Summary of the risk management plan

Summary of risk management plan for ADCETRIS (brentuximab vedotin)

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

ADCETRIS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ADCETRIS should be used.

This summary of the RMP for ADCETRIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all 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 ADCETRIS's RMP.

I. The medicine and what it is used for

ADCETRIS is indicated for the treatment of adult patients with previously untreated CD30+ Stage IV HL in combination with doxorubicin, vinblastine and dacarbazine (AVD), relapsed or refractory CD30+ Hodgkin lymphoma (HL) following autologous stem cell transplant (ASCT), or following at least 2 prior therapies when ASCT or multiagent chemotherapy is not a treatment option; treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT; treatment of adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL), and treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy (see SmPC for the full indication).

ADCETRIS is also indicated in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). It contains brentuximab vedotin as the active substance and it is given by intravenous infusion.

Further information about the evaluation of ADCETRIS’s benefits can be found in the ADCETRIS’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage:

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002455/WC500135004.pdf

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

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

If important information that may affect the safe use of ADCETRIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of ADCETRIS are risks that need special risk management activities to further investigate or minimize 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 ADCETRIS. 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 (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	1. Peripheral neuropathy (sensory and motor) 2. Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) 3. Infections (including Bacteriemia, Sepsis, Septic shock and Opportunistic infections) 1. Infusion-related reactions 2. Hyperglycaemia 6. Anti-drug antibodies
Important potential risks	7. Severe hepatotoxicity 8. Pulmonary toxicity 9. Thymus depletion (pediatric)
Missing information	10. Long term safety

II.B Summary of important risks

The safety information in the proposed product information is aligned to the reference medicinal product.

Important identified risk: Peripheral neuropathy (sensory and motor)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Prior exposure to neurotoxic chemotherapy regimens with subclinical nerve injury; history of diabetes or alcohol use; hypothyroidism. Among lymphoma patients, disease-specific risk factors include paraneoplastic, vasculitic, or paraproteinemic neuropathies.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC sections 4.2 and 4.4 where there are recommendations regarding monitoring patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paraesthesia, discomfort, burning sensation, neuropathic pain or weakness) and the possibility of delaying or reducing the dose in patients who experience new or worsening neuropathy. Package Leaflet section 2 and section 4 Legal status

	Additional risk minimization measures: None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101 See section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Myelosuppression (including Neutropenia, Febrile Neutropenia, Thrombocytopenia and Anaemia)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Prior ASCT, chemotherapy, patients with neutropenia, decreased WBC and/or platelet count, hemoglobin, hematocrit, or red blood cell counts at baseline. The risk of febrile neutropenia is increased for patients with lower absolute neutrophil counts. The risk of febrile neutropenia in oncology patients receiving chemotherapy increases with duration of neutropenia and with degree of mucosal damage, (UpToDate.com, Overview of neutropenic fever syndromes, accessed 13 Mar 2013). Thus, the incidence is often higher in patients receiving multiagent chemotherapy as the cumulative toxicities of multiple chemotherapeutics can increase both duration of neutropenia and mucosal damage. Other risk factors that may increase the likelihood of developing febrile neutropenia include advanced stage of underlying malignancy, older age, high body surface area, poor performance status, and poor nutritional status, (UpToDate.com, Use of granulocyte colony stimulating factors in patients with chemotherapy-induced neutropenia, and risk assessment of adults with chemotherapy-induced neutropenia, accessed 13 Mar 2013).
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Sections 4.2 and 4.4 where there are recommendations for patients to have a full blood count prior to administration of each dose of brentuximab vedotin and for close monitoring of patients who develop neutropenia. If patients develop febrile neutropenia, they should be managed according to best medical practice. Dose delays should be considered in patients who develop neutropenia and growth factor support (G-CSF or GM-CSF) should be considered in subsequent cycles for patients who develop Grade 3 or Grade 4 neutropenia in monotherapy with brentuximab vedotin. In combination therapy for the frontline treatment of HL, primary prophylaxis with G-CSF is recommended for all patients beginning with the first dose Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101

	See section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Infections (including Bacteriemia, Sepsis, Septic shock and Opportunistic infections)	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Patients with alterations in immune function, including patients with pre-existing neutropenia or leukopenia, or secondary to prior ASCT or chemotherapy.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation for patients to be carefully monitored during treatment for the emergence of possible serious infections and opportunistic infections. Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101. See section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Infusion-related reactions	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Patients with allergy to brentuximab vedotin or excipients.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.2 and Section 4.4 where there is information about the possibility of patients developing immediate and delayed IRRs including anaphylactic reactions and a recommendation that administration of brentuximab vedotin should either be interrupted or immediately and permanently discontinued and appropriate medical therapy administered if an IRR or anaphylactic reaction occurs. The SmPC also recommend restarting the infusion at a slower rate after symptom resolution and pre-medicating patients who have experienced a prior IRR with pre-medications such as paracetamol, an antihistamine, and a corticosteroid. Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101 See section II.C of this summary for an overview of the post-authorization development plan.

Important identified risk: Hyperglycemia	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Potential factors that may be associated with an increased risk of developing hyperglycemia following the administration of brentuximab vedotin include a fasting glucose above the ULN, pre-existing diabetes mellitus, or concurrent steroid use.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that any patient who experiences hyperglycemia should have their serum glucose closely monitored and antidiabetic treatment should be administered as appropriate. Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101 See section II.C of this summary for an overview of the post-authorization development plan.
Important identified risk: Anti-drug antibodies	
Evidence for linking the risk to the medicine	Immunoassay data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Patients with allergy to brentuximab vedotin or excipients. Patients with chronic infection may be more prone to an immune response. Patients exposed to similar proteins may be at higher risk.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Section 4.4, where there is a statement that a higher incidence of IRRs has been observed in patients with persistently positive ADAs relative to patients with transiently positive ADA and never positive ADA. It is recommended that the infusion should be interrupted if patients develop IRRs. Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** C25006 See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Severe hepatotoxicity	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.

Risk factors and risk groups	Persons who consume high levels of alcohol are generally susceptible to drug toxicity because alcohol induces liver injury and cirrhotic changes that alter drug metabolism. Elderly persons are at increased risk of hepatic injury because of decreased clearance, drug-to drug interactions, reduced hepatic blood flow, variation in drug binding, and lower hepatic volume. Hepatic dysfunction may also arise from liver involvement by malignant lymphoma in a subgroup of patients. Prior or current treatments and medications administered to lymphoma patients may negatively impact the liver on a temporary or permanent basis. Genetic differences in the P-450 enzymes can result in abnormal reactions to drugs, including idiosyncratic reactions. In addition, poor diet, infections, and multiple hospitalizations are important contributing factors of drug-induced hepatotoxicity.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 4.8 SmPC Section 4.4 where there is a recommendation that patients receiving brentuximab vedotin therapy should have a liver function test before initiating treatment and routinely monitored during treatment with brentuximab vedotin. Patients who experience hepatotoxicity may require a dose delay, change in dose, or discontinuation of brentuximab vedotin. Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101 See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Pulmonary toxicity	
Evidence for linking the risk to the medicine	Nonclinical study data; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous reports from the post-marketing setting.
Risk factors and risk groups	Exact risk factors with brentuximab vedotin are not known. However, general risk factors for pulmonary toxicity include smoking history, underlying lung disease, radiation exposure, advanced age, and infectious complications. The MAH is actively monitoring cases of pulmonary toxicity originating from study MA25101 (PASS and the post-marketing setting) with a focus on cases with reported prior medical history of renal and/or hepatic impairment, as well as history of prior treatment with bleomycin, in order to assess whether these conditions/prior therapies represent a discernible risk factor for patients experiencing events of pulmonary toxicity.

Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.8 SmPC Sections 4.3 and 4.4 prohibits the combined use of brentuximab vedotin and bleomycin as it causes pulmonary toxicity. The SmPC also contain a recommendation that if new or worsening pulmonary symptoms are observed, a prompt diagnostic evaluation should be performed and patients should be treated appropriately. Brentuximab vedotin therapy should be stopped during evaluation and until symptomatic improvement. Package Leaflet section 2 and section 4 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: MA25101 See section II.C of this summary for an overview of the post-authorization development plan.
Important potential risk: Thymus depletion (pediatric)	
Evidence for linking the risk to the medicine	Nonclinical toxicology data in rats and monkeys; adverse event reports from phase 1, 2, and 3 clinical trials; and spontaneous adverse event reports from the post-marketing setting.
Risk factors and risk groups	Pediatric patients prior to puberty onset, before involution of the thymus.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 5.3 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** C25004 See section II.C of this summary for an overview of the post-authorization development plan.
Missing information: Long term safety	
Evidence for linking the risk to the medicine	It is not known if it is safe to use brentuximab vedotin for longer than 1 year.
Risk minimization measures	**Routine risk minimization measures:** SmPC Section 4.2 SmPC Section 5.1 Legal status **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** MA25101 See section II.C of this summary for an overview of the post-authorization development plan.

II.C. Post-authorization development plan

II.C.1. Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

C25006

Purpose of the study: An open-label, single-arm phase 4 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma (r/r sALCL) with the objective of investigating single-agent efficacy [ORR, duration of tumor control (including duration of response rate), PFS, and CR; proportion of patients proceeding to SCT and OS], safety and tolerability, PK and immunogenicity.

MA25101

Purpose of the study: A PASS: An observational cohort study of the safety of brentuximab vedotin in treatment of relapsed or refractory CD30+ HL and r/r sALCL with the objective of identification of potential risk factors for peripheral neuropathy (sensory and motor), and gathering safety data (peripheral neuropathy (sensory or motor), myelosuppression (including neutropenia, febrile neutropenia, anaemia and thrombocytopenia); infections (including bacteremia, sepsis, septic shock, opportunistic infections); IRRs, hyperglycemia, severe hepatotoxicity, pulmonary toxicity (devoid of concomitant bleomycin) and long term safety).

II.C.2. Other studies in post-authorization development plan

C25004

Purpose of the study: This is an open-label study of brentuximab vedotin plus Adriamycin, vinblastine and dacarbazine in pediatric patients with advanced stage newly diagnosed Hodgkin lymphoma (PIP Study3).