RMP SUMMARY

EBVALLO (Tabelecleucel)

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DISCLAIMER

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Ebvallo is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ebvallo in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Pierre Fabre Pharma is fully responsible for the accuracy and correctness of the content of the published summary RMP of Ebvallo.

SUMMARY OF RISK MANAGEMENT PLAN FOR EBVALLO (TABELECLEUCEL)

This is a summary of the risk management plan (RMP) for Ebvallo. The RMP details important risks of Ebvallo, and how these risks can be minimised, and how more information will be obtained about Ebvallo's risks and uncertainties (missing information).

Ebvallo's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Ebvallo should be used.

This summary of the RMP for Ebvallo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Ebvallo's RMP.

I. The Medicine and What It Is Used For

Ebvallo is authorised for the treatment of adult and pediatric 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 (see SmPC for the full indication).

Ebvallo contains tabelecleucel as the active substance and it is given by intravenous injection.

Further information about the evaluation of Ebvallo's benefits can be found in Ebvallo's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage Ebvallo | European Medicines Agency (europa.eu).

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

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

Measures to minimise the risks identified for medicinal products can include the following:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and Package Leaflet (PL) addressed to healthcare professionals and patients.
- Important advice on the medicine's packaging.
- Ebvallo should be administered under the supervision of a physician experienced in the treatment of cancer.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of Ebvallo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Ebvallo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Important identified risk: Tumour flare reaction (TFR)	
Evidence for linking the risk to the medicine	Tumour flare reaction (TFR) was identified in the clinical development program as an adverse drug reaction based on a plausible mechanism of action and aggregate review of all TFR events, which include a case with positive rechallenge.
Risk factors and risk groups	The patients at risk of severe TFR are those with high tumour burden prior to treatment.[a,b] Depending on the anatomic location of the tumour or lymphadenopathy, complications may arise from mass effect including compression and/or obstruction of adjacent anatomic structures.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4. Additional risk minimiation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important identified risk: Graft-versus-host Disease (GvHD)	
Evidence for linking the risk to the medicine	Graft-versus-host disease (GvHD) was identified in the tabelecleucel clinical development program as an adverse drug reaction based on a plausible mechanism of action. A causal relationship between tabelecleucel and GvHD cannot be excluded. As GvHD can be life-threatening or cause chronic comorbidities, it is considered an important identified risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing GvHD after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.4 and 4.8 Package Leaflet: Sections 2 and 4 Additional risk minimisation measures: Not required

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important identified risk: Cytokine release syndrome (CRS)	
Evidence for linking the risk to the medicine	Cases of CRS possibly related to tabelecleucel were reported in the clinical development programme (frequency common), and in the postmarketing setting. CRS is considered an important identified risk due to its potential for severe outcomes if left untreated and based on accumulated cases with possible relationship to tabelecleucel in the treatment of EBV+ PTLD and other EBV+ diseases
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing CRS after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 and 4.8 Package Leaflet: Section 2 and 4 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Solid Organ Transplant (SOT) Rejection	
Evidence for linking the risk to the medicine	The evidence of SOT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived SOT is limited, as the small number of reported cases of SOT rejection after administration of tabelecleucel had other risk factors including decrease of immunosuppressants as standard of care or a medical history of previous episodes of SOT rejection. As SOT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing SOT rejection after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Bone marrow transplant (BMT) rejection	
Evidence for linking the risk to the medicine	There is no evidence of BMT rejection after administration of tabelecleucel in patients with previous allogeneic donor-derived HCT, as no cases have been reported in the clinical development program. In addition, a diminished host immune system after HCT would unlikely facilitate immune reactions. As BMT rejection can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing HCT graft after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Immune effector cell-associated neurotoxicity syndrome (ICANS)	
Evidence for linking the risk to the medicine	There have been no reports of the PT: ICANS in the clinical development program. Applying a broader search criterion, only 1 grade 3 event of confusional state that was considered related by the investigator was reported in Studies ATA129-EBV-302 and EBV-CTL-201. The majority of events were assessed as not related and occurred in the context of confounding factors, suggesting that tabelecleucel is not associated with ICANS. ICANS is considered an important potential risk due to its potential for severe outcomes if left untreated.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing ICANS after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities:

	Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Infusion-related reaction (IRR)	
Evidence for linking the risk to the medicine	Evidence for relationship of IRR with tabelecleucel is limited. As IRR can be life-threatening or cause chronic comorbidities, it is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing IRR after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Immunogenicity	
Evidence for linking the risk to the medicine	HLA antibodies can potentially reduce the efficacy of tabelecleucel and can cause clinical manifestations of immunogenicity such as anaphylaxis and SOT rejection that may require medical intervention. No immunogenicity adverse events were specific to development of anti-HLA antibodies therefore, no definitive conclusions regarding the association of HLA antibody positivity with immunogenicity adverse events can be drawn, and hence, immunogenicity is an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of developing immunogenicity after tabelecleucel administration, however, patient- and disease-related factors may influence the development of an immune response and it would be expected that in the immunocompromised PTLD population, an immune response might be less likely to occur.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.8 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.

Important potential risk: Transmission of infectious agents (including cytomegalovirus)	
Evidence for linking the risk to the medicine	The risk associated with tabelecleucel is considered very low. Strict precautions to prevent transmission of infectious agents and to ensure microbial safety of tabelecleucel are in place in compliance with principles of good manufacturing practices and regulatory guidelines.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of transmission of infectious agents after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.4 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Important potential risk: Decrease in cell viability due to inappropriate handling of the product	
Evidence for linking the risk to the medicine	Based on potential inconsistencies that may arise due to product handling, decrease in cell viability due to inappropriate handling of the product is considered an important potential risk.
Risk factors and risk groups	No risk factors have been identified leading to increased risk of decrease in cell viability due to inappropriate handling of the product after tabelecleucel administration.
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 6.3, 6.4, and 6.6 Package Leaflet: Healthcare Professional tear-off Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE See Section II.C of this summary for an overview of the postauthorisation development plan.
Missing Information: Use in paediatric population	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.2, 4.8, and 5.1 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE

Missing Information: Use in elderly population	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Sections 4.2, 4.4, and 5.1 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE
Missing Information: Use in pregnancy and lactation	
Risk minimisation measures	Routine risk minimisation measures: SmPC: Section 4.6 Package Leaflet: Section 2 Additional risk minimisation measures: Not required
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE
Missing Information: Long-term safety	
Risk minimisation measures	No risk minimisation measures
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Short study name: EBVOLVE

II.B. Postauthorisation Development Plan

II.B.1. Studies Which are Conditions of the Marketing Authorisation

The following studies are specific obligations in the context of a marketing authorisation under exceptional circumstances:

Study short name: EBVOLVE

Purpose of the study:

- Primary objective: To describe the safety of tabelecleucel in patients with EBV^+ PTLD following HCT or SOT in a real-world setting
- Secondary objectives: To describe the effectiveness of tabelecleucel in patients treated for EBV^+ PTLD following HCT or SOT in a real-world setting, to describe the patient population treated with tabelecleucel for EBV^+PTLD in a real-world setting, and to describe tabelecleucel treatment patterns, including dosing and schedule in patients treated for EBV^+ PTLD in a real-world setting

Study short name: ATA129-EBV-302

Purpose of the study:

- Primary objective: To determine the clinical benefit of tabelecleucel in subjects with EBV^+ PTLD following (1) SOT and after failure of rituximab (Subgroup A) and rituximab plus chemotherapy (Subgroup B) or (2) allogeneic HCT after failure of rituximab, as measured by the objective response rate
- Secondary objectives:
    - To evaluate duration of response in the SOT and HCT cohorts separately
    - To evaluate objective response rate and duration of response in the SOT and HCT cohorts combined
    - To evaluate rates of complete response and partial response
    - To evaluate time to response and time to best response
    - To evaluate overall survival
    - To evaluate graft status (SOT subjects only)
    - To characterise the safety profile of tabelecleucel in this subject population

II.B.2. Other Studies in Postauthorisation Development Plan

There are no studies required for Ebvallo.