swissmedic

Date: 30 July 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ebvallo

International non-proprietary name: tabelecleucel
Pharmaceutical form: Dispersion for injection
Dosage strength(s): $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL
Route(s) of administration: Ebvallo is for intravenous use only
Marketing authorisation holder: Pierre Fabre Pharma SA
Marketing authorisation no.: 69052
Decision and decision date: approved on 3 May 2024

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

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
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
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
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)

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for tabelecleucel in the above-mentioned medicinal product.

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 17 October 2022.

Authorisation as human medicinal product in accordance with Article 13 TPA
The applicant requested a reduced assessment procedure in accordance with Article 13 TPA.

2.2 Indication and dosage

2.2.1 Requested indication

Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

2.2.2 Approved indication

Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Ebvallo contains 2 × 10^6 viable T cells per kg of the patient's body weight

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	27 December.2022
Formal control completed	13 January 2023
List of Questions (LoQ)	15 May 2023
Response to LoQ	7 September 2023
Preliminary decision	6 December 2023
Response to preliminary decision	2 February 2024
Final decision	3 May 2024
Decision	approval

Swissmedic has not assessed the primary data (e.g. study reports) submitted with this application and relies for its decision on the assessment of the foreign reference authority EMA. This SwissPAR relates to the publicly available assessment report Ebvallo (Ref. EMA/858618/2022, 13.10.2022, Last update published: 01.11.2023 issued by EMA (Procedure no. EMEA/H/C/004577/0000)).

3 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. The SwissPAR relating to quality aspects refers to the publicly available assessment report Ebvallo (Ref. EMA/858618/2022, 13.10.2022, Last update published: 01.11.2023 issued by EMA (Procedure no. EMEA/H/C/004577/0000)).

4 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. The nonclinical aspects in this SwissPAR refer to the publicly available assessment report Ebvallo (Ref. EMA/858618/2022, 13.10.2022, Last update published: 01.11.2023 issued by EMA (Procedure no. EMEA/H/C/004577/0000)).

5 Clinical aspects

Swissmedic has not assessed the primary data relating to clinical aspects submitted with this application and relies on the assessment of the foreign reference authority EMA. The clinical aspects in this SwissPAR refer to the publicly available assessment report Ebvallo (Ref. EMA/858618/2022, 13.10.2022, Last update published: 01.11.2023 issued by EMA (Procedure no. EMEA/H/C/004577/0000)

6 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.

7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Ebvallo 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.

Ebvallo

Composition

Active substances

Ebvallo (tabelecleucel) is an allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy which targets and eliminates EBV-positive cells in a human leukocyte antigen (HLA)-restricted manner. Each vial contains 1 mL deliverable volume of Ebvallo at a concentration of 2.8×10^7 - 7.3×10^7 cells/mL dispersion for injection.

Excipients

Dimethyl sulfoxide, human serum albumin 25% (human serum albumin 250 g/L, sodium chloride 5.1 g/L, N-acetyl-DL-tryptophan 4.9 g/L, caprylic acid 2.9 g/L, water for injection), phosphate buffered saline (sodium chloride 9.0 g/L, disodium phosphate 0.795 g/L, potassium dihydrogen phosphate 0.144 g/L, water for injection).

Pharmaceutical form and active substance quantity per unit

Each vial contains 1 mL deliverable volume of Ebvallo at a concentration of 2.8×10^7 - 7.3×10^7 viable T cells/mL dispersion for injection. The quantitative information regarding actual concentration, HLA profile and patient dose calculation is provided in the Lot Information Sheet included with the shipper used to transport the medicinal product.
The total number of vials in each carton (between 1 vial and 6 vials) corresponds to the dosing requirement for each individual patient, depending on the patient's body weight (see sections *«Dosage/Administration»* and *«Nature and content of Container»*)

Indications/Uses

Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior therapy. For solid organ transplant patients, prior therapy includes chemotherapy unless chemotherapy is inappropriate.

Dosage/Administration

Ebvallo should be administered under the supervision of a physician experienced in the treatment of cancer in a controlled setting where adequate facilities for handling of adverse reactions, including those requiring urgent measures, are available.

Dosage

Treatment consists of multiple doses for injection containing a dispersion of viable T cells in one or more vials.
The recommended dose of Ebvallo contains 2×10^6 viable T cells per kg of the patient's body weight.

Dose calculations

Patient weight (kg) × target dose (2×10^6 viable T cells/kg) = Viable T cells to be administered
Viable T cells to be administered ÷ actual concentration (viable T cells/mL)* = Volume of thawed cell dispersion required (mL)**

*See the accompanying Lot Information Sheet and carton for information pertaining to the actual concentration of cells per vial.
**Volume of thawed cell dispersion requires dilution, see section «*Instructions for handling*».

Note: The viable T-cell concentration on the Lot Information Sheet and carton is the actual concentration of each vial. This may be different than the nominal concentration listed on the vial label, which should not be used for dose preparation calculations. Each vial contains 1 mL deliverable volume.

The medicinal product is administered over multiple 35-day cycles, during which patients receive Ebvallo on days 1, 8 and 15, followed by observation through day 35. A response is assessed at approximately day 28.

The number of cycles of the medicinal product to be administered is determined by the response to treatment shown in Table 1. If a complete or partial response is not obtained, patients may be switched to an Ebvallo lot with a different HLA restriction (up to 4 different restrictions) selected from the existing product inventory.

Table 1: Treatment algorithm

Response observed[a]	**Action**
Complete response (CR)	Administer another cycle of Ebvallo with the same HLA restriction. If the patient achieves 2 consecutive CRs (maximal response), no further treatment with Ebvallo is recommended.
Partial response (PR)	Administer another cycle of Ebvallo with the same HLA restriction. If the patient achieves 3 consecutive PRs (maximal response), no further treatment with Ebvallo is recommended.
Stable disease (SD)	Administer another cycle of Ebvallo with the same HLA restriction. If the subsequent cycle results in a second SD, administer Ebvallo with a different HLA restriction.
Progressive disease (PD)	Administer another cycle of Ebvallo with a different HLA restriction.
Indeterminate response (IR)	Administer another cycle of Ebvallo with the same HLA restriction. If the subsequent cycle results in a second IR, administer Ebvallo with a different HLA restriction.

[a] Complete response at the end of a cycle followed by partial response or other response at any subsequent cycle is considered progressive disease.

Monitoring

It is recommended to monitor vital signs immediately prior to each Ebvallo injection, within 10 minutes following the conclusion of the injection and 1 hour after the initiation of the injection (see section *«Warnings and Precautions»*).

Missed dose

If a patient misses a dose, the missed dose should be given as soon as reasonably possible.

Special populations

Elderly

No dose adjustment is required in patients ≥ 65 years of age (see section *«Pharmacokinetics»*). Ebvallo should be used with caution in elderly (see section *«Warnings and Precautions»*).

Hepatic and renal impairment

No dose adjustment is required for patients with hepatic or renal impairment (see section *«Pharmacokinetics»*).

Paediatric population

Posology and administration in paediatric patients 2 years of age and older are the same as for adult patients.
The safety and efficacy of Ebvallo in paediatric patients below 2 years of age have not yet been established. No data are available.

Method of administration

Ebvallo is for intravenous use only.

Administration

- Administer Ebvallo as a single dose intravenously after dilution.
- Connect the final medicinal product syringe to the patient's intravenous catheter and inject over 5 to 10 minutes.
- Once Ebvallo is fully dispensed from the syringe, flush the intravenous line with ≥ 10 mL of sodium chloride 9 mg/mL (0.9%) solution for injection.

For detailed instructions on preparation, accidental exposure and disposal of the medicinal product, see «*Instructions for handling*».

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section «Composition».

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 after expiry date of the product.

Tumour flare reaction (TFR)

TFR has occurred with Ebvallo use, generally within the first few days after receiving the treatment. TFR presents as an acute inflammatory reaction involving tumour sites which may include a sudden and painful increase in the tumour size or enlargement of disease-involved lymph nodes. TFR may mimic progression of disease.
Patients with high tumour burden prior to treatment are at risk of severe TFR. Depending on the location of the tumour or lymphadenopathy, complications (e.g. respiratory distress and cognitive disorders) may arise from mass effect, including compression/obstruction of adjacent anatomic structures. Analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) or localised radiotherapy could be considered prior to Ebvallo administration for those patients in whom the location of the tumour could potentially lead to complications. Patients should be closely monitored for signs and symptoms of TFR, especially during the first cycle (see *«Undesirable effects»*).

Graft-versus-host disease (GvHD)

GvHD has been reported after treatment with Ebvallo. This could be related to the decrease or discontinuation of immunosuppressive therapies for the treatment of PTLD rather than to a direct action of Ebvallo. The benefit of treatment with Ebvallo versus the risk of possible GvHD should be considered. Patients should be monitored for signs and symptoms of GvHD, such as skin rash, abnormal liver enzymes in the blood, jaundice, nausea, vomiting, diarrhoea and bloody stools.

Solid organ transplant rejection

Solid organ transplant rejection has been reported after treatment with Ebvallo. Treatment with Ebvallo may increase the risk of rejection in solid organ transplant recipients. This could be related to the decrease or discontinuation of immunosuppressive therapies for the treatment of PTLD rather than to a direct action of Ebvallo. The benefit of treatment with Ebvallo versus the risk of possible solid organ transplant rejection should be considered prior to the start of treatment. Patients should be monitored for signs and symptoms of solid organ transplant rejection.

Bone marrow transplant rejection

There is a potential risk of bone marrow transplant rejection based on humoral or cell-mediated immune reactions. No event of bone marrow transplant rejection has been reported in clinical studies. Patients should be monitored for signs and symptoms of bone marrow transplant rejection.

Cytokine release syndrome (CRS)

CRS has been reported after treatment with Ebvallo. Patients should be monitored for signs and symptoms of CRS, such as pyrexia, chills, hypotension and hypoxia. Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. CRS should be managed at the physician's discretion, based on the patient's clinical presentation.

Immune effector cell-associated neurotoxicity syndrome (ICANS)

ICANS has been reported after treatment with Ebvallo. Patients should be monitored for signs and symptoms of ICANS, such as depressed level of consciousness, confusion, seizures and cerebral oedema. Diagnosis of ICANS requires excluding alternate causes.

Infusion-related reactions

After injection of Ebvallo, infusion-related reactions such as pyrexia and non-cardiac chest pain have been reported. Patients should be monitored for at least 1 hour after treatment for signs and symptoms of infusion-related reactions.

Hypersensitivity reactions

Serious hypersensitivity reactions, including anaphylaxis, may occur due to dimethyl sulfoxide (DMSO) in Ebvallo.

Transmission of infectious agents

Ebvallo is obtained from human donor blood cells. Donors are screened and have tested negative for relevant communicable disease agents and diseases, including HBV, HCV and HIV. Although tabelecleucel lots are tested for sterility, mycoplasma and adventitious agents, a risk of transmission of infectious agents exists.

Some tabelecleucel lots are manufactured from donors who are cytomegalovirus (CMV) positive. All lots are tested to ensure no detection of adventitious agents, including CMV. During clinical development, tabelecleucel lots derived from CMV-positive donors were administered to CMV-negative patients when an appropriate lot derived from a CMV-seronegative donor was unavailable; in this subpopulation no seroconversions were observed.

Healthcare professionals administering Ebvallo must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Blood, organ, tissue and cell donation

Patients treated with Ebvallo must not donate blood, organs, tissues and cells for transplantation.

Elderly population

There are only limited data available for the elderly population. Based on available data, the elderly population (≥ 65 years of age) may be at increased risk of serious adverse events leading to

hospitalisation/prolonged hospitalisation, psychiatric disorders, vascular disorders, and infections and infestations. Ebvallo should be used with caution in elderly patients.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.

DMSO

This medicinal product contains 100 mg dimethyl sulfoxide (DMSO) per mL.

Interactions

No interaction studies have been performed.

Immunosuppressive and cytotoxic therapies

Certain concomitant or recently administered medicinal products including chemotherapy (systemic or intrathecal), anti-T-cell antibody-based therapies, extracorporeal photopheresis or brentuximab vedotin could potentially impact the efficacy of Ebvallo. Ebvallo should only be administered after an adequate washout period of such agents.
For patients receiving chronic corticosteroid therapy, the dose of these drugs should be reduced as much as is clinically safe and appropriate; recommended no greater than 1 mg/kg per day of prednisone or equivalent. Ebvallo has not been evaluated in patients receiving corticosteroid doses greater than 1 mg/kg per day of prednisone or equivalent.
In clinical studies, patients received ciclosporin, tacrolimus, sirolimus and other immunosuppressive therapies at the lowest dose considered clinically safe and appropriate.

CD20-targeting antibodies

Because in vitro characterisation data demonstrated the absence of CD20 expression on tabelecleucel, it is not expected that anti-CD20 antibody treatments will affect tabelecleucel activity.

Pregnancy, lactation

Pregnancy

There are no available data with tabelecleucel use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with tabelecleucel. It is not known if tabelecleucel has the potential to be transferred to the foetus or can cause foetal harm when administered to a pregnant woman. Ebvallo is not recommended during pregnancy and in women of childbearing potential not using contraception. Pregnant women should be advised on potential risks for the foetus.
There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with Ebvallo.

Breast-feeding

It is unknown whether tabelecleucel is excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding women should be advised of potential risks to the breast-fed child. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tabelecleucel therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on the effect of tabelecleucel on fertility.

Effects on ability to drive and use machines

Ebvallo has minor influence on the ability to drive and use machines, e.g. dizziness, fatigue (see section «*Undesirable effects*»).

Undesirable effects

Summary of the safety profile

The most common adverse reactions were pyrexia (31.1%), diarrhoea (26.2%), fatigue (23.3%), nausea (18.4%), anaemia (16.5%), decreased appetite (15.5%), hyponatraemia (15.5%), abdominal pain (14.6%), neutrophil count decreased (14.6%), white blood cell count decreased (14.6%), aspartate aminotransferase increased (13.6%), constipation (12.6%), alanine aminotransferase increased (11.7%), blood alkaline phosphatase increased (11.7%), hypoxia (11.7%), dehydration (10.7%), hypotension (10.7%), nasal congestion (10.7%) and rash (10.7%). The most serious adverse reactions were tumour flare reaction (1%) and graft-versus-host disease (4.9%).

Tabulated list of adverse reactions

The safety database is comprised of data from 340 patients (EBV^+ PTLD and other EBV-associated diseases) from clinical studies, an expanded access protocol, and compassionate use requests. Frequencies of adverse reactions were calculated in 103 patients from the ALLELE study and Study EBV-CTL-201 for which all events (serious and non-serious) were collected. In the rest of the clinical development program, only serious events were collected. Adverse reactions reported from clinical trials are presented below in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000).

Table 2: Adverse reactions identified with Ebvallo

System organ class (SOC)	Adverse reaction	Frequency
Infections and infestations	Upper respiratory tract infection	Common
	Skin infection	Common
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Tumour pain	Common
	Tumour flare reaction	Common
Blood and lymphatic system disorders	Neutrophil count decreased	Very common
	White blood cell count decreased	Very common
	Anaemia	Very common
	Febrile neutropenia	Common
	Platelet count decreased	Common
	Blood fibrinogen decreased	Common
	Lymphocyte count decreased	Common
Immune system disorders	Graft-versus-host disease[a]	Common
Metabolism and nutrition disorders	Decreased appetite	Very common
	Hyponatraemia	Very common
	Dehydration	Very common
	Hypomagnesaemia	Common
	Hypokalaemia	Common
	Hypocalcaemia	Common
	Blood lactate dehydrogenase increased	Common
Psychiatric disorders	Confusional state	Common
	Delirium	Common
	Disorientation	Common
Nervous system disorders	Dizziness	Common
	Headache	Common
	Depressed level of consciousness	Common
	Somnolence	Common
	Peripheral sensory neuropathy	Common
Cardiac disorders	Tachycardia	Common
Vascular disorders	Hypotension	Very common
	Hot flush	Common
	Cyanosis	Common
Respiratory, thoracic and mediastinal disorders	Hypoxia	Very common
	Nasal congestion	Very common
	Wheezing	Common
	Pneumonitis	Common
	Upper-airway cough syndrome	Common
	Pulmonary haemorrhage	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain[b]	Very common
	Constipation	Very common
	Colitis	Common
	Abdominal distension	Common
	Flatulence	Common
	Dyschezia	Common
Skin and subcutaneous tissue disorders	Rash[c]	Very common
	Pruritus	Common
	Skin ulcer	Common
	Skin hypopigmentation	Common
Musculoskeletal and connective tissue disorders	Muscular weakness	Common
	Arthralgia	Common
	Back pain	Common
	Myalgia	Common
	Arthritis	Common
	Joint Stiffness	Common
	Soft tissue necrosis	Common

System organ class (SOC)	Adverse reaction	Frequency
General disorders and administration site conditions	Pyrexia	Very common
	Fatigue	Very common
	Chills	Common
	Chest pain[d]	Common
	Pain	Common
	Localised oedema	Common
	General physical health deterioration	Common
Hepatobiliary disorders	Aspartate aminotransferase increased	Very common
	Alanine aminotransferase increased	Very common
	Blood alkaline phosphatase increased	Very common
Renal and urinary disorder	Blood creatinine increased	Common
Injury, poisoning and procedural complications	Post procedural oedema	Common

[a] Graft-versus-host disease (GvHD) includes GvHD in gastrointestinal tract, GvHD in liver, rash maculo-papular (skin GvHD)
[b] Abdominal pain includes abdominal pain, abdominal discomfort, abdominal pain lower
[c] Rash includes rash, rash erythematous, rash maculo-papular, rash pustular
[d] Chest pain includes musculoskeletal chest pain, non-cardiac chest pain

Description of selected adverse reactions

Tumour flare reaction (TFR)

TFR was reported in 1 patient (1%). The event was Grade 3 and the patient recovered. The onset was on the day of dosing and the duration was 60 days.

Graft-versus-host disease (GvHD)

GvHD was reported in 5 (4.9%) patients. Two (40%) patients had Grade 1, 1 patient (20%) had Grade 2, 1 patient (20%) had Grade 3, and 1 (20%) patient had Grade 4 events. No fatal events were reported. Four (80%) patients recovered from GvHD. The median time to onset was 42 days (range: 8 to 44 days). The median duration was 35 days (range: 7 to 133 days).

Immunogenicity

There is potential for immunogenicity with Ebvallo. There is currently no information indicating that potential immunogenicity to Ebvallo impacts safety or efficacy.

Children and adolescents

There are limited data in paediatric patients (see section «*Pharmacodynamics*»). Eight patients were ≥ 2 to < 6 years of age, 16 patients were ≥ 6 to < 12 years of age, 17 patients were ≥ 12 to < 18 years of age. Frequency, type and severity of adverse reactions in children were similar to adults. The adverse reactions of alanine aminotransferase increased, aspartate aminotransferase increased and osteomyelitis were reported as serious only in paediatric patients.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via EIViS (Electronic Vigilance System). Information see www.swissmedic.ch.

Overdose

There are no data regarding overdose with Ebvallo.

Properties/Effects

ATC Code

L01XL09

Mechanism of action

Ebvallo is an allogeneic, EBV-specific T-cell immunotherapy which targets and eliminates EBV-infected cells in an HLA-restricted manner. Ebvallo has an equivalent mechanism of action to that demonstrated by endogenous circulating T cells in the donors from which the medicinal product is derived. The T-cell receptor of each clonal population within Ebvallo recognises an EBV peptide in complex with a specific HLA molecule on the surface of target cells (the restricting HLA allele) and allows the medicinal product to exert cytotoxic activity against the EBV-infected cells.

Pharmacodynamics

Across multiple clinical studies, systemic cytokine levels of IL-1β, IL-2, IL-6 and TNFα did not meaningfully change from baseline after administration of Ebvallo.

Clinical Efficacy

ALLELE is an ongoing, multicentre, open-label, single-arm, Phase 3 study in 43 adult and paediatric patients with EBV+ PTLD following solid organ transplant (SOT) or haematopoietic cell transplant (HCT) after failure of previous therapy. Patients were assigned to prespecified cohorts based on transplant type and treatment failure of prior therapy for EBV+ PTLD. The SOT cohort (29 patients) consisted of SOT patients who had failed rituximab monotherapy (13 patients) and SOT patients who had failed rituximab plus chemotherapy (SOT-R+C, 16 patients). The HCT cohort (14 patients) consisted of HCT patients who had failed rituximab.

Eligible patients had a prior HCT or SOT (kidney, liver, heart, lung, pancreas, small bowel or any combination), a diagnosis of biopsy-proven EBV+ PTLD with radiographic measurable disease, and failure of rituximab monotherapy or rituximab plus any concurrent or sequentially administered chemotherapy regimen for treatment of EBV+ PTLD. The most commonly administered chemotherapy combination was cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate and prednisone. Patients with Grade ≥ 2 graft-versus-host disease (GvHD), active central nervous system (CNS) PTLD, Burkitt lymphoma, classical Hodgkin lymphoma, or any T-cell lymphoma were excluded. Patients received standard prophylactic anti-viral therapy until 30 days after the last dose of Ebvallo. Table 3 summarizes the demographics and baseline characteristics from the SOT-R+C and HCT indicated cohorts.

Table 3: Summary of demographics and baseline characteristics in ALLELE from cohorts SOT-R+C and HCT

	Ebvallo SOT EBV⁺ PTLD[a,b]	**Ebvallo HCT EBV⁺ PTLD[a]**
	After rituximab and chemotherapy (N = 16)	**After rituximab (N = 14)**
Age		
Median years (min, max)	39.2 (16.7, 81.5)	51.9 (3.2, 73.2)
Male, n (%)	7 (43.8)	8 (57.1)
ECOG score (age ≥ 16)[c]		
patients in the age group	16	13
ECOG < 2	9 (56.3)	10 (76.9)
ECOG ≥ 2	6 (37.5)	3 (23.1)
Missing	1 (6.3)	0
Lansky score (age < 16)[c]		
patients in the age group	0	1
Lansky < 60	0	0
Lansky ≥ 60	0	1 (100)
Elevated LDH (age ≥ 16), n (%)	12 (75.0)	11 (84.6)
PTLD-adapted prognostic index[d] (age ≥ 16), n (%)		
Low risk	1 (6.3)	1 (7.7)
Intermediate risk	6 (37.5)	6 (46.2)
High risk	8 (50.0)	6 (46.2)
Unknown	1 (6.3)	0
PTLD morphology/histology, n (%)		
DLBCL	10 (62.5)	10 (71.4)
Other[e]	4 (25.0)	3 (21.4)
Plasmablastic lymphoma	2 (12.5)	1 (7.1)
Extranodal disease	13 (81.3)	9 (64.3)
Prior therapies		
Median number of prior systemic therapies (min, max)	2.0 (1, 5)	1.0 (1, 4)
Rituximab monotherapy, n (%)	10 (62.2)	14 (100)
Rituximab monotherapy as first line, n (%)	9 (56.3)	14 (100)
Chemotherapy-containing regimen[f], n (%)	16 (100)	3 (21.4)

DLBCL = diffuse large B-cell lymphoma; EBV⁺ PTLD = Epstein-Barr virus positive post-transplant lymphoproliferative disease; ECOG = Eastern Cooperative Oncology Group; HCT = haematopoietic cell transplant; LDH = lactate dehydrogenase; max = maximum; min = minimum; SOT = solid organ transplant; SOT-R+C = SOT patients who had failed rituximab plus chemotherapy

[a] Patients received at least one dose of Ebvallo.

[b] SOT types included kidney, heart, liver, lung, pancreas, bowel and multiviscera.

[c] Percentages for ECOG and Lansky scores were based on the number of patients in the corresponding age group.

[d] Disease risk for PTLD patients was assessed at baseline using the PTLD-adapted prognostic index (based on age, ECOG score and serum LDH level).

[e] Morphologies not clearly DLBCL or plasmablastic lymphoma were categorized as Other and were consistent with PTLD.

[f] Chemotherapy regimens could have also been combined with rituximab or other immunotherapy agents.

The primary efficacy endpoint was objective response rate (ORR) per evaluation by independent oncologic response adjudication (IORA), using Lugano classification criteria with lymphoma response to immunomodulatory therapy criteria (LYRIC) modification. ORR was obtained following administration of Ebvallo with up to 2 different HLA restrictions (one restriction switch). Ebvallo was selected for each patient from an existing product inventory based on an appropriate HLA restriction. The treatment plan

consisted of administration of Ebvallo by intravenous injection at 2 × 10^6 viable T cells/kg on days 1, 8 and 15 followed by observation through day 35, during which a response was assessed at approximately day 28. The number of cycles of Ebvallo administered to patients was determined by the response to treatment as shown in Table 1 (see section «*Dosage/Administration*»). Seventeen (39.5%) patients required treatment with an Ebvallo lot that had a different HLA restriction (restriction switch). Of these 17 patients, 15 received one restriction switch, 2 received 2 restriction switches and 5 (29.4%) patients achieved a first response following the first restriction switch. Table 4 summarizes efficacy results from the SOT-R+C and HCT indicated cohorts.

Table 4: Summary of efficacy results in ALLELE from cohorts SOT-R+C and HCT

	Ebvallo SOT EBV$^+$ PTLD[a]	**Ebvallo HCT EBV$^+$ PTLD[a]**
	After rituximab and chemotherapy (N = 16)	**After rituximab (N = 14)**
Objective response rate[b, c], n (%) **95% CI**	9 (56.3) 29.9, 80.2	7 (50.0) 23.0, 77.0
Best overall response[c], n (%)		
Complete response	5 (31.3)	6 (42.9)
Partial response	4 (25.0)	1 (7.1)
Stable disease	0	3 (21.4)
Progressive disease	4 (25.0)	2 (14.3)
Not evaluable	3 (18.8)	2 (14.3)
Time to response[c] (first complete response or partial response)		
Median (min, max) time to response, months	1.1 (0.7, 4.1)	1.0 (1.0, 4.7)
Duration of response[c]		
Median (min, max) follow-up in response, months	2.3 (0.8, 15.2)	15.9 (1.3, 23.3)
Median DOR, months (95% CI)	15.2 (0.8, 15.2)	23.0 (15.9, NE)
Patients with durable response (DOR > 6 months), n	4	6
Median duration of complete response, months (95% CI)	14.1 (6.8, NE)	23.0 (15.9, NE)

CI = confidence interval; DOR = duration of response; EBV$^+$ PTLD = Epstein-Barr virus positive post-transplant lymphoproliferative disease; HCT = haematopoietic cell transplant; KM = Kaplan-Meier; max = maximum; min = minimum; NE = not estimable; SOT = solid organ transplant; SOT-R+C = SOT patients who had failed rituximab plus chemotherapy

[a] Patients received at least one dose of Ebvallo.

[b] Objective response rate was the proportion of patients who achieved a response (complete response or partial response).

[c] Independent oncologic response adjudication (IORA)-assessed response.

Special populations

Elderly

Based on limited data, no overall differences in efficacy were observed between patients ≥ 65 years of age and younger. Seventeen patients were ≥ 65 to < 75 years of age, 3 patients were ≥ 75 to < 85 years of age, no patients were ≥ 85 years of age.

Children and adolescents

Paediatric patients with EBV+ PTLD 2 years of age and older were treated with Ebvallo. Eight patients were ≥ 2 to < 6 years of age, 16 patients were ≥ 6 to < 12 years of age, 17 patients were ≥ 12 to < 18 years of age. Based on limited data, the efficacy and safety results in paediatric patients were consistent with those in adults.
The European Medicines Agency has deferred the obligation to submit the results of studies with Ebvallo in one or more subsets of the paediatric population in the treatment of Epstein-Barr virus associated post-transplant lymphoproliferative disorder (see section «*Dosage/Administration*» for information on paediatric use).

Pharmacokinetics

Upon administration of Ebvallo, circulating EBV-targeting cytotoxic T lymphocytes show a 1.33-median fold increase from baseline to peak expansion. Responders demonstrate a 1.74-median fold increase whereas non-responders show a 0.67-median fold decrease. The specific timing of this expansion varies widely among patients; however, peak expansion has been shown to correlate with response to Ebvallo.
Ebvallo is an ex vivo expanded T-cell product that is not genetically modified. Hence, the nature and the intended use of the product are such that conventional studies including absorption, distribution, metabolism and excretion are not applicable.

Renal and hepatic impairment

The safety and efficacy of tabelecleucel have not been studied in patients with severe renal or hepatic impairment. However, the influence of renal or hepatic impairment on the pharmacokinetics of tabelecleucel is considered to be very unlikely.

Preclinical data

Ebvallo is comprised of human T cells that are not genetically modified; therefore, *in vitro* assays and studies in *ex vivo* models or *in* vivo models cannot accurately assess and predict the toxicological characteristics of this product in humans. Hence, conventional toxicology, carcinogenicity, genotoxicity, mutagenicity and reproductive toxicology studies have not been performed with Ebvallo.
Studies conducted in immunodeficient animal models for EBV^+ PTLD revealed no overt signs of toxicity (e.g. loss of activity or weight loss) associated with a single dose of Ebvallo.

Other information

Incompatibilities

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

Shelf life

5 years when stored in the vapour phase of liquid nitrogen at ≤ -150 °C. The drug product lot manufacturing date is provided on the vial. The expiry date is provided on the Lot Information Sheet and carton. The medicinal product may only be used until the date labelled 'EXP' on the packaging.
The medicinal product should be thawed and diluted within 1 hour from the start of thaw. Administration must be completed within 3 hours from the start of thaw (see section «*Instructions for handling*»).
Store between 15 °C to 25 °C after thawing and dilution are complete. Protect product from light. Do not refreeze. Do not irradiate.

Special precautions for storage

The Ebvallo carton must be stored in the vapour phase of liquid nitrogen at ≤ -150 °C until immediately prior to preparation for administration. The liquid nitrogen vapour shipper provided can maintain the appropriate temperature from the sealing of the shipper until the scheduled dose. The temperature should be monitored regularly. Three temperature excursions up to -80 °C are permittable.
For storage conditions after thawing and dilution of the medicinal product, see section «*Shelflife*».
Store out of reach of children.

Nature and content of container

Ebvallo is supplied in a cyclo-olefin copolymer 2 mL stoppered vials with a thermoplastic elastomer closure containing 1 mL deliverable volume of cell dispersion.
The carton contains a variable number of vials (between 1 vial and 6 vials) according to the patient-specific dose required.

Instructions for handling

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains human blood cells. Healthcare professionals handling Ebvallo must take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

Preparation prior to administration

The patient's identity must match the patient identifiers (PFPIN and Institution Patient ID) on the accompanying Ebvallo Lot Information Sheet and carton. Product-patient reconciliation must be performed by matching information on the Lot Information Sheet against 1) the carton (matching PFPIN and FDP Number) and against 2) the vial label (matching Lot Number and Donor ID). Do not prepare or administer Ebvallo if the patient's identity or the product-patient reconciliation cannot be confirmed. Prior to thawing, ensure that the required dose calculations are completed (see section «*Dosage/Administration*»), all materials needed to prepare the dose are available, and the patient is onsite and has been clinically evaluated.

Materials required for dose preparation

- Sterile syringes:
    - Dosing syringe (select a syringe size that can accommodate required diluent [see Prepare the diluent] and cell dispersion volume)
    - Product draw syringe [select a syringe size that can appropriately measure and will accommodate the calculated volume of cell dispersion needed (see section see «Dosage/Administration»)]
- Diluent (sterile, non-pyrogenic multiple electrolytes solution for injection Type 1 pH 7.4)
- Aseptic devices for transferring product (18-gauge unfiltered syringe needles, Luer Lock adapter, Luer Lock cap)

Prepare the diluent

- Select the appropriate diluent volume (30 mL for patient weight ≤ 40 kg; 50 mL for patient weight > 40 kg).
- Aseptically draw the selected volume of diluent into the dosing syringe.

Thawing

- The thawing process of Ebvallo can begin after the patient is onsite and has been clinically evaluated.
- Remove the carton from the vapour phase of liquid nitrogen at ≤ -150 °C.
- Frozen vial(s) of Ebvallo should be placed inside a sterile bag during thawing to protect from contamination and thawed upright in a 37 °C water bath or dry thawing chamber.
- Record the start of thaw time. While the medicinal product thaws, swirl the product vial(s) gently until fully thawed by inspection (approximately 2.5 to 15 minutes). Product should be removed from the thawing device immediately upon completion of thaw.
- Dose preparation must be completed within 1 hour from the start of thaw.
- Thawed or prepared product must not be refrozen. Do not irradiate.

Dilution and dose preparation

- Gently invert the vial(s) until the cell dispersion is mixed.
- Aseptically withdraw the required cell dispersion volume from the provided product vial(s) into the product draw syringe using an 18-gauge unfiltered needle (see *«Dosage/Administration»*).
- Aseptically transfer the cell dispersion from the product draw syringe to the dosing syringe (previously filled with diluent). Ensure entire content is transferred from the product draw syringe.
- Inspect the diluted Ebvallo in the dosing syringe: cell dispersion should appear as a translucent, hazy solution. If visible clumps appear, continue to gently mix the solution. Small clumps of cellular material should disperse with gentle manual mixing.

- Maintain Ebvallo between 15 °C to 25 °C during dose preparation and administration. Dose preparation must be completed within 1 hour from the start of thaw. Administration must be completed within 3 hours from the start of thaw.

Measures to take in case of accidental exposure

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

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Ebvallo (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.

Authorisation number

69052 (Swissmedic)

Packs

The carton contains a variable number of vials (between 1 vial and 6 vials) according to the patient-specific dose required. [A]

Marketing authorisation holder

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