ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ebvallo $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL dispersion for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

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. Tabelecleucel is produced from T cells harvested from human donors. Each Ebvallo lot is tested for specificity of lysis of EBV^+ targets, T-cell HLA restriction of specific lysis and verification of low alloreactivity. An Ebvallo lot is selected for each patient from the existing product inventory based on an appropriate HLA restriction.

2.2 Qualitative and quantitative composition

Each vial contains 1 mL deliverable volume of Ebvallo at a concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ 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 (LIS) 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 4.2 and 6.5).

Excipient(s) with known effect

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dispersion for injection
A translucent, colourless to slightly yellow cell dispersion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of 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.

Posology

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 (LIS) and carton for information pertaining to the actual concentration of cells per vial.
**Volume of thawed cell dispersion requires dilution, see section 6.6.

Note: The viable T-cell concentration on the LIS 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 4.4).

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 5.1). Ebvallo should be used with caution in elderly (see section 4.4).

Hepatic and renal impairment
No dose adjustment is required for patients with hepatic or renal impairment (see section 5.2).

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 section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 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.

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.

Sodium content

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

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.

4.6 Fertility, pregnancy and 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.

4.7 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 4.8).

4.8 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	Anaemia	Very common
	Febrile neutropenia	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
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
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

System organ class (SOC)	Adverse reaction	Frequency
Investigations	Neutrophil count decreased	Very common
	White blood cell count decreased	Very common
	Aspartate aminotransferase increased	Very common
	Alanine aminotransferase increased	Very common
	Blood alkaline phosphatase increased	Very common
	Lymphocyte count decreased	Common
	Blood creatinine increased	Common
	Blood lactate dehydrogenase increased	Common
	Platelet count decreased	Common
	Blood fibrinogen decreased	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.

Paediatric population

There are limited data in paediatric patients (see section 5.1). 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 of suspected adverse reactions

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 the national reporting system listed in Appendix V.

4.9 Overdose

There are no data regarding overdose with Ebvallo.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, 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.

Pharmacodynamic effects

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 and safety

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 summarises 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)

	Ebvallo SOT EBV+ PTLD[a,b]	Ebvallo HCT EBV+ PTLD[a]
	After rituximab and chemotherapy (N = 16)	**After rituximab (N = 14)**
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 4.2). 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 summarises 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	1.1 (0.7, 4.1)	1.0 (1.0, 4.7)

	Ebvallo SOT EBV+ PTLD[a]	Ebvallo HCT EBV+ PTLD[a]
	After rituximab and chemotherapy (N = 16)	**After rituximab (N = 14)**
response, months		
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.

Paediatric population

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 4.2 for information on paediatric use).

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

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.

Special populations

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.

5.3 Preclinical safety 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dimethyl sulfoxide
Human serum albumin
Phosphate buffered saline

6.2 Incompatibilities

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

6.3 Shelf life

7 years when stored in the vapour phase of liquid nitrogen at ≤ -150 °C. The drug product lot manufacturing date (MFD) is provided on the vial. The expiry date is provided on the Lot Information Sheet (LIS) and carton.

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 6.6). Ebvallo contains 10% DMSO. Ebvallo should be injected to the patient as soon as possible after thawing.

Store between 15 °C to 25 °C after thawing and dilution are complete. Protect product from light. Do not refreeze. Do not irradiate.

6.4 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 6.3.

6.5 Nature and contents 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.

6.6 Special precautions for disposal and other 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 (LIS) and carton. Product-patient reconciliation must be performed by matching information on the LIS 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 4.2), 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 4.2)]
- 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 section 4.2).
- 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. Ebvallo contains 10% DMSO. Ebvallo should be injected to the patient as soon as possible after thawing.

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.

7. MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1700/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 December 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Charles River Laboratories, Inc.
4600 E. Shelby Drive, Suite 108
Memphis, TN 38118
USA

Fujifilm Diosynth Biotechnologies California
2430 Conejo Spectrum Street
Thousand Oaks, CA 91320
USA

Name and address of the manufacturer(s) responsible for batch release

PIERRE FABRE MEDICAMENT PRODUCTION
Parc industriel de la Chartreuse
81100 Castres
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
In order to ensure adequate monitoring of safety and efficacy of tabelecleucel in the treatment of patients with EBV^+ PTLD, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of tabelecleucel.	Annually (with re-assessment)
Non-interventional post-authorisation safety study (PASS): An Observational, Post-authorisation Safety Study to Describe the Safety and Effectiveness of Tabelecleucel in Patients with Epstein-Barr Virus-Positive Posttransplant Lymphoproliferative Disease in Real-world Setting in Europe.	Protocol submission: Within 3 months of marketing authorisation Study progress reports: Annually (with annual re-assessment)
In order to further characterise the long-term efficacy and safety of tabelecleucel in patients with EBV^+ PTLD, the MAH shall provide the final results of the ongoing study ATA129-EBV-302: A Multicentre, Open-Label, Phase 3 Study of Tabelecleucel for Solid Organ or Allogeneic Haematopoietic Cell Transplant Subjects with Epstein-Barr Virus-Associated Post-Transplant Lymphoproliferative Disease after Failure of Rituximab or Rituximab and Chemotherapy.	Interim reports: With annual re-assessment Final CSR: December 2027

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Ebvallo $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL dispersion for injection
tabelecleucel (EBV-specific viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

An allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy. Each vial contains 1 mL deliverable volume at a concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ viable T cells/mL dispersion for injection.
This medicine contains cells of human origin.

3. LIST OF EXCIPIENTS

Excipients: dimethyl sulfoxide, human serum albumin, phosphate buffered saline. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for injection

Carton contains a single dose (between 1 vial to 6 vials) according to the patient-specific dose required. Each vial contains 1 mL deliverable volume.
See actual concentration and Lot Information Sheet (LIS) for patient dose calculation.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not thaw vial(s) until patient is onsite and awaiting dosing.
Prior to thawing ensure:
1. Patient identifiers and product-patient reconciliation are confirmed
2. Dose calculations are complete
3. Required materials are available
4. Patient is ready for dosing
For intravenous use after dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen at ≤ -150 °C until immediately prior to preparation for administration. Do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1700/001

13. BATCH NUMBER, DONATION AND PRODUCT CODES

PFPIN:
Institution Patient ID:
Lot Number:
FDP Number:
Number of Vials:
Actual Concentration: X.X × 10^7 viable T cells/mL
Donor ID:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Ebvallo $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL dispersion for injection
tabelecleucel (EBV-specific viable T cells)
IV use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot XXXXXXXXXX
Donor ID XXXX-XXXX-X

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

MFD
allogeneic

PARTICULARS TO APPEAR ON THE LOT INFORMATION SHEET (LIS) INCLUDED WITH EACH SHIPMENT FOR ONE PATIENT

1. NAME OF THE MEDICINAL PRODUCT

Ebvallo $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL dispersion for injection
tabelecleucel (EBV-specific viable T cells)

2. STATEMENT OF ACTIVE SUBSTANCE

An allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy. Each vial contains 1 mL deliverable volume at a concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ viable T cells/mL dispersion for injection.
This medicine contains cells of human origin.

The actual concentration noted below should be used to calculate the patient dose.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT, AND DOSE OF THE MEDICINAL PRODUCT

PATIENT DOSE CALCULATION

Volume of diluent to be used (mL) _____

Patient weight (kg) _____

× target dose (2×10^6 viable T cells/kg) =

Viable T cells to be administered _____

÷

Actual concentration (viable T cells/mL) _____

=

Volume of thawed cell dispersion required (mL) _____

4. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not thaw vial(s) until patient is onsite and awaiting dosing.
Prior to thawing ensure:
1. Patient identifiers and product-patient reconciliation are confirmed
2. Dose calculations are complete
3. Required materials are available
4. Patient is ready for dosing
For intravenous use after dilution.

5. OTHER SPECIAL WARNING(S), IF NECESSARY

Save this document and have it available when preparing for administration of Ebvallo.

6. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen at ≤ -150 °C until immediately prior to preparation for administration. Do not refreeze.

Transport security and product quality during shipment are monitored through transport and shipper service providers. At the time of dose preparation, confirmation of drug product storage at ≤ - 150 °C must be performed. Additionally, product-patient reconciliation must be performed by matching information on this document against 1) the carton (matching PFPIN and FDP Number) and against 2) the vial label (matching Lot Number and Donor ID).

7. EXPIRY DATE AND OTHER BATCH SPECIFIC INFORMATION

INFORMATION ON SUPPLIED LOT

The following lot was manufactured and included in this shipment:

Lot Number		
Donor ID		
Finished Drug Product (FDP) Number		
Number of Vials		
Actual Concentration (viable T cells/mL)		
Expiry Date		
Donor/Donated Cells Cytomegalovirus (CMV) Markers	IgM Antibodies	
	IgG Antibodies	
	Nucleic Acid Testing (NAT)	

PRODUCT LOT HLA PROFILE (restrictions in **bold red**)

HLA	ALLELE 1	ALLELE 2
A		
B		
C		
DRB1		
DQB1		

8. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPLICABLE

This medicine contains human blood cells. Unused medicine or waste material must be disposed of in compliance with the local guidelines on handling of waste of human-derived material.

9. DONATION AND PRODUCT CODES

PATIENT INFORMATION

Pierre Fabre Patient Identification Number (PFPIN)	
Institution Patient Identification	
Patient Weight (kg)	
SEC	

10. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

11. MARKETING AUTHORISATION NUMBER

EU/1/22/1700/001

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ebvallo 2.8 × 10^7 – 7.3 × 10^7 cells/mL dispersion for injection
tabelecleucel (EBV-specific viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ebvallo is and what it is used for

Ebvallo contains the active substance tabelecleucel.

Tabelecleucel is an allogeneic T-cell immunotherapeutic. It is called an allogeneic immunotherapeutic because the blood cells used to make this medicine come from human donors who are not related to the patient who is being treated. Ebvallo is made in a laboratory from T cells (a type of white blood cell) from a healthy donor who is immune to the Epstein-Barr virus. These cells have been individually selected to match with the patient receiving Ebvallo. Ebvallo is given as an injection into a vein.

Ebvallo is used to treat a rare kind of cancer called Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV^+ PTLD) for adults and children 2 years of age and older. Some people experience this condition months or years after they have had a transplant. Patients will have received treatment with other medicines for this condition, such as monoclonal antibodies or chemotherapy, before they are given Ebvallo.

2. What you need to know before you are given Ebvallo

You must not be given Ebvallo
- if you are allergic to tabelecleucel or any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions
Talk to your doctor or nurse before you are given Ebvallo if:
- you have had a solid organ transplant or bone marrow transplant, so your doctor can monitor you for signs and symptoms of transplant rejection.
- you are 65 years of age or older, so your doctor can monitor you for serious side effects. Ebvallo should be used with caution in elderly patients.

Talk to your doctor or nurse after you are given Ebvallo if:

- you have signs and symptoms of tumour flare reaction. Depending on the location of the tumour, Ebvallo can cause a side effect called tumour flare reaction. The tumour or enlarged lymph nodes may become suddenly painful or increase in size and could cause problems for organs next to the tumour. Tumour flare reaction generally occurs in the first few days after receiving Ebvallo. Your doctor will monitor you after the first few doses to see if your tumour or lymph node could get big enough to cause problems. Your doctor may give you other medicines to treat/prevent tumour flare reaction.

- you have signs and symptoms of graft-versus-host disease (GvHD), such symptoms include skin rash, abnormal liver enzymes in the blood, yellowing of the skin, nausea, vomiting, diarrhoea and bloody stools.

- you have signs and symptoms of a serious immune reaction called cytokine release syndrome (CRS), such as fever, chills, low blood pressure and shortness of breath.

- you have signs and symptoms of a serious immune reaction called immune effector cell-associated neurotoxicity syndrome (ICANS), such as depressed level of consciousness, confusion, seizures and swelling of the brain.

- you have signs and symptoms of infusion-related reactions, such as fever.

An ingredient of Ebvallo called dimethyl sulfoxide (DMSO) may cause an allergic reaction. Your doctor or nurse will monitor you for signs and symptoms of an allergic reaction. See section 2 “Ebvallo contains sodium and dimethyl sulfoxide (DMSO)”.

Ebvallo is tested for the presence of infectious microbes, but a small risk of infection remains. Your doctor or nurse will monitor you for signs and symptoms of infections and provide treatment as needed.

After treatment with Ebvallo, you must not donate blood, organs, tissues or cells.

Other medicines and Ebvallo
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given Ebvallo, tell your doctor or nurse if you are taking medicines such as chemotherapy or corticosteroids. If you are taking chemotherapy, this medicine may affect how well Ebvallo works. If you are taking corticosteroids, your doctor will reduce the dose of corticosteroids.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine. This is because the effects of this medicine in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child. Ebvallo is not recommended during pregnancy and in women who could become pregnant not using contraception.

- If you are pregnant or think you may be pregnant after you have started treatment with Ebvallo, talk to your doctor immediately.
- Discuss the need for contraception with your doctor.
- Tell your doctor if you are breast-feeding or plan to do so. Your doctor will then help you decide whether to stop breast-feeding or whether to stop taking Ebvallo, considering the benefit of breast-feeding the baby and the benefit of Ebvallo to the mother.

Driving and using machines
Ebvallo has minor influence on the ability to drive or use machines. If you experience changes in your thinking or level of alertness after being treated with this medicine, do not drive or operate machines and tell your doctor immediately.

Ebvallo contains sodium and dimethyl sulfoxide (DMSO)
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

This medicine contains 100 mg DMSO per mL. See Section 2 "Warnings and precautions".

3. How Ebvallo is given

Ebvallo will always be given to you by a doctor or nurse in a treatment centre.

Your doctor or nurse will give you Ebvallo by injection into a vein. This usually takes 5 to 10 minutes for each injection.

Each cycle of treatment consists of 35 days. You will be given 1 injection per week for 3 weeks, followed by approximately 2 weeks of observation to see if you will need more than one cycle. Your doctor will decide the number of cycles you will receive based on how your disease responds to Ebvallo.

Before you are given Ebvallo
Your doctor or nurse will monitor your vital signs prior to each injection.

After you are given Ebvallo
Your doctor or nurse will monitor your vital signs, including blood pressure, for about 1 hour following the injection.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor immediately if you get any of the following side effects after receiving Ebvallo:
- Tumour flare reaction with symptoms such as shortness of breath, changes in your thinking or level of alertness, pain at the tumour site, tender swollen lymph nodes at the tumour site, low grade fever
- Graft-versus-host disease (GvHD) with symptoms such as skin rash, abnormal liver enzymes in the blood, yellowing of the skin, nausea, vomiting, diarrhoea and bloody stools

Other possible side effects

Very common (may affect more than 1 in 10 people)

- Fever
- Diarrhoea
- Tiredness
- Feeling sick (nausea)
- Low levels of red blood cells (anaemia)
- Decreased appetite
- Decreased levels of sodium in the blood
- Abdominal pain or discomfort

- Decreased number of white blood cells (including neutrophils)
- Increased liver enzymes in the blood
- Constipation
- Increased levels of the enzyme alkaline phosphatase in the blood
- Decreased oxygen levels
- Dehydration
- Low blood pressure
- Stuffy nose
- Skin rash which may be red, bumpy or pus-filled

Common (may affect up to 1 in 10 people)

- Dizziness
- Headache
- Decreased levels of magnesium, potassium or calcium in the blood
- Itching
- Chills
- Decreased number of white blood cells (lymphocytes)
- Decreased number of white blood cells (neutrophils) with fever
- Muscular weakness
- Joint pain, swelling and stiffness
- Increased levels of creatinine in the blood
- Wheezing
- Confusion and disorientation
- Back pain
- Muscle pain
- Nose and throat infection
- Chest pain
- Increased levels of lactate dehydrogenase in the blood
- Inflammation of the colon
- Pain
- Decreased number of platelets in the blood
- Bloating
- Delirium
- Depressed level of consciousness
- Hot flush
- Inflammation of the lungs
- Sleepiness
- Fast heartbeat
- Tumour pain
- Decreased levels of fibrinogen in the blood (a protein involved in blood clotting)
- Flatulence
- Swelling
- Skin ulcer
- Blue skin colour due to low oxygen levels
- Difficult or painful bowel movement
- General physical health deterioration
- Numbness, tingling or burning sensation in hands or feet
- Bleeding in the lungs
- Skin discolouration
- Skin infection
- Destruction of soft tissue
- Persistent cough

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Ebvallo

Your doctor, pharmacist or nurse is responsible for storing this medicine and disposing of any unused product correctly. The following information is intended for healthcare professionals.
Do not use this medicine after the expiry date. The expiry date is provided on the Lot Information Sheet (LIS) and carton.

Store Ebvallo frozen in the vapour phase of liquid nitrogen at -150 °C or below until thawed for use. The medicine 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.

Store between 15 °C to 25 °C after thawing and dilution are complete. Protect product from light. Do not refreeze. Do not irradiate.

6. Contents of the pack and other information

What Ebvallo contains
- Ebvallo contains tabelecleucel at an approximate concentration of $2.8 \times 10^7 – 7.3 \times 10^7$ cells/mL.
- The other ingredients (excipients) are: dimethyl sulfoxide, human serum albumin, phosphate buffered saline. See section 2 “Ebvallo contains sodium and dimethyl sulfoxide (DMSO)”.

What Ebvallo looks like and contents of the pack
Ebvallo is a translucent, colourless to slightly yellow cell dispersion for injection.

Ebvallo is provided in individual patient cartons containing 1 vial to 6 vials according to the patient-specific dose required. Each vial contains 1 mL of this medicine.

Marketing Authorisation Holder
PIERRE FABRE MEDICAMENT
Les Cauquillous
81500 Lavaur
France

Manufacturer
PIERRE FABRE MEDICAMENT PRODUCTION
Parc industriel de la Chartreuse
81100 Castres
France

This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease, it has been impossible to get complete information on this medicine. The

European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

It is important that you read the entire content of this procedure prior to administering Ebvallo.

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 (LIS) and carton. Product-patient reconciliation must be performed by matching information on the LIS 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, all materials needed to prepare the dose are available, and the patient is onsite and has been clinically evaluated.

Dose calculations
- See the accompanying Lot Information Sheet (LIS) and carton for information pertaining to the concentration of cells per vial.
- Note: The viable T-cell concentration on the LIS 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.

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.
- 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. Ebvallo contains 10% DMSO. Ebvallo should be injected to the patient as soon as possible after thawing.

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.

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.