EBVALLO® ▼ tabelecleucel

Physician Guide

A therapy management guide
to help support your patients receiving
EBVALLO (tabelecleucel).

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.[1]

Pierre Fabre

▼ *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.*

EBVALLO®
tabelecleucel

Physician Guide

Glossary

- **ALT:** Alanine transaminase
- **AST:** Aspartate transaminase
- **CR:** Complete response
- **CRS:** Cytokine release syndrome
- **DMSO:** Dimethyl Sulfoxide
- **EBV:** Epstein-Barr virus
- **EBV+ PTLD:** Epstein-Barr Virus Positive Post-Transplant Lymphoproliferative Disease
- **GvHD:** Graft-versus-host disease
- **HBV:** Hepatitis B virus
- **HCT:** Hematopoietic Stem Cell Transplant
- **HCV:** Hepatitis C virus
- **HIV:** Human Immunodeficiency Virus
- **HLA:** Human Leukocyte Antigen
- **ICANS:** Immune effector cell-associated neurotoxicity syndrome
- **IR:** Indeterminate response
- **NSAIDs:** Non-Steroidal Anti-inflammatory Drugs
- **ORR:** Objective Response Rate
- **OS:** Overall Survival
- **PD:** Progressive disease
- **PR:** Partial response
- **PTLD:** Post-transplant Lymphoproliferative Disease
- **SD:** Stable disease
- **SOT:** Solid Organ Transplant
- **TFR:** Tumour flare reaction

References

1. EBVALLO Summary of Product Characteristics. **2.** Dierickx D, et al. Post-Transplantation Lymphoproliferative Disorders in Adults. N Engl J Med. 2018;378:549–562. **3.** Nijland ML, et al. Epstein-Barr virus-positive posttransplant lymphoproliferative disease after solid organ transplantation: pathogenesis, clinical manifestations, diagnosis, and management. Transplant Direct. 2016;2(1):e48. **4.** Dharnidharka V., et al. Clinical Outcomes of Solid Organ Transplant Patients with Epstein-Barr Virus-Driven (EBV +) Post-Transplant Lymphoproliferative Disorder (PTLD) Who Fail Rituximab Plus Chemotherapy: A Multinational, Retrospective Chart Review Study. Blood 2021 138 Supplement 1 (2528-). **5.** Sanz J., et al. Clinical Outcomes of Patients with Epstein-Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Following Hematopoietic Stem Cell Transplantation Who Fail Rituximab: A Multinational, Retrospective Chart Review Study. Blood 2021 138 Supplement 1 (1454-). **6.** Mahadeo KM, et al. New and Updated Results from a Multicenter, Open-Label, Global Phase 3 Study of Tabelecleucel (Tab-cel) for Epstein-Barr Virus-Positive Post-Transplant Lymphoproliferative Disease (EBV+ PTLD) Following Allogeneic Hematopoietic Cell (HCT) or Solid Organ Transplant (SOT) after Failure of Rituximab or Rituximab and Chemotherapy (ALLELE). Blood 2022; 140 (Supplement 1): 10374–10376. doi: https://doi.org/10.1182/blood-2022-157766. **7.** EBVALLO EPAR.

SUMMARY

1. EBV+ PTLD OVERVIEW [2-5]

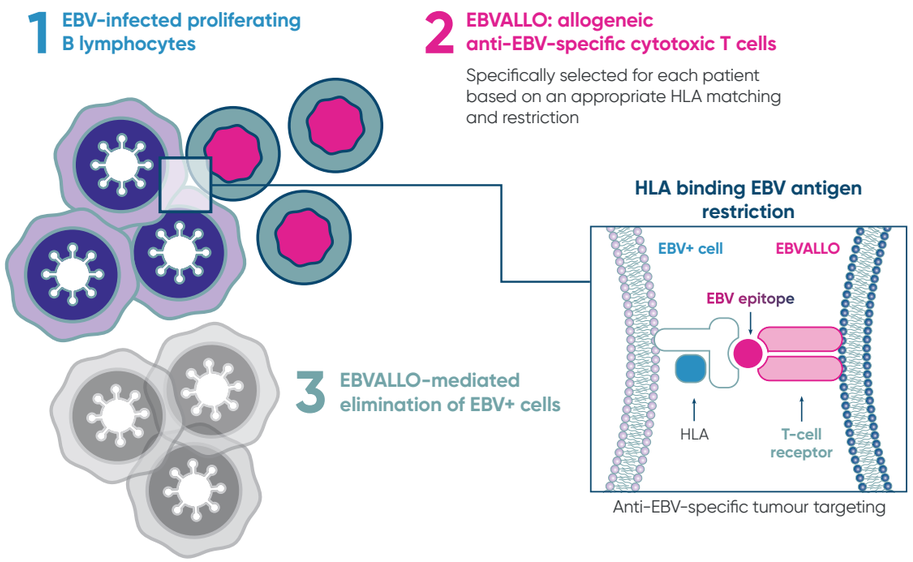
Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) is a rare, acute and potentially life-threatening group of lymphoid disorders that arise after transplantation:[2-3]

- **EBV** infection primarily infects B-cells.
- **In immunocompetent host :**
  - T-cells kill infected B-cells during intermittent EBV lytic phases, keeping the infection under control.
  - At the same time, EBV DNA integrates in infected B-cells DNA, and establishes a latent infection that the immune system can usually control but cannot clear.
- **In immunosuppressed transplanted patients:**
  - Suppression of T-cell activity causes the EBV infection to remain undetected by the immune system.
  - EBV-infected B-cells may transform and rapidly proliferate causing PTLD.

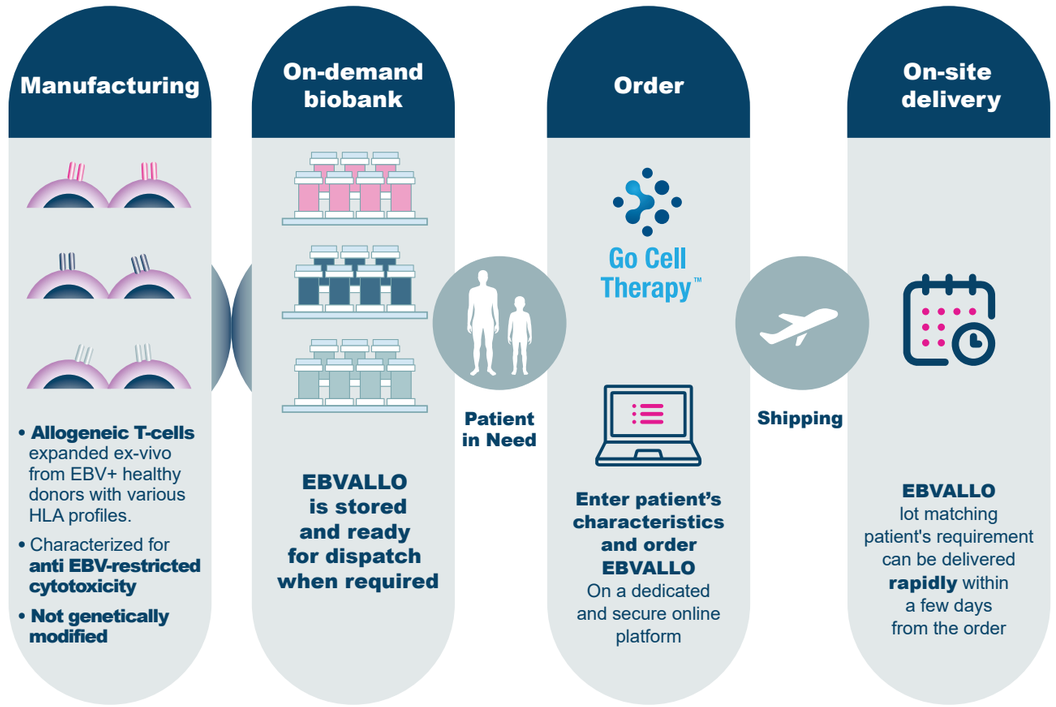
The **poor patient prognosis** associated with EBV+ PTLD upon rituximab-based treatment failure calls for an urgent intervention. The median OS post rituximab +/- chemotherapy failure is **0.7 months** post HCT (hematopoietic cell transplantation) and **4.1 months** post SOT (solid organ transplantation).[4-5]

2. EBVALLO OVERVIEW

A • WHAT IS EBVALLO ? [1]



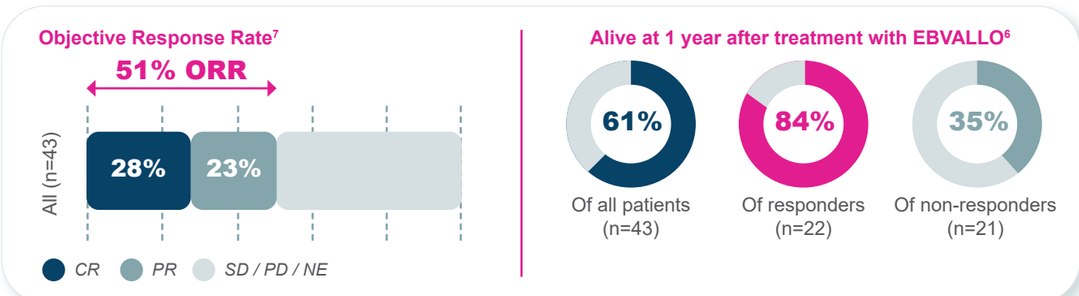
EBVALLO (tabelecleucel) is an allogeneic Epstein-Barr virus (EBV)-specific T-cell immunotherapy which targets and eliminates EBV-infected proliferating cells in a human leukocyte antigen (HLA)-restricted manner



B • INDICATION [1]

- 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.

C • EFFICACY [6,7]

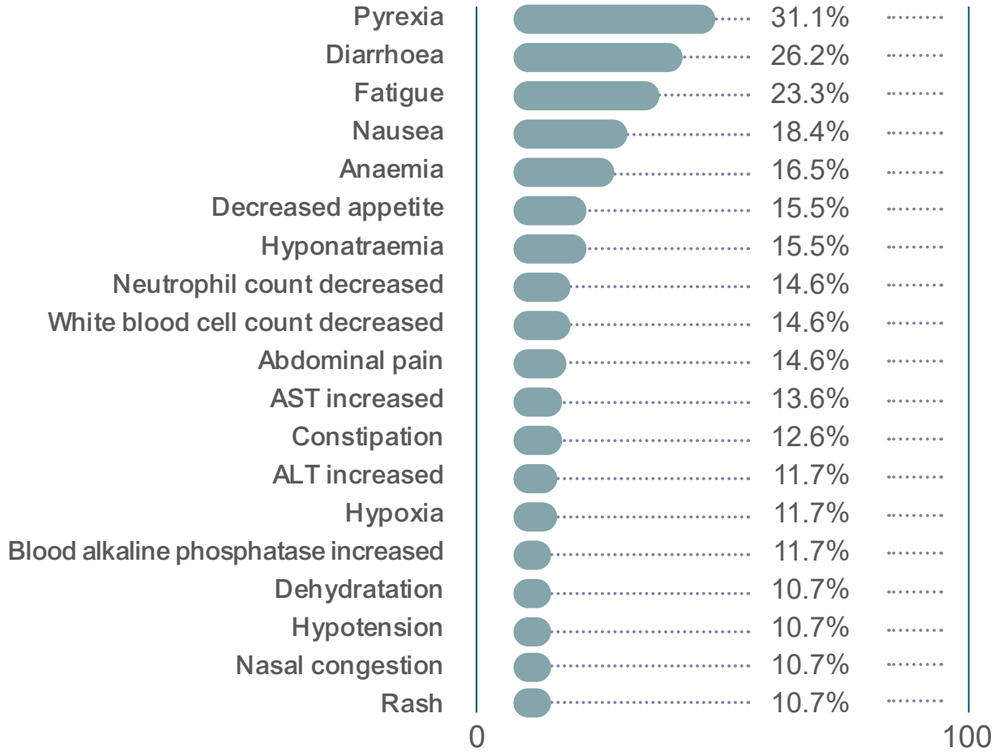


ORR: Objective Response Rate ; OS: Overall Survival ; CR: complete response ; PR: partial response ; SD: stable disease ; PD: progressive disease ; NE: includes not evaluable, missing, and indeterminate response.

D • SAFETY [1]

Frequencies of adverse reactions with EBVALLO were evaluated in 103 patients in PTLD development program:

Most common Adverse Reactions [1]



Most serious Adverse Reactions [1]

Adverse events	Nb of patients (%)	Grade	Outcome
Tumour flare reaction	1 (1%)	3	Recovered
Graft-versus-host disease	5 (4,9%)	2 grade 1 1 grade 2 1 grade 3 1 grade 4	No fatal events were reported. 4 patients recovered from GvHD.

3. EBVALLO ADMINISTRATION [1]

A • DOSE CALCULATIONS [1]

To define the volume of EBVALLO that you need to administer to your patient, you need to take into account :

- Your patient's weight
- The actual concentration of the lot provided in the LIS (Lot Information Sheet)

The calculation is as follows :

Elderly (>= 65 years old)

No dose adjustment

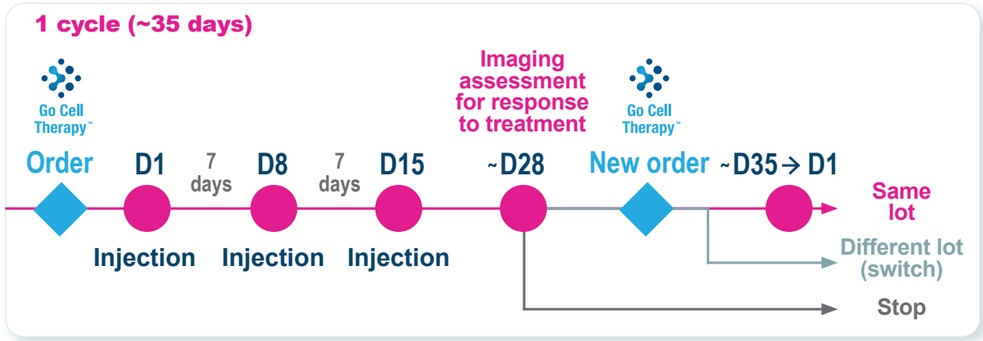
Hepatic and renal impairment

No dose adjustment

Pediatric population

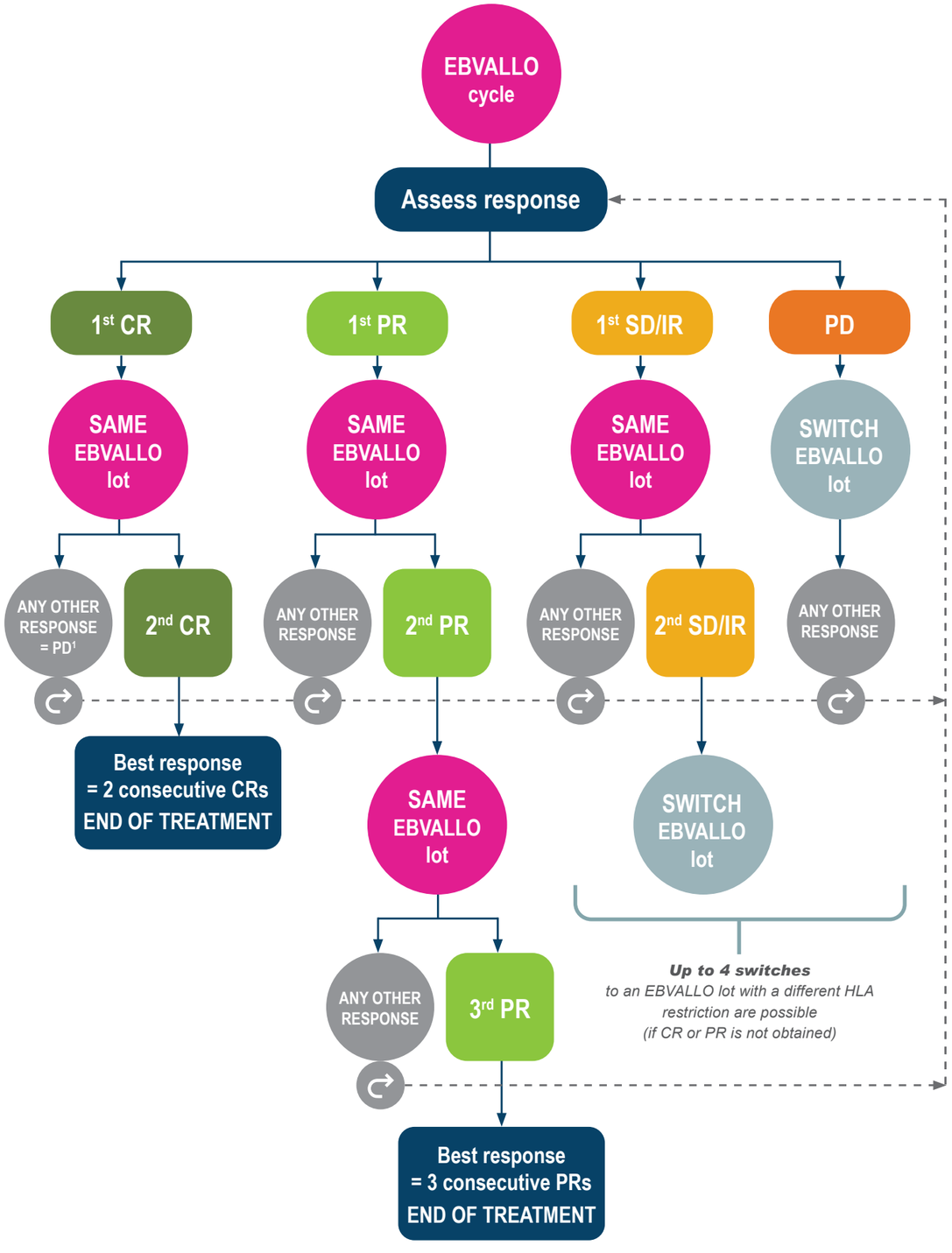
Same posology and administration in paediatric patients 2 years of age and older as for adult patients

B • ADMINISTRATION [1]



- EBVALLO 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.

C • TREATMENT ALGORITHM [1]



1. CR at the end of a cycle followed by PR or other response at any subsequent cycle is considered PD
***CR:** complete response; **PR:** partial response; **SD:** stable disease; **ID:** indeterminate response; **PD:** progressive disease*

D • MONITORING [1]

It is recommended to monitor vital signs :

- Immediately prior to each EBVALLO injection.
- Within 10 minutes following the conclusion of the injection.
- 1 hour after the initiation of the injection.

4. CONTRAINDICATIONS [1]

Hypersensitivity to the active substance or to any of the excipients: Dimethyl sulfoxide, Human serum albumin, Phosphate buffered saline.

Fertility, pregnancy and lactation

- EBVALLO is not recommended during pregnancy and in women of childbearing potential not using contraception.
- Breast-feeding women should be advised of potential risks to the breast-fed child.
- There are no data on the effect of tabelecleucel on fertility.

5. INTERACTIONS [1]

No interaction studies have been performed.

5. INTERACTIONS [1]

Immunosuppressive and cytotoxic therapies :

- EBVALLO should only be administered **after an adequate washout period** of cytotoxic 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.

CD20-targeting antibodies :

- **Not expected that anti-CD20 antibody treatments** will affect EBVALLO activity.

6. SPECIAL WARNINGS AND PRECAUTIONS FOR USE [1]

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.
- **Consider the benefit of treatment with EBVALLO** versus the risk of possible GvHD. 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.
- **Consider the benefit of treatment with EBVALLO** versus the risk of possible solid organ transplant rejection 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 EBVALLO lots are tested for sterility, mycoplasma and adventitious agents, **a risk of transmission of infectious agents exists.**
- **All lots are tested to ensure no detection of adventitious agents, including CMV.** Some EBVALLO lots are manufactured from donors who are cytomegalovirus (CMV) positive. During clinical development, EBVALLO 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.

7. PATIENT COUNSELING

Patient Support :

- Patient education and engagement are key to the treatment process.

Your support helps the patient better understand:

The disease

The treatment

The adverse reactions

Patient documents are available for your patient, please ask your Pierre Fabre representative.

NOTES

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Summary SmPC

EBVALLO ABBREVIATED PRESCRIBING INFORMATION

▼ 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 below for how to report any adverse events.

NAME OF THE MEDICINAL PRODUCT: Ebvallo 2.8×10^7 –7.3×10^7 cells/mL dispersion for injection

CLINICAL PARTICULARS:

Therapeutic indications: Ebvallo is indicated as monotherapy for treatment of adult and paediatric patients 2 years of age and older with relapse and refractory Epstein-Barr virus 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.

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: The recommended dose of Ebvallo contains 2×10^6 viable T-cells per kg of patient's body weight. Treatment consists of multiple doses for injection containing a dispersion of viable T-cells in one or more vials. Ebvallo is administered over multiple 35-day cycles, during which patients receive it on days 1, 8 and 15, followed by observation through day 35. A response is assessed at approximately day 28. (see SmPC Section 4.2).

Method of administration: Ebvallo should be administered under the supervision of a physician experienced in the treatment of cancer in a control setting where adequate facilities for handling of adverse reactions, including those for required urgent measures, are available. Ebvallo is for intravenous use only. 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 IV 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 SMPC section 6.6

Contraindications: Hypersensitivity to the active substance or to any of the excipients: Dimethyl sulfoxide, Human serum albumin, Phosphate buffered saline.

Interaction with other medicinal products and other forms of interaction: No interaction studies have been performed. Ebvallo should only be administered after an adequate washout period of certain concomitant or recently administered medicinal products including chemotherapy (systemic or intrathecal), anti T-cell antibody-based therapies, extracorporeal photopheresis or brentuximab vedotin. They could potentially impact the efficacy of Ebvallo. For patients receiving chronic corticosteroid therapy, the dose of these drugs should be reduced; recommended no greater than 1 mg/kg per day of prednisone or equivalent. For complete information, please refer to SmPC Section 4.5

Contraceptives and breastfeeding: 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. Breast-feeding women should be advised of potential risks to the breast-fed child. There are no data on the effect of Ebvallo on fertility. For complete information, please refer to SmPC Section 4.6

Undesirable effects: Summary of 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%). For complete information, please refer to SmPC Section 4.8.

MARKETING AUTHORISATION HOLDER :

Pierre Fabre Médicament -Les Cauquillous, 81500 Lavaur, France.

DATE OF REVISION OF THE TEXT:

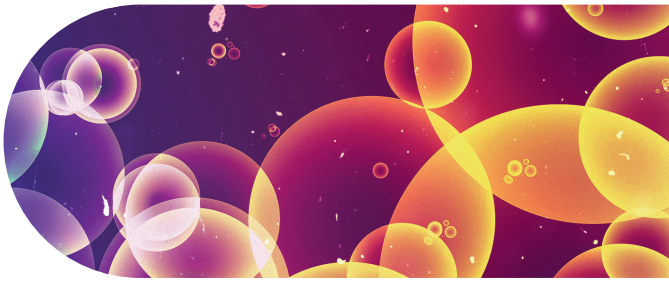
February 2023. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu. For complete information, please refer to SmPC. Latest review of EU SmPC: 2023.

REPORTING OF SUSPECTED ADVERSE REACTIONS:

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions via the national reporting system (Appendix V - European Medicines Agency - Europa EU) and/or to the Pharmacovigilance department of Pierre Fabre laboratories (www.pierre-fabre.com/en/pharmacovigilance).

For complete information, please refer to:
EBVALLO Summary of Product Characteristics

https://www.ema.europa.eu/en/documents/product-information/ebvallo-epar-product-information_en.pdf



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