in overexpression of the cell cycle regulator cyclin D1.

Most patients present with advanced lymphadenopathy, and approximately 25% have extra-nodal presentation including the spleen, bone marrow, and GI tract. They are thus often diagnosed with advanced disease (Stage III or IV) and as a result have an aggressive clinical course and poor prognosis[1].

First-line therapy for MCL typically includes chemotherapy in combination with a CD20-targeting antibody. There is no single standard of care, with regimens such as rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); rituximab in combination with cyclophosphamide, vincristine, and prednisone (R-CVP); and bendamustine and rituximab (BR) demonstrating high initial response rates. Autologous stem cell transplants performed upfront or in first remission have led to improved progression-free survival at the expense of additional toxicity. Despite high initial response rates to these therapies, almost all patients eventually develop progressive disease.

The active substance ibrutinib (brand name: Imbruvica), a BTK inhibitor, has marketing authorisation in Switzerland for MCL and CLL. According to NCCN and ESMO guidelines[2], recommendations for relapsed or refractory disease include high-dose therapy with autologous stem cell rescue and the second-line agents bendamustine, bortezomib, temsirolimus, ibrutinib, or lenalidomide with rituximab; allogeneic stem cell transplantation can be considered in selected patients as part of second-line consolidation.

[1] Prognosis varies based on clinical and laboratory parameters and can be estimated using the mantle cell international prognostic index (MIPI). This index uses the 4 independent prognostic factors of age, Eastern Cooperative Oncology Group [ECOG] performance status, blood lactate dehydrogenase (LDH), and leukocyte count. It has been used to classify patients as low (60-83% 5 yr OS), intermediate (35-63% 5 yr OS), or high-risk (20-34% 5 yr OS).

[2] ESMO/EHA and NCCN treatment guidelines: (Source: https://www.annalsofoncology.org/article/S0923-7534(19)42151-0/pdf https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf)

4 Quality aspects

4.1 Drug substance

Tecartus (brexucabtagene autoleucel) comprises autologous Tcells, genetically modified using an integrating, replication-incompetent γ-retroviral vector carrying a transgene that encodes for a chimeric antigen receptor (CAR) directed against CD19 antigen. CD19 is a potential target for treatment of B-cell malignancies. Anti-CD19 CAR consists of the extracellular part, the murine anti-CD19 single-chain variable fragment linked to the intracellular co-stimulatory domains derived from CD28 and CD3ζ receptors.
Tecartus is classified as an *ex vivo* gene therapy product.

Gamma-retroviral vector PG13-CD19-H3
A retroviral vector (PG13-CD19-H3) carrying a transgene for anti-CD19 CAR is used for *ex vivo* gene transfer into the target cells. The vector is based on a murine stem cell virus containing the necessary regulatory sequences and an anti-CD19 CAR transgene. A stably transfected packaging mammalian cell line is used in the upstream manufacturing process. A 2-tiered cell bank system was established and qualified according to ICH Q5D.
After cell expansion, supernatant containing the vector is collected, filtered, and filled into a cryopreservation bag. Sufficient information on the vector manufacturing process and control strategy was provided. The process was validated and the control strategy and data presented demonstrated that the manufacturing process is capable of producing vector batches which consistently meet the predefined requirements.
Within the scope of characterisation studies, the PG13-CD19-H3 vector was confirmed to encode an anti-CD19 CAR transgene, and its ability to infect and stably integrate the transgene into the genome of T cells was demonstrated. Successful production of functional CD19 CAR in the cells upon transgene integration was shown.
The vector-release specification contains a panel of tests to confirm identity, purity, and biological activity, and to determine infectious titre. In addition to other safety parameters, an absence of replication-competent retroviruses is confirmed on a routine basis. Analytical methods were described in sufficient detail. Non-compendial methods have been validated according to ICH guidelines and compendial methods adequately verified.
A proposed shelf-life for the PG13-CD19-H3 vector under the proposed long-term storage conditions was accepted.
The PG13-CD19-H3 vector is also used in the previously approved *ex vivo* gene therapy product Yescarta.

Tecartus (KTE-X19)
Tecartus is a patient-specific *ex vivo* gene therapy, derived from the patient's own peripheral blood cells (apheresis). One manufacturing run initiated from a single patient's apheresis corresponds to 1 batch of the drug product. Patient apheresis material is collected at a qualified centre and transported to the manufacturing site under validated conditions.
The patient's cells undergo a T-cell selection procedure with specific antibody-coated beads using an automatic system in order to enrich the target T cells and reduce cellular impurities. Isolated T cells may be directly processed or cryopreserved and stored until further processing. The enriched T cells undergo activation with suitable reagents followed by transduction using the replication-incompetent retroviral vector PG13-CD19-H3 and by cell expansion in a selective medium. The expanded transduced cells are washed and concentrated prior to formulation into the final product.
The manufacturing process is continuous and proceeds directly to the drug product formulation and filling steps. The drug substance is not isolated and individual specification at this level was not established.
Overall, the manufacturing process including process parameters and controls was described in sufficient detail.

Process performance qualification (PPQ) was performed using material from healthy donors. Process qualification was adequately designed to cover all process options, such as in-process cryopreservation of selected cells, repeating of the washing procedure, filling at 2 target doses, and use of a semi-automated formulation and filling procedure. PPQ runs fulfilled the predefined validation acceptance criteria for process parameters or process controls as well as release specification. Transport of apheresis material in a qualified shipper was validated. Extended characterisation of the PPQ batches demonstrated that the product's cellular composition is within the expected ranges, with variability that can be attributed to the starting material.

The manufacturing process for Tecartus is based on the process for the approved product Yescarta. Changes to the Yescarta manufacturing process were described and Tecartus-specific process steps were characterised. The T-cell selection step accounts for a major difference from the Yescarta process and is justified by the differences in composition of the apheresis material derived from patients with 2 different indications (diffuse large B-cell lymphoma in the case of Yescarta and mantle cell lymphoma for Tecartus). The impact of apheresis material composition, type of equipment used for apheresis material collection, as well as apheresis time and storage temperatures on the process performance and drug product quality attributes was evaluated.
The biological and physical properties as well as the subcellular composition of the Tecartus and its impact on biological activity were extensively characterised. Product-related and process-related impurities were addressed and, wherever applicable, their removal to acceptable levels was demonstrated.

4.2 Drug product

Tecartus contains 1.0 to 2.0 $\times 10^6$ anti-CD19 CAR-positive viable T-cells per kg of patient weight in a target volume of 68 mL as a single dose. The maximum allowable dose is limited to 2.0×10^8 anti-CD19 CAR-positive viable T-cells. The drug product is supplied cryopreserved in cryopreservation bags and administered by infusion after thawing.
The excipients used for the formulation of the drug product are 0.9% sodium chloride, human serum albumin 25%, and cryopreservation medium containing 5% dimethyl sulfoxide (CryoStor CS10).
The primary container used for storage of Tecartus is an ethylene vinyl acetate (EVA) cryopreservation bag with 2 spike ports and 1 single line. Two alternative primary containers of the same material were proposed and their suitability for Tecartus was demonstrated. The secondary container is an aluminium cryocassette.

The manufacturing process for the drug product consists of cell harvest at the end of expansion, filtration of the cell suspension, formulation, filling into the primary containers, inspection, and labelling. After that, the drug product is cryopreserved and stored in the vapour phase of liquid nitrogen. Formulation and filling can be performed by manual or semi-automated procedure. Comparability between the 2 procedures was demonstrated.
To formulate the target dose, cells are sampled prior to harvest and prior to formulation, and relevant parameters are assessed. The volumes needed for formulation are calculated using the total cell number, viability, and transduction efficiency, taking into account the patient's body weight.
The manufacturing process was validated as a continuous process. Transport to the healthcare centres is performed in the vapour phase of liquid nitrogen using qualified dry shippers and was validated.

The drug product release specification covers all relevant tests to confirm identity, purity, potency, and safety. The analytical methods were adequately described. The non-compendial methods have been validated according to ICH guidelines and compendial methods verified for corresponding matrices.

The drug product is stored at a temperature not higher than -150 °C in the vapour phase of liquid nitrogen in its original container. A preliminary shelf-life of 12 months has been granted based on the data provided during assessment.

The proposed in-use shelf-life for the thawed drug product is up to 3 hours at room temperature. The drug product is thawed at room temperature for 30 min prior to administration and the target in-use time for infusion is 30 min.

Tecartus is a cell-based therapy and not amenable to terminal sterilisation or viral inactivation. Thus, adventitious agent safety is reliant on the proper control and qualification of all incoming materials, maintenance of the sterile process under aseptic conditions in closed systems, and use of single-use disposables wherever possible.
Aseptic processing was adequately validated. Confirmation of sterility at the level of the final product is available prior to administration. Sufficient information on the viral safety of the reagents as well as for the retroviral vector was provided.
It can be concluded that the manufacturing process of Tecartus as well as that of the PG13-CD19-H3 retroviral vector incorporate adequate control measures to prevent contamination and maintain control with regard to adventitious agent contamination.

4.3 Quality conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

5 Nonclinical aspects

5.1 Pharmacology

Tecartus (brexucabtagene autoleucel) is an autologous CD19-targeting chimeric antigen receptor T-cell (CAR T) immunotherapy developed for the treatment of relapsed or refractory mantle cell lymphoma (MCL). Autologous peripheral blood T cells are genetically modified *ex vivo* using a gamma-retroviral vector to express a CAR comprising a murine anti-CD19 single-chain variable fragment (scFv) linked to a CD28 co-stimulatory domain and a CD3-zeta cytoplasmic signalling domain. The published literature demonstrates that B cells from most B-cell malignancies, including MCL, as well as from the normal B-cell lineage express CD19 on their surface and that CD19 expression is restricted to those cells. While variable in distinct B-cell malignancies, CD19 expression levels were consistently above reference cells. The inclusion of negative controls such as CD19-negative cells, non-CD19 CAR transduced T cells (SP6-28z), and untransduced T cells ascertained the specificity of CD19-targeting CAR T cells to the target antigen. Cell proliferation and cytotoxicity against CD19-positive cells and viability were demonstrated with CD19-targeting CAR T cells from patients with advanced B-cell haematological malignancies and healthy donors in cell co-cultures and in *in vivo* studies. The anti-CD19 CAR T cells used in the nonclinical studies were generated using a similar scaled-down manufacturing process used to produce brexucabtagene autoleucel. CD19-targeting CAR-transduced CD4+ and CD8+ T cells generated from 2 healthy donors were characterised *in vitro* by measurement of cell expansion, diameter, and viability on Days 0, 1, 6, 9, and 13. Within the first day, both sets of donor T cells increased in diameter and between Days 1 and 13, the T cells from donors 1 and 2 expanded 393- and 155-fold, respectively. Over the same 13-day period, T-cell viability ranged from 77% to 92%. Flow cytometry using scFv-binding fluorophore-labelled antibodies (KIP-1 and KIP-3) demonstrated that transduction of CAR T cells from both donors was stable over the time (Days 6, 9, 13, and 16). Three CD19-targeting CAR T cell products from healthy donors were manufactured, either following a scaled-down (2 donors) or at-scale (1 donor) manufacturing process used for brexucabtagene autoleucel and functionally assessed. Each product was co-cultured with CD19-positive B-lineage acute lymphoblastic leukaemia (Nalm6) cells, CD19-positive B-cell lymphoma (Raji) cells, and CD19-knockout (Raji CD19KO) control cells. In cytotoxicity and cytokine release assays, the CD19-positive Nalm6 and Raji cells were co-cultured overnight with CD19-targeting CAR T cells and showed CD19-dependent cytotoxicity and cytokine release (TNFα, IFNγ, IL-2) with all 3 donors. Results with negative controls confirmed that proliferation, cytokine release, and cytotoxicity were specific to CD19-targeting CAR T cells and dependent on CD19 antigen engagement. A proof-of-concept study in a syngeneic mouse model using a murine surrogate of the anti-CD19 scFV was carried out because the anti-CD19 scFV expressed in brexucabtagene autoleucel solely recognises human CD19.With the exception of the scFV, this anti-murine CD19 CAR construct is identical to the CAR construct used in brexucabtagene autoleucel. The anti-tumour activity of the CD19 murine-targeting CAR-T cells was investigated using a syngeneic lymphoma mouse model. Murine T cells transduced with the anti-murine CD19 CAR construct were injected into mice that underwent total body irradiation (TBI 5Gy) and challenged with CD19-expressing 38c13 lymphoma cells. Administration of CAR T cells both prevented the formation of lymphoma and abolished lymphoma already established with metastasis. The impact of TBI was further evaluated in the same syngeneic mouse model. TBI-induced lymphodepletion prior to CAR T cell and tumour cell administration was important for the prolonged survival of these syngeneic mice, indicating that lymphodepletion is key to successful treatment with brexucabtagene autoleucel.

5.2 Pharmacokinetics

Conventional ADME studies are not applicable to CAR T-cell therapy products. The pharmacokinetic data provided are restricted to *in vivo* persistence for anti-murine CD19 CAR T cells. Taking into account the aforementioned limitations, this is considered acceptable. The persistence of the anti-murine CD19 CAR T cells in a syngeneic mouse model was quantified by flow cytometry, which revealed that CD19-targeting murine CD19 CAR T cells distributed to and remained in the spleen up to 1-week post-administration. No CAR T cells were detected at Day 63 following injection of anti-

murine CD19 CAR T cells and no additional investigation for longer CAR T persistence follow-up was carried out. Evidence from additional investigations demonstrated that mice treated with CD19-targeting CAR T cells remained free of leukaemia up to 209 days post-administration of CAR T cells, indicating long-lasting anti-tumour effects.

5.3 Toxicology

Due to the absence of a relevant animal model for the toxicology assessment of brexucabtagene autoleucel, the nonclinical safety aspects that were investigated were restricted to 1) on-target/off-tumour investigations in the syngeneic mouse model and 2) integration studies to investigate integration diversity and vector integration sites (VIS). The on-target/off-tumour evaluation of CD19-targeting CAR T cells was carried out during the proof-of-concept experiment along with the pharmacology and persistence studies. While B-cell aplasia was observed upon administration of CD19-targeting CAR T cells, B cells were detected at Day 8 in mice treated with control CAR T cells. When animals were treated with CD19-targeting CAR T cells, the lack of B cells persisted in the spleen at Days 63, 143, and 209 (last time point analysed). In contrast, T cell recovery was noted with normal levels measured at 143 days post-infusion of CAR T cells. This on-target/off-tumour effect was expected, and no evidence of overt toxicity was associated with this expected treatment-related B-cell aplasia. Integration site analysis was performed in CAR T cells generated from healthy donor T cells transduced with the retroviral vector utilised for the manufacture of brexucabtagene autoleucel. The VIS analysis showed non-random integration of the vector, which preferentially distributed near the active transcription start site with 10.2% to 10.6% of the identified VIS located within exons. In addition, the analysis revealed that the vector integration was evenly distributed across the chromosomes and the number of VIS nearly matched the number of transcription start sites on each chromosome. Based on further analysis, the applicant concluded that no sign of over-representation of a single VIS could be observed.

5.4 Nonclinical conclusions

While only a limited non-clinical development package was provided, the submitted data support the proposed mechanism of action of brexucabtagene autoleucel. The data adequately demonstrated the specific activity against CD19, effector mechanism, and activation of brexucabtagene autoleucel. While the syngeneic mouse model provided a relevant proof-of-concept for brexucabtagene autoleucel, several limitations are associated with this immunocompetent model such as i) binding affinity differences of the murine and human CD19-targeting CAR T cells to the target antigen ii) T-cell subgroup composition, and iii) expansion and transduction of T cells. While having its own limitations, this approach is considered acceptable, in particular since it overcomes some of the limitations that would be present with the investigation of brexucabtagene autoleucel in immunocompromised mice.

The pharmacokinetic investigations were limited to the persistence of CD19-targeting CAR T cells in the proof-of-concept syngeneic mouse model, which is acceptable for this type of product. While adequate preconditions for the activation, expansion, and survival of CAR T cells were considered to be met, the anti-murine CD19 CAR T cells were detected only for a short period. It should be noted that both the anti-tumour effect and the B-cell aplasia were maintained over the course of the experiment.

No GLP-compliant toxicology studies were performed due to the absence of a relevant animal model. On-target/off-tumour investigation and integration analysis of the vector were carried out to evaluate the nonclinical safety of brexucabtagene autoleucel. Based on the tissue distribution of CD19, the observed B-cell aplasia in the proof-of-concept studies was expected and this effect was similarly observed in patients treated with CD19-targeting CAR T cells. Due to differences in antigen tissue distribution and possible off-target binding to other antigens, the murine anti-CD19 CAR T cells in syngeneic mouse models were not expected to fully replicate the off-target toxicity that could be observed in patients treated with brexucabtagene autoleucel. The vector integration analysis showed

a typical integration pattern as observed with gamma-retroviral vectors, characterised by integration close to the transcription start site and near transcriptionally active genes. More rarely, vector integration was also observed into exons. Finally, the report concluded that no predominance of single integration sites was observed. For this type of product, the absence of genotoxicity, carcinogenicity, reproductive, and developmental toxicity studies is acceptable. From a non-clinical point of view, brexucabtagene autoleucel can be approved.

6 Clinical aspects

ZUMA-2 is a Phase 2, multicentre, open-label study. Patients with r/r MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib) were enrolled in Cohort 1 (pivotal cohort) or Cohort 2 ("dose-finding").

6.1 Clinical pharmacology

Biopharmaceutical development
The autologous CD3-positive T cells that have been transduced with an anti-CD19 CAR using a retroviral vector are defined as the drug substance, whereas these transduced T cells formulated in a cryopreservation medium constitute the drug product for IV infusion. The final drug product KTE-X19 (brexucabtagene autoleucel, trade name Tecartus™) is commercialised in a ready-to-use 68 mL cryostorage bag.

Notably, the CAR construct and the manufacturing process for KTE-X19 are identical to those for Yescarta®, except for an additional T-cell selection/enrichment step due to the presence of circulating tumour cells in patients with MCL.
ADME
Considering the level of complexity of adoptive cell therapies including CAR T cells, classical pharmacological concepts such as ADME and other pharmacokinetic aspects are hardly applicable to these emerging new medicinal products. Pharmacokinetic parameters are used to describe cellular kinetics in terms of expansion ("absorption", "distribution") and persistence ("elimination"). The maximum expansion and the time when the maximum expansion is reached are described by C_{max} and t_{max}; information about the persistence of CAR T cells is provided by AUC, $t_{1/2}$, and t_{last}.

The pharmacokinetic and pharmacodynamic properties of KTE-X19 were investigated in a pivotal Phase 2 study in patients with relapsed/refractory mantle cell lymphoma.

Following the target dose of 2×10^6 anti-CD19 CAR T cells per kg body weight, with a maximum flat dose of 2×10^8 anti-CD19 CAR T cells for subjects >100 kg, the median peak blood cell level of 88.64 cells/µL was reached on average within 14 days post-infusion. The median $AUC_{0\text{-}28d}$ was determined at 1136.61 cells/µL*day.
Elimination was characterised by a rapid decline followed by a slower decrease towards baseline. In 6out of 10 patients, anti-CD19 CAR T cell levels were still detectable at the last time point, i.e. after 24 months, suggesting considerable persistence.

Dose linearity was not investigated. As part of an interim analysis of 28 patients in Cohort 1 of the study, it was observed that the values for C_{max} and $AUC_{0\text{-}28}$ were 3- to 5-fold higher compared to those following the same dose of Yescarta® in the ZUMA-1 study. Therefore, a lower dose of 0.5×10^6 anti-CD19 CAR T cells per kg body weight was evaluated in a second cohort. The comparison of the cellular kinetics between the 2 cohorts indicated that the KTE-X19 exposure levels increased with the dose.

In a small subset of subjects, it was shown that there are CAR T cells present in the CSF; however, the variability was substantial. Overall, the data should be considered with caution due to the limited number of patients and collection time points.

Associations between a number of product characteristics and anti-CD19 CAR T-cell levels were explored. Significant associations between anti-CD19 CAR T-cell levels and the 2 product characteristics "IFN-γ in co-culture" and "CD4:CD8 ratio" were observed. However, the associations were not monotonic, and no trend was observed with disease response and toxicity. Due to the exploratory nature of these correlative analyses, the validity of these findings is limited.

Special populations / intrinsic factors
No studies in patients with renal and hepatic impairment were conducted.

Various subgroup analyses were conducted. Sex did not have a significant impact on the anti-CD19 CAR T-cell levels. Lower median KTE-X19 exposures were observed in patients younger than 65 years. No paediatric patients were enrolled in in the study. Since primarily Caucasian subjects were included in the study, a comparison across race/ethnicity was not possible.
The association of anti-CD19 CAR T-cell levels with tumour burden is inconclusive. Whereas KTE-X19 exposures increased from the lowest tumour burden quartile (Q1) to Q3, they decreased again in Q4. Overall, these analyses must be interpreted with caution due to the high variability of the cellular kinetics of KTE-X19 and the small sample size.

Interactions
No pharmacokinetic drug-drug interactions are expected for adoptive cell therapies. Therefore, no dedicated DDI studies were conducted.

Tocilizumab and corticosteroids were administered for the treatment of CRS and neurologic events. Subjects receiving these concomitant medications showed considerably higher anti-CD19 CAR T-cell levels. It is likely that the increased anti-CD19 CAR T-cell levels were not caused by the administration of these medications but by the fact that subjects with higher cell levels had more severe adverse events.

Mechanism of action and primary pharmacology
KTE-X19 is an autologous cancer immunocelluar therapy using genetically engineered T cells. Following binding to CD19-positive target cells, downstream signalling pathways are triggered by the CD28 and CD3ζ co-stimulatory domains, leading to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. Ultimately, this series of events results in the killing of the CD19-positive target cells.

The pharmacodynamics of KTE-X19 were assessed, analysing a panel of 17 core serum biomarkers (pre-selected from a larger panel of 40 analytes), including homeostatic (IL-2, IL-7, IL-15), pro-inflammatory, and immune-modulating cytokines (CRP, IFN-γ, IL-1RA, IL-2Rα, IL-6, IL-10, TNF-α), chemokines (CXCL10, IL-8), immune effectors (granzyme B, perforin), and other analytes (ICAM-1, VCAM-1).
The median serum levels of IL-15, CRP, ferritin, and IL-7 increased, whereas the perforin levels declined, following conditioning chemotherapy and prior to infusion of KTE-X19. IL-15 showed the most pronounced increase (approx. 10-fold) suggesting that the induction of IL-15 may be crucial for the effect of the lymphodepleting conditioning chemotherapy. Following the KTE-X19 infusion, serum levels of all of the 17 analytes evaluated increased by 2-fold or more at peak in ≥ 50% of subjects except for ICAM-1, perforin, TNF-α, and VCAM-1. The serum levels of the majority of the biomarkers returned to approximately baseline levels after 4 weeks except for CXCL10, ferritin, IFN-γ, IL-6, IL-8, and IL-15, which remained elevated.

Secondary pharmacology (safety)
B-cell aplasia was investigated as a potential on-target, off-tumour effect. KTE-X19 induced B-cell aplasia; however, the B-cell levels recovered by Month 18.

Relationship between plasma concentration and effect
The relationship between exposure and response was assessed based on exploratory correlative analyses; however, the validity of these findings must be considered limited due to the exploratory nature.

A statistically significant correlation was observed between KTE-X19 exposure in terms of C_{max} and $AUC_{0\text{-}28d}$, and efficacy, specified as no response as well as partial and complete response. An ongoing response was not necessarily associated with persistent anti-CD19 CAR T-cell levels. Patients with an ongoing response showed B-cell recovery, suggesting that continuous B-cell aplasia at Month 24 was not required for maintaining disease response. Higher median CAR T-cell levels were observed in subjects with an ongoing response who had B-cell aplasia. Anti-CD19 CAR T cells were detected in some subjects with an ongoing response at Month 24, despite the presence of recovered B-cell levels. These could be non-functional CAR T-cells. In non-responders, no B-cell aplasia was observed and B-cell levels increased following KTE-X19 infusion.

The exposure-safety analysis focused on the association of KTE-X19 exposure and levels of serum biomarkers with the incidence of Grade 3 or higher neurologic events and CRS.
Overall, anti-CD19 CAR T-cell levels correlated with Grade 3 and higher neurologic events and Grade 3 and higher CRS.

Immunogenicity
Based on an initial screening assay, 17 subjects tested positive for antibodies against FMC63. All samples were negative in the confirmatory assay.

6.2 Dose finding and dose recommendation

ZUMA-2 is a Phase 2, multicentre, single-arm, open-label study. Patients with r/r MCL whose disease had progressed on anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 antibody, and a BTK inhibitor (ibrutinib and/or acalabrutinib) were enrolled in Cohort 1 (pivotal cohort) or Cohort 2 (dose-finding). The two cohorts received a different dose.

	Cohort 1 (N = 74) n (%)	Cohort 2 (N = 17) n (%)	Overall (N = 91) n (%)
Full analysis set[a], n (%)	74 (100)	17 (100)	91 (100)
Inferential analysis set[b], n (%)	60 (81)	n/a	n/a
Safety analysis set[c], n (%)	68 (92)	14 (82)	82 (90)
Modified intent-to-treat analysis set[d], n (%)	68 (92)	14 (82)	82 (90)
Safety retreatment analysis set, n (%)	2 (3)	1 (6)	3 (3)
Modified intent-to-treat retreatment analysis set, n (%)	2 (3)	1 (6)	3 (3)

Data cut-off date: 24JUL2019
Abbreviation: n/a, not applicable.
Note: Percentages are based on the number of subjects enrolled.
a Full analysis set is defined as all enrolled (leukapheresed) subjects.
b Inferential analysis set consists of the first 60 subjects treated with KTE-X19 in Cohort 1 and who have had the opportunity to be evaluated for response 6 months after the Week 4 disease assessment after KTE-X19 infusion.
c Safety analysis set is defined as all subjects treated with any dose of KTE-X19.
d Modified intent-to-treat analysis set is defined as all subjects treated with KTE-X19.

The study evaluated 2 doses of KTE-X19. Subjects in **Cohort 1** were to receive a target dose of 2×10^6 anti-CD19 CAR T cells/kg, with a maximum dose of 2×10^8 anti-CD19 CAR T cells for subjects ≥ 100 kg. Subjects in **Cohort 2** were to receive a target dose of 0.5×10^6 anti-CD19 CAR T cells/kg, with the same maximum dose as used in Cohort 1.a
Initially, the dose administered to subjects in Cohort 1 was based on the Applicant's previous registrational study (ZUMA-1) of axicabtagene ciloleucel (Yescarta) in subjects with refractory aggressive large B-cell lymphoma. An interim analysis of the first 28 subjects in ZUMA-2 Cohort 1 treated with Tecartus demonstrated that peak expansion and cumulative exposure ($AUC_{0\text{-}28}$) of anti-

CD19 CAR T cells in these subjects were approximately 3- to 5-fold higher than the peak and AUC_{0-28} observed in subjects with r/r diffuse large B-cell lymphoma (DLBCL) treated with axicabtagene ciloleucel (Yescarta) in ZUMA-1. Because the anti-CD19 CAR T-cell peak and AUC_{0-28} were associated with Grade 3 or higher neurologic events in ZUMA-1 {Neelapu 2017}, **the applicant added Cohort 2** to ZUMA-2 to evaluate the safety and efficacy of KTE-X19 at the lower dose of 0.5×10^6 anti-CD19 CAR T cells/kg. Fourteen subjects were treated at this dose and an assessment was made by the safety review team after these subjects were followed for 2.97 months (median follow-up, range: 0.83 to 4.96 months).

The pharmacokinetic and pharmacodynamic data in Cohort 2 revealed that anti-CD19 CAR T-cell expansion in these subjects was less robust than anticipated, with peak expansion and AUC_{0-28} of CAR-T levels that were approximately 60% lower than those observed in subjects treated with the higher dose level. As the peak CART-cell expansion also is associated with durable responses in DLBCL patients {Neelapu 2017}, the applicant was concerned that low expansion could negatively impact clinical efficacy. Furthermore, the safety profile observed at the 0.5×10^6 anti-CD19 CAR T cells/kg dose showed no significant improvement in the safety profile compared to the 2×10^6 anti-CD19 CAR T cells/kg dose level.

A further interim analysis of 28 subjects in Cohort 1 treated with KTE-X19 at the dose of 2×10^6 anti-CD19 CAR T cells/kg and who had the opportunity to be followed for 6 months after Tecartus infusion demonstrated durable responses and a manageable safety profile.

Based on the review of the cumulative clinical and pharmacokinetic data from the patients treated at the 2 dose levels, the dose of 2×10^6 anti-CD19 CAR T cells/kg was considered to offer the best benefit-risk profile. It was therefore deemed to be the optimal dose for treatment of subjects with MCL and was used for the treatment of all subsequently enrolled subjects in ZUMA-2.

6.3 Efficacy

The MA application is based on 1 pivotal study, ZUMA-2 (NCT02601313), Cohort 1, an open-label, multicentre, single-arm trial of 74 patients with relapsed or refractory MCL (mantle cell lymphoma).

The study was conducted at a total of 33 study centres in the US, France, Germany, and the Netherlands.

In order to be eligible for the study, the patients had to have had previous treatment with all of the following:
- Anthracycline or bendamustine-containing chemotherapy
- An anti CD20 antibody, and
- A Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib).

Eligible patients also had to have disease progression after their last treatment regimen or refractory disease to the most recent therapy.

A total of 74 patients met all criteria and underwent leukapheresis (**full analysis set, FAS, or ITT**).

Three of the 74 patients did not receive Tecartus due to a manufacturing failure (up to 2 leukapheresis attempts were allowed). Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus due to ongoing atrial fibrillation after receiving lymphodepleting chemotherapy. Lymphodepletion is carried out after successful manufacture of Tecartus but before Tecartus administration.

Thus 68 of the initial 74 patients received a single infusion of brexucabtagene autoleucel (Tecartus) following completion of lymphodepleting chemotherapy (**mITT analysis set**).

The **prespecified primary analysis** occurred after **60 Tecartus subjects** in the modified intent-to-treat (mITT) set of Cohort 1 had been enrolled and treated with Tecartus and had had the opportunity to be assessed for response 6 months after the Week 4 disease assessment. This constituted the **inferential analysis set.**

The primary efficacy outcome measure was objective response rate (ORR) per Lugano [2014] criteria as assessed by an independent review committee. Thus the first 60 subjects who received Tecartus in Cohort 1 formed the basis for the statistical hypothesis testing of the primary efficacy outcome measure.

Secondary endpoints
The main secondary endpoints were duration of response (DOR), progression free survival (PFS), overall survival (OS), and severity of adverse events.

Results
The results of the prespecified primary analysis set were submitted to Swissmedic initially with a study cut-off dated 24 July 2019 and included the following results:

Inferential analysis set
Analysis of the 60 patients evaluable for efficacy based on the minimum duration of follow-up for response of 6 months after the initial 1-month assessment showed an **ORR of 87% (95% CI: 75, 94), with a complete remission (CR) rate of 62% (95% CI: 48, 74)**. After a median follow-up time for duration of response of 8.6 months, the estimated median duration of response (**DOR**) was not reached (range of 0+ to 29.2+ months).

Full analysis set
For the full analysis set, the **ORR** as assessed by independent review committee (IRC) was **80% (95% CI: 69, 88), with a CR rate of 55% (95% CI: 43, 67)**.

Of 42 subjects who initially had a PR (partial response) or SD (stable disease), 24 subjects (57%) went on to achieve a CR after a median of 2.2 months (range: 1.8 to 8.3 months). Of the 24 subjects whose responses improved over time, 21 subjects (88%) converted from PR to CR, and 3 subjects (13%) converted from SD to CR.

Objective response and CR using the investigators' assessment had concordance rates of 95% (κ = 0.70; 95% CI: 0.39, 1.00) and 90% (κ = 0.77, 95% CI: 0.60, 0.94), respectively, with the ORR and CR rate using central assessment.

Summary of efficacy results for ZUMA-2 (24 July 2019 cut-off)

Category	All leukapheresed [a] (ITT) (N = 74)	Inferential Analysis Set [b] (N = 60)
Objective Response Rate [c] (ORR), n (%) [95% CI]	**63 (85%)** [75.0, 92.3]	**56 (93%)** [83.8, 98.2]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]	40 (67%) [53.3, 78.3]
PR n (%) [95% CI]	19 (26%) [16.2, 37.2]	16 (27%) [16.1, 39.7]
Duration of Response [d]		
Median in months [95% CI]	NR [8.6, NE]	NR [8.6, NE]
Range [e] in months	0.0+, 29.2+	0.0+, 29.2+
Ongoing Responses, CR+PR, CR, n (%) [f]	39 (53%), 34 (46%)	34 (57%), 31 (52%)
Progression Free Survival		
Median, months [95% CI]	NR [9.9, NE]	NR [9.2, NE]
Overall Survival		
Median, months [95% CI]	NR [21.1, NE]	NR [24.0, NE]
6 month OS (%) [95% CI]	83.2 [72.3, 90.1]	86.7 [75.1, 93.1]
12 month OS (%) [95% CI]	77.1 [65.3, 85.3]	83.2 [71.0, 90.6]
18 month OS (%) [95% CI]	67.5 [52.1, 78.9]	72.9 [56.4, 84.0]
Median Follow-up in months (min, max)	11.6 (1.9, 32.3)	12.3 (7.0, 32.3)

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

a. Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received conditioning chemotherapy, and 68 patients received [TRADENAME].
b. Inferential analysis set (IAS) consists of the first 60 patients treated with [TRADENAME] who were evaluated for response 6 months after the Week 4 disease assessment after [TRADENAME] infusion.
c. Per the International Working Group Lugano Classification (Cheson 2014), as assessed by the Independent Radiology Review Committee.
d. Among all responders. DOR is measured from the date of first objective response to the date of progression or death.
e. A + sign indicates a censored value.
f. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Both the inferential analysis and the full analysis set results showed an ORR which was superior to the pre-specified historical rate from studies in a similar patient population undergoing salvage therapy as assessed by the applicant. The statistical hypothesis testing of the primary endpoint as prespecified in the study protocol ("… The hypothesis is that the objective response rate to KTE-C19 is significantly greater than 20% …") was met, as ORR was significantly higher than the prespecified control rate of 25% at the 1-sided significance level of 0.025 ($p < 0.0001$).

Analysis of the key secondary endpoints DOR, PFS, and OS showed that at the time of the initial review of Tecartus by Swissmedic, median DOR, PFS, and OS were not reached (see table above). Overall, the data are still immature, even if the ORR appears to be superior to that achieved by salvage therapy in historical data. As ORR by itself does not reveal much about the actual efficacy of an oncology treatment, a risk-benefit analysis was not yet possible.

The applicant subsequently submitted 18-month follow-up data with a **new cutoff date of 31 December 2020** (received on 31 May 2021) to Swissmedic. The secondary endpoints were not fully mature yet but gave substantially more information.
Using the full analysis set, which includes all leukapheresed patients (N=74), median **PFS** reached 19.1 months (95% C.I.: 9.9 months to 38.2 months).

The **OS** at 24 months is 64.4% (95% C.I. 52.3, 74.2).

With the newly available ORR, CR, PFS, and OS data, the data were clinically relevant for a relapsed, refractory MCL population with previous BTK inhibitor treatment.

A regular approval was therefore granted, with adoption of the EMA's post-marketing requirement:
In order to confirm the long-term efficacy and safety of Tecartus in adult patients with relapsed or

refractory MCL, the MAH shall submit the 24-month follow-up data from all treated patients in Cohort 1 of the pivotal study ZUMA-2.

6.4 Safety

A total of 82 subjects (68+14) were treated with Tecartus in ZUMA-2 Cohorts 1 and 2.
The most relevant safety data are those of Cohort 1, as they reflect the safety of the dosage applied for in this MAA.

The 82 patients received a single dose of CAR-positive viable T cells (2×10^6 which was the dosage used in pivotal Cohort 1 or 0.5×10^6 anti-CD19 CAR T cells/kg as used in Cohort 2). The most significant and frequently occurring adverse reactions were **CRS (91%), infections (55%), and encephalopathy (51%)**. **Serious adverse reactions** occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%). Grade 3 or higher adverse reactions were reported in 67% of patients. The most common **Grade 3 or higher non-haematological adverse reactions** included infections (34%) and encephalopathy (24%). The most common **Grade 3 or higher haematological adverse reactions** included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%), and anaemia (56%). Grade 3 or higher cytopenias not resolved by Day 30 following Tecartus infusion occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). Hypogammaglobulinemia was reported in 16% (13/82) of patients with MCL. Febrile neutropenia was observed in 6% of patients after Tecartus infusion and may be concurrent with CRS.

The most common (≥ 10%) Grade 3 or higher reactions were anaemia, neutropenia, thrombocytopenia, hypotension, hypophosphatemia, encephalopathy, leukopenia, hypoxia, pyrexia, hyponatremia, hypertension, infection-pathogen unspecified, pneumonia, hypocalcaemia, and lymphopenia.

Serious **hypersensitivity reactions**, including anaphylaxis, may occur due to dimethyl sulfoxide (DMSO) or residual gentamicin in Tecartus

6.5 Final clinical benefit-risk assessment

Beneficial effects
The ORR in both the IAS and the FAS, as described above under “Efficacy”, is significantly higher than the prespecified historical control rate of 25%. Although the historical control rate could possibly be slightly higher than that calculated by the applicant’s meta-analysis if the most recent studies are added, the ZUMA-2 ORR rates are still clearly higher than the historical control rate for salvage therapy in this r/r population already having received all available therapies according to current guidelines.
The PFS and OS, although not fully mature yet, confirm that longer survival can be achieved in a substantial number of patients.
Uncertainties in the knowledge about the beneficial effects
The ZUMA-2 study is currently ongoing. Analyses of time-to-event endpoints are not completely mature yet, as median DOR, PFS, and OS still have not been reached. More follow-up time is needed to see how durable the benefits of treatment are.

Unfavourable effects (risks)
Leukapheresis and lymphodepletion are needed prior to treatment with Tecartus, which delays the start of treatment. The manufacture of Tecartus may not be possible for some patients. Once Tecartus is administered, CRS and neurotoxicity are potentially fatal and require close monitoring as immediate treatment may be needed. Other adverse events of Tecartus such as haematological

adverse events and severe infections may last and cause a risk to the patient for several months after treatment.

Benefit-risk assessment

The risks are acceptable in light of the expected efficacy. For the approved indication (i.e. patients meeting the criteria of the ZUMA-2 Cohort 1 patients), the benefit-risk assessment is positive, especially considering that these patients do not have many options left.
The applicant will provide a longer term follow-up of ZUMA-2, which will give more information on how durable the response is. Also, one must keep in mind that although some patients may have very prolonged survival, others may not show a durable response after treatment. Last but not least, the risk-benefit evaluation of Tecartus is based on the premise that all safety measures, as delineated in the Information for healthcare professionals, are followed. The patients should join a registry that looks at the long-term safety and efficacy of CAR T-cells.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tecartus was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Tecartus®

Composition

Active substances

Tecartus (autologous anti-CD19-transduced CD3+ cells) is a gene therapy medicinal product containing autologous T cells genetically modified ex vivo using a retroviral vector encoding an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 and CD3-zeta co-stimulatory domains.

Excipients

Cryostor CS10 (DMSO; Dextran 40), sodium chloride, human serum albumin (sodium chloride, N-acetyl-DL-tryptophan, caprylic acid, water), 5% DMSO.
Tecartus contains 300 mg sodium per infusion.

Pharmaceutical form and active substance quantity per unit

Dispersion for infusion.
A clear to opaque, white to red dispersion of cells, supplied in an infusion bag individually packed in a metal cassette.
Each patient specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2×10^6 CAR-positive viable T cells/kg body weight (range: 1.0×10^6–2.0×10^6 cells/kg), with a maximum of 2×10^8 anti-CD19 CAR-positive viable T cells.

Indications/Uses

Tecartus is a genetically modified autologous T-cell immunotherapy directed against CD19 and is indicated 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 tyrosine kinase (BTK) inhibitor.

Dosage/Administration

Tecartus must be administered in a qualified treatment centre by a physician with experience in the treatment of haematological malignancies and trained for administration and management of patients treated with Tecartus, including treatment of cytokine release syndrome (CRS) and neurotoxicity, with immediate access to appropriate intensive care units. A minimum of four doses of tocilizumab for use

in the event of cytokine release syndrome (CRS) must be available prior to infusion of Tecartus. Patients are expected to enrol in a registry and will be followed in the registry in order to better understand the long-term safety and efficacy of Tecartus.

Tecartus is a single infusion product, for autologous and intravenous use only (see “Warnings and precautions”).
The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen. There may be reasons why a patient cannot be treated with Tecartus despite completing leukapheresis (for details see “Properties/Effects”).

Pre-treatment (lymphodepleting chemotherapy)

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 and fludarabine 30 mg/m^2 should be administered intravenously on the 5th, 4th, and 3rd day before infusion of Tecartus. An absolute neutrophil count (ANC) ≥ 1000/µL and a platelet count ≥ 75,000/µL before initiating lymphodepleting chemotherapy is recommended.

Clinical evaluation prior to Tecartus infusion

Treatment with Tecartus should be postponed in certain high-risk patients (see “Warnings and precautions”).

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500-1000 mg given orally and diphenhydramine 12.5-25 mg, intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic steroids is not recommended (see “Interactions”).

Dosage

A patient specific single infusion bag of Tecartus with a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2x10^6 CAR-positive viable T cells/kg body weight (range: 1.0x10^6 – 2.0x10^6 cells/kg), with a maximum of 2x10^8 CAR-positive viable T cells for patients of 100 kg and above.

Monitoring after infusion

- Patients should be monitored at a qualified treatment centre, daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician’s discretion.

- Patients should be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

Special dosage instructions

Patients with impaired hepatic function

Data from patients with hepatic impairment are insufficient to draw conclusions on this population.

Patients with impaired renal function

Data from patients with renal impairment are insufficient to draw conclusions on this population.

Elderly patients

No dose adjustment is required in patients ≥ 65 years of age.

Children and adolescents

The safety and efficacy of Tecartus in children and adolescents aged less than 18 years have not yet been established. No data are available.

Patients seropositive for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV)

There is no experience with manufacturing Tecartus for patients with a positive test for HIV, active HBV, or active HCV infection. Therefore, the benefit/risk has not yet been established in this population.

Mode of administration

Intravenous use.
Tecartus is solely intended for autologous use via intravenous infusion.
Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified human blood cells. Standard precautions regarding handling of this type of product should be followed. For special precautions for disposal and other instructions for handling, see “Other information”.
Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation of Tecartus

- Verify that the patient’s identity (ID) matches the patient identifiers on the Tecartus metal cassette.
- The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.

- Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
- Check that the patient information on the metal cassette label matches that on the bag label.
- Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).
- Place the infusion bag inside a sterile second bag or per local guidelines.
- Thaw Tecartus at approximately 37°C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, Tecartus is stable at room temperature (20°C - 25°C) for up to 3 hours. However, Tecartus infusion should begin within 30 minutes of thaw completion.

Administration

- For autologous single use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of Tecartus.
- Verify the patient ID again to match the patient identifiers on the Tecartus bag.
- Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.
- Gently agitate the bag during infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

Contraindications

Hypersensitivity to the active substance, any of the excipients (see “Composition”).
Contraindications of the lymphodepleting chemotherapy must be considered.

Warnings and precautions

Traceability

The traceability requirements of cell-based advanced therapy medicinal products must apply. To ensure traceability the name of the product, the batch number and the name of the treated patient should be kept for a period of 30 years.

General

Warnings and precautions of lymphodepleting chemotherapy must be considered.

Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within the proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS or neurological adverse reactions occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction. The patient must also be made aware that although most CRS and neurological symptoms occur within the first 4 weeks after infusion, undesirable effects can occur at any time and may require treatment.

Reasons to delay treatment

Due to the risks associated with Tecartus treatment, infusion should be delayed if a patient has any of the following conditions:

- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.
- Active uncontrolled infection or inflammatory disease.
- Active graft-versus-host disease (GvHD).
- Development of clinically relevant worsening of lymphoma, that results in medically significant organ dysfunction or clinical deterioration, following chemotherapy for lymphocyte depletion.

In some cases, the treatment may be delayed after administration of the lymphodepleting chemotherapy regimen. If the infusion is delayed for more than 2 weeks after the patient has received the lymphodepleting chemotherapy, lymphodepleting chemotherapy regimen should be administered again (see "Dosage/Administration").

Serological testing

Screening for HBV, HCV, and HIV should be performed before collection of cells for manufacturing of Tecartus (see section "Dosage/Administration").

Blood, organ, tissue and cell donation

Patients treated with Tecartus should not donate blood, organs, tissues, cells for transplantation.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of Tecartus. Serious hypersensitivity reactions including anaphylaxis may be due to DMSO or residual gentamicin in Tecartus.

Concomitant disease

Patients with a history of or active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function and patients with thrombocytopenia or low fibrinogen levels are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention. In addition, there is no clinical experience with the use of Tecartus in patients with moderate to severe organ function impairment.

Active nervous system (CNS) lymphoma

There is no experience of use of Tecartus in patients with active CNS lymphoma defined as detectable cerebrospinal fluid malignant cells and/or brain metastases confirmed by imaging. Therefore, the risk/benefit of Tecartus has not been established in this population.

Cytokine Release Syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, which can be life-threatening and fatal, was very commonly observed with Tecartus with a median time to onset of 3 days (range: 1 to 13 days) (see “Undesirable effects”). Patients should be closely monitored for signs or symptoms of these events, such as high fever, hypotension, hypoxia, chills, tachycardia and headache (see section “Undesirable effects”). CRS should be managed at the physician’s discretion, based on the patient’s clinical presentation and according to the CRS management algorithm provided in Table 1.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including active infection.

Management of cytokine release syndrome associated with Tecartus

Ensure that a minimum of 4 doses of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are available for each patient prior to infusion of Tecartus.

Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on Tecartus. These include the use of tocilizumab or /and corticosteroids, as summarised in Table 1 below. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an

echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition, worsening of underlying organ pathologies can occur in the setting of CRS. Low fibrinogen, especially in the setting of thrombocytopenia, may increase the risk of bleeding. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered. In some cases, macrophage activation syndrome (MAS) and haemophagocytic lymphohistiocytosis (HLH) may occur in the setting of CRS.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

Tecartus continues to persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of Tecartus -associated CRS.

Table 1: CRS grading and management guidance

CRS Grade *(a)*	Tocilizumab	Corticosteroids
Grade 1 Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise).	If not improving after 24 hours, administer tocilizumab 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).	N/A
Grade 2 Symptoms require and respond to moderate intervention. Oxygen requirement < 40% FiO_2 or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity *(b).*	Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. If improving, discontinue tocilizumab.	If no improvement within 24 hours after starting tocilizumab, manage per Grade 3. If improving, taper corticosteroids, and manage as Grade 1.
Grade 3 Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO_2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis.	Per Grade 2 If improving, discontinue tocilizumab.	Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours) until Grade 1, then taper corticosteroids. If improving, manage as Grade 2. If not improving, manage as Grade 4.
Grade 4 Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis).	Per Grade 2 If improving, discontinue tocilizumab.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, taper corticosteroids, and manage as Grade 3. If not improving, consider alternate immunosuppressants.

N/A = not available/not applicable
(a) Lee et al 2014
(b) Refer to Table 2 for management of neurologic adverse reactions
(c) Refer to tocilizumab product information for details

Neurologic adverse reactions

Severe neurologic adverse reactions (encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly observed in patients treated with Tecartus with a median time to onset of 8 days (range: 1 to 262 days) (see “Undesirable effects”). Patients with a history of CNS disorders such as seizures or cerebrovascular ischemia may be at increased risk. Serious cases of cerebral oedema which may become fatal have

occurred in patients treated with Tecartus. Patients should be monitored for signs and symptoms of neurologic adverse reactions (Table 2).

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

Table 2: Neurologic adverse reaction grading and management guidance

Grading Assessment	Concurrent CRS	No concurrent CRS
Grade 2	Administer tocilizumab as per Table 1 for management Grade 2 CRS. If not improving within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab. If still not improving, manage as Grade 3.	Administer dexamethasone 10 mg intravenously every 6 hours until the event is Grade 1 or less. If improving, taper corticosteroids
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 3	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If improving, discontinue tocilizumab and manage as Grade 2. If still not improving, manage as Grade 4.	Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper corticosteroids. If not improving, manage as Grade 4.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	
Grade 4	Administer tocilizumab as per Table 1 for management of Grade 2 CRS. Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.	Administer methylprednisolone 1000 mg intravenously per day for 3 days. If improving, then manage as Grade 3. If not improving, consider alternate immunosuppressants.
	Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis.	

Infections and febrile neutropenia

Severe infections, which could be life-threatening, were very commonly observed with Tecartus (see “Undesirable effects”).

Patients should be monitored for signs and symptoms of infection before, during and after Tecartus infusion and treated appropriately. Prophylactic antibiotics should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after Tecartus infusion (see section “Undesirable effects”) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

In immunosuppressed patients, life -threatening and fatal opportunistic infections including disseminated fungal infections and viral reactivation (e.g., HHV-6 and progressive multifocal leukoencephalopathy) have been reported. The possibility of these infections should be considered in patients with neurologic events and appropriate diagnostic evaluations should be performed.

Viral reactivation

Viral reactivation, e.g. Heptitis B Virus (HBV) reactivation, can occur in patients treated with medicinal products directed against B cells and could result in fulminant hepatitis, hepatic failure, and death.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Tecartus infusion and should be managed according to standard guidelines. Grade 3 or higher prolonged cytopenias following Tecartus infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia (see section “Undesirable effects”). Patient blood counts should be monitored after Tecartus infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with Tecartus. Hypogammaglobulinaemia was very commonly observed in patients treated with Tecartus (see section “Undesirable effects”). Hypogammaglobulinaemia predisposes patients to have infections. Immunoglobulin levels should be monitored after treatment with Tecartus and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement in case of recurrent infections. Immunoglobulin replacement should be administered according standard guidelines.

Live vaccines

The safety of immunisation with live viral vaccines during or following Tecartus treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during Tecartus treatment, and until immune recovery following treatment.

Secondary malignancies

Patients treated with Tecartus may develop secondary malignancies or recurrence of their treated maligancy. Patients should be monitored life-long for secondary malignancies. In the event that a secondary malignancy occurs, the company should be contacted to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to Tecartus infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Prior stem cell transplantation (GvHD)

It is not recommended that patients who underwent an allogeneic stem cell transplant and suffer from active acute or chronic GvHD receive treatment because of the potential risk of Tecartus worsening GvHD.

Prior treatment with anti CD19 therapy

Tecartus is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

Tecartus contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

No pharmacokinetic or pharmacodynamic interaction studies have been performed with Tecartus. Prophylactic use of systemic corticosteroids may interfere with the activity of Tecartus. Prophylactic use of systemic corticosteroids is therefore not recommended before infusion (see section Dosage/Administration).

Administration of corticosteroids as per the toxicity management guidelines has not been demonstrated to impact the expansion and persistence of CAR T cells.

Pregnancy, lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of women of childbearing potential must be verified before starting Tecartus treatment.

See the product information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Tecartus.

Pregnancy

There are no available data with Tecartus use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with Tecartus to assess whether it can cause foetal harm when administered to a pregnant woman (see section “Preclinical data”).

It is not known if Tecartus has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced T cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, Tecartus is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after Tecartus therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborn infants of mothers treated with Tecartus should be considered.

Lactation

It is unknown whether Tecartus is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of Tecartus on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Tecartus has major influence on the ability to drive and use machines.

Due to the potential for neurologic events, including altered mental status or seizures, patients should not drive or operate heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

Serious adverse reactions occurred in 57% of patients. The most common serious adverse reactions included infections (28%), encephalopathy (26%), and cytokine release syndrome (15%).

The most significant and frequently occuring adverse reactions were cytokine release syndrome (91%), infections (56%) and encephalopathy (51%).

Grade 3 or higher adverse reactions were reported in 65% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (32%) and encephalopathy (24%). The most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Summary of adverse reactions

Adverse reactions described in this section were identified in patients exposed to Tecartus in ZUMA-2. These reactions are presented by system organ class and by frequency. Frequencies are defined as follows: very common (≥ 1/10); common (≥ 1/100, < 1/10). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Infections and infestations:
Very common: Unspecified pathogen infections (43%), Viral infections (17%), Bacterial infections (13%), Fungal infections (10%).

Blood and lymphatic system disorders:
Very common: Neutropenia[a] (99%), Leukopenia[a] (98%), Lymphopenia[a] (96%), Thrombocytopenia[a] (65%), Anaemia[a] (56%), Coagulopathy (10%).

Immune system disorders:
Very common: Cytokine Release Syndrome[b] (91%), Hypogammaglobulinaemia (16%).

Metabolism and nutrition disorders:
Very common: Hypophosphataemia[a] (30%), Decreased appetite (26%), Hypocalcaemia [a] * (21%).

Common: Dehydration, Hypoalbuminaemia[a].

Psychiatric disorders:
Very common: Insomnia (21%), Delirium (18%), Anxiety (17%).

Nervous system disorders:
Very common: Encephalopathy (51%), Tremor (38%), Headache (23%), Aphasia (20%), Dizziness (16%), Neuropathy (13%).
Common: Ataxia, Seizure, Increased intracranial pressure.

Cardiac disorders:
Very common: Tachycardias (16%), Bradycardias (11%).
Common: Non-ventricular arrhythmias.

Vascular disorders:
Very common: Hypertension (20%), Thrombosis (17%), Hypotension (16%).
Common: Haemorrhage.

Respiratory, thoracic and mediastinal disorders:
Very common: Cough (39%), Dyspnoea (21%), Pleural effusion (21%), Hypoxia (10%).
Common: Respiratory failure, Pulmonary oedema.

Gastrointestinal disorders:
Very common: Constipation (29%), Nausea (28%), Diarrhoea (21%), Oral pain (17%), Abdominal pain (16%), Vomiting (11%), Dysphagia (10%).
Common: Dry mouth.

Hepatobiliary disorders:
Very common: Blood uric acid increased [a] (17%), Hyponatraemia [a] (16%), Alanine aminotransferase increased [a] (15%), Aspartate aminotransferase increased [a] (%), Hypokalaemia [a] (10%).

Skin and subcutaneous tissue disorders:
Very common: Rash (20%).

Musculoskeletal and connective tissue disorders:
Very common: Muscoloskeletal pain (35%), Motor dysfunction (33%).

Renal and urinary disorders:
Very common: Renal insufficiency (17%), Urine output decreased (11%).

General disorders and administration site conditions:
Very common: Fatigue (48%), Oedema (35%), Pyrexia (27%), Pain (17%), Chills (12%).

[a] Frequency based on Grade 3 or higher laboratory parameter.
[b] See section Description of selected undesirable effects*.*

Description of selected undesirable effects

Cytokine release syndrome

CRS occurred in 91% of patients. Fifteen percent (15%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was 10 days (range: 1 to 50 days). All patients (100%) recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (99%), hypotension (60%), hypoxia (37%), chills (33%), tachycardia (27%), headache (24%), fatigue (16%), nausea (13%), alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%). Serious adverse reactions that may be associated with CRS included hypotension, pyrexia, hypoxia, acute kidney injury, and tachycardia. See “Warnings and precautions” for monitoring and management guidance. In addition, serious adverse reactions that have been observed with similar treatments and which may occur with Tecartus treatment include: haemophagocytic lymphohistiocytosis/macrophage activation syndrome, cardiac failure, cardiac arrhythmia (including supraventricular tachycardia, atrial fibrillation, ventricular extrasystoles).

Neurologic events and adverse reactions

Neurologic adverse reactions occurred in 68% of patients. Thirty-three percent (33%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 8 days (range: 1 to 262 days). Neurologic events resolved for 47 out of 56 patients with a median duration of 13 days (range: 1 to 567 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. Eighty-five percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions included encephalopathy (51%), tremor (38%), aphasia (20%), and delirium (18%). Serious adverse reactions including encephalopathy (26%),

aphasia (6%) and seizure (2%) have been reported in patients administered with Tecartus. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. Serious cases of muscular weakness suggestive of spinal cord involvement, including myelitis and paralysis syndromes, have occurred in patients treated with Tecartus and/or similar treatments. See “Warnings and precautions for monitoring and management guidance.

In addition, serious neurologic adverse reactions that have been observed with similar treatments and which may occur with Tecartus treatment include: depressed level of consciousness and restlessness

Febrile neutropenia and infections

Febrile neutropenia was observed in 6% of patients after Tecartus infusion. Infections occurred in 56% of patients in ZUMA-2. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in 32% of patients including unspecified pathogen, bacterial, and viral infections in 26%, 6%, and 4% of patients respectively. See “Warnings and precautions” for monitoring and management guidance.

Prolonged Cytopenias

Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy. Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in 55% of patients and included thrombocytopenia (38%), neutropenia (37%), and anaemia (17%). See “Warnings and precautions” for management guidance.

Hypogammaglobulinaemia

In ZUMA-2, hypogammaglobulinaemia occurred in 16% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See “Warnings and precautions” for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. To date, no anti-CD19 CAR T cell antibody mediated immunogenicity has been confirmed. Based on an initial screening assay, 17 patients tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients were antibody negative at all time points tested. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, was altered in these patients.

Other Serious Adverse Reactions

Serious adverse reactions that have been observed with similar treatments and which may occur with Tecartus treatment include: deep vein thrombosus, embolism (including pulmonary embolism), muscle spasms, syncope, and weight decreased.

Reporting of suspected undesirable effects

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There are no data regarding the signs of overdose with Tecartus.

Properties/Effects

ATC code

Not yet assigned.

Mechanism of action

Tecartus, a CD19-directed genetically modified autologous T cell immunotherapy, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 co-stimulatory domain and CD3-zeta signalling domain activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions and secretion of inflammatory cytokines and chemokines. This sequence of events leads to killing of CD19-expressing cells.

Pharmacodynamics

In ZUMA-2, after Tecartus infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, interferon-gamma (IFN-γ) and IL-2 receptor alpha were analysed. Peak elevation was generally observed between 4 and 8 days after infusion and levels generally returned to baseline within 28 days.

Due to the on target, off-tumour effect of Tecartus a period of B-cell aplasia is expected following treatment. From 32 patients, who had evaluable samples at basline and were in ongoing response, 75% had detectable B cells, whereas the B cell aplasia observed in 25% of patients was attributed to prior therapies. Following Tecartus treatment, the proportion of patients in ongoing response with detectable B cells decreased with 41% of evaluable patients having detectable B cells at Month 3, 62% had detectable B cells at Month 6 and 46% had detectable B cells at month 12. By Month 24, 75% of evaluable subjects in ongoing response had detectable B cells.

Clinical efficacy

Relapsed or refractory MCL: ZUMA-2

The efficacy of Tecartus in adult patients with relapsed or refractory MCL who had previously received anthracycline or bendamustine-containing chemotherapy, an anti CD20 antibody, and a Bruton's tyrosine kinase inhibitor (BTKi) (ibrutinib or acalabrutinib), was evaluated in a phase 2 single-arm, open-label, multicenter trial. Eligible patients also had disease progression after last regimen or refractory disease to the most recent therapy. Patients with active or serious infections, prior allogeneic haematopoietic stem cell transplantation (HSCT), detectable cerebrospinal fluid malignant cells or brain metastases, and any history of central nervous system lymphoma or CNS disorders were ineligible. Also, patients with a serum creatinine > 1.5 mg/dL, cardiac ejection fraction of less than 50%, or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were excluded. In total, 74 patients were enrolled (*i.e.* leukapheresed) and 68 patients were treated with Tecartus. Three patients did not receive Tecartus due to manufacturing failure. Two other patients were not treated due to progressive disease (death) following leukapheresis. One patient was not treated with Tecartus after receiving lymphodepleting chemotherapy due to ongoing active atrial fibrillation. ITT was defined as all patients who underwent leukapheresis. A summary of the patient baseline characteristics is provided in Table 3.

Table 3: Summary baseline characteristics for ZUMA-2

Category	**All leukapheresed (ITT) (N=74)**
Age (years)	
Median (min, max)	65 (38, 79)
≥ 65	58%
Male gender	84%
Median number of prior therapies (min, max)	3 (1; 5)
Relapsed/refractory subgroup	
Relapsed after auto-SCT	42%
Refractory to last MCL therapy	39%
Relapsed after last MCL therapy	19%
Patients with disease stage IV	86%
Patients with bone marrow involvement	51%
Morphological characteristics	
Classical MCL	54%
Blastoid MCL	26%
Other	1%
Unknown	19%
Received bridging therapy	
Yes	38 %
No	62%
Ki-67 IHC by central laboratory	

Category	**All leukapheresed (ITT) (N=74)**
Age (years)	
N	49
Median	65%

Auto-SCT, autologous stem cell transplant; IHC, immunohistochemistry; Max, maximum; MCL, mantle cell lymphoma; Min, minimum;

Tecartus was administered to patients as a single intravenous infusion at a target dose of 2×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 2×10^8 cells) after lymphodepleting chemotherapy regimen of cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously, both given on the 5th, 4th, and 3rd day before Tecartus. Bridging therapy between leukapheresis and lymphodepleting chemotherapy was permitted to control disease burden.

For patients treated with Tecartus, the median time from leukapheresis to product release was 13 days (range: 9 to 20 days) and the median time from leukapheresis to Tecartus infusion was 27 days (range: 19 to 74 days, with the exception of one outlier of 134 days). The median dose was 2.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was objective response rate (ORR) as determined by Lugano 2014 criteria by an independent review committee. Secondary endpoints included duration of response (DOR), overall survival (OS), progression free survival (PFS) and severity of adverse events.

An analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$).

At an updated ad-hoc descriptive efficacy analysis (median follow-up time of 25.5 months (range: 1.21 to 49.6 months), among the 68 patients who received a single infusion of Tecartus, the OOR was 91% with a CR rate of 68%. The median DOR was 24.8 months with a median follow-up time of 23.1 months (95% CI: 22.6, 35.9 months) and median OS was not reached after a median follow-up time of 25.5 months (range: 1.2 to 49.6 months).
Results in the ITT set are shown in Table 4.

Table 4: Summary of efficacy results for ZUMA-2

Category	All leukapheresed [a] (ITT) (N=74)
Objective Response Rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	46 (62%) [50.1, 73.2]
PR n (%) [95% CI]	16 (22%) [12.9, 32.7]
Duration of Response [b]	
Median in months [95% CI]	24.8 [13.5, NE]
Range [c] in months	0.0+, 47.0+
Ongoing Responses, CR+PR, CR, n (%) [d]	27 (36.5%), 27 (36.5%)
Progression Free Survival	
Median, months [95% CI]	19.1 [9.9, 38.2]
Overall Survival	
Median, months [95% CI]	NR [25.9, NE]
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.7 [65.3, 84.8]
24 month OS (%) [95% CI]	64.4 [52.3, 74.2]
36 month OS (%) [95% CI]	55.0 [41.9, 66.4]
48 month OS (%) [95% CI]	52.0 [38.3, 64.0]
Follow-up time from Tecartus infusion (months)	
N	68
Median	25.5
Min, max	1.2, 49.6

CI, confidence interval; CR, complete remission; ITT, intent to treat; NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.
a. Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received conditioning chemotherapy, and 68 patients received Tecartus.
b. Among all responders. DOR is measured from the date of first objective response to the date of progression or death.
c. A + sign indicates a censored value.
d. At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

Pharmacokinetics

Absorption

Following infusion of Tecartus, anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Peak levels of anti-CD19 CAR T cells occurred within the first 7 to 15 days after the Tecartus infusion.

The number of anti-CD19 CAR T cells in blood was associated with objective response (CR or PR).

The median peak anti-CD19 CAR T-cell level in responders vs nonresponders was 97.52 cells/µL (range: 0.24 to 2589.47 cells/µL; n=62), and 0.39 cells/µL (range: 0.16 to 22.02 cells/µL, n=5; Wilcoxon rank rank-sum test p = 0.0020), respectively. The median $AUC_{0\text{-}28}$ in subjects with an objective response was 1386.28 cells/µL•days (range: 3.83 to 2.77E+04 cells/µL•days; n=62) vs 5.51 cells/µL•days in nonresponders (range: 1.81 to 293.86 cells/µL•days; Wilcoxon rank-sum p = 0.0013; n = 5). The median T_{max} was 15 days for both responders and non-responders.

Some patients required tocilizumab and corticosteroids for management of CRS and neurologic toxicities. Patients who received tocilizumab (n = 10) alone had 230% and 250% higher anti-CD19 CAR T-cell levels and patients who received tocilizumab and corticosteroids (n = 38) had 577% and 454% higher anti-CD19 CAR T-cell levels measured by C_{max} and $AUC_{Day\ 0\text{-}28}$ respectively, as compared to patients who did not receive these medications (n = 18).

Distribution

No data available.

Metabolism

No data available.

Elimination

Tecartus comprises human autologous T cells, the anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time. Anti-CD19 CAR T-cell levels peaked in blood 15 days (median, range: 8 to 31 days) after the Tecartus infusion and decreased toward near background levels by Month 3 (range: < LLOQ to 10.86 cells/µL). 100% (30 of 30) of evaluable subjects, who were in ongoing response, had detectable CAR at Month 3, 88% (28 of 32) of subjects had detectable CAR at Month 6, 85% (11 of 13) of subjects had detectable CAR at Month 12 and 56% (5 of 9) of subjects had detectable CAR at Month 24. No secondary expansion of CAR T cells was observed.

Kinetics in specific patient groups

Age, gender and ethnicity

Median peak anti-CD19 CAR T cell values were 74.08 cells/µL in patients ≥ 65 years of age (n=39) and 112.45 cells/µL in patients < 65 years of age (n=28). Median anti-CD19 CAR T cell AUC values were 876.48 cells/µL·day in patients ≥ 65 years of age and 1640.21 cells/µL·day in patients < 65 years of age.
Gender had no significant impact on $AUC_{Day\ 0\text{-}28}$ and C_{max} of Tecartus.

Hepatic impairment

Hepatic impairment studies of Tecartus were not conducted.

Renal impairment

Renal impairment studies of Tecartus were not conducted.

Preclinical data

Tecartus comprises engineered human T cells; therefore, there are no representative in vitro assays, ex vivo models, or in vivo models that can accurately address the toxicological characteristics of the

human product. Hence, traditional toxicology studies used for medicinal product development were not performed.

Mutagenicity

No genotoxicity studies have been conducted with Tecartus.

Carcinogenicity

No carcinogenicity studies have been conducted with Tecartus.

Reproductive toxicity

No studies have been conducted to evaluate the effects of this treatment on fertility, reproduction, and development.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Tecartus is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ −150°C).

Tecartus is stable at room temperature (20°C to 25°C) for up to 3 hours after thawing. However, Tecartus infusion should begin within 30 minutes of thaw completion and the total infusion time should not exceed 30 min. Thawed product should not be refrozen.
Thawed product should not be refrozen.

Do not use Tecartus after the expiry date (“EXP”) stated on the container.

Special precautions for storage

Tecartus must be stored in the vapor phase of liquid nitrogen (≤ −150˚C) and [Tradename] must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are available for patient administration.

For storage conditions after thawing of the medicinal product, see “Shelf life”.

Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the transport and disposal of the medicinal product
Tecartus should be transported within the facility in closed, break-proof, leak-proof containers.

Tecartus contains genetically modified human blood cells. Local guidelines on handling of waste of human-derived material should be followed for unused medicinal products or waste material. All material that has been in contact with Tecartus (solid and liquid waste) should be handled and disposed of in accordance with local guidelines on handling of waste of human-derived material.

Accidental exposure to Tecartus must be avoided. Local guidelines on handling of human-derived material should be followed in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes. Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

Authorisation number

67884 (Swissmedic)

Packs

Tecartus, maximum of $2x10^8$ cells/68 mL dispersion for infusion [A]
Tecartus is supplied in an ethylene-vinyl acetate cryostorage bag with sealed addition tube and two availble spike ports.
One cryostorage bag is individually packed in a shipping metal cassette.

Marketing authorisation holder

Gilead Sciences Switzerland Sàrl, Zug

Date of revision of the text

May 2021

Revision history

Application ID	Milestone	Created on	Change	Initials
102635994	Approval	25. August 2021	Initial MAA	CVA