Swiss Summary of the Risk Management Plan (RMP) for Brentuximab vedotin (ADCETRIS)

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Marketing Authorization Holder: Takeda Pharma AG

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 ADCETRIS 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 ADCETRIS in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedicinfo.ch) approved and authorized by Swissmedic. Takeda Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of ADCETRIS.

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 minimised, 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 III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD), relapsed or refractory CD30+ 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), treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy, and other CD30-expressing peripheral T-cell lymphoma (PTCL) in combination with chemotherapy (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.

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).

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:

https://www.ema.europa.eu/en/medicines/human/EPAR/adcetris

II. Risks associated with the medicine and activities to minimise or further characterise the risks

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

Measures to minimise 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 authorised 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 minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continually and regularly analysed, 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 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 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) 4. Infusion-related reactions 5. Hyperglycaemia
Important potential risks	1. Severe hepatotoxicity 2. Pulmonary toxicity
Missing information	1. Long term safety

II.B Summary of important risks and missing information

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 minimisation 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 minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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, haemoglobin, haematocrit, 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 cancer patients receiving chemotherapy increases with duration of neutropenia and with degree of mucosal damage. 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.
Risk minimization measures	**Routine risk minimisation 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 fever. 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 adult patients beginning with the first dose. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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 minimisation 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 and opportunistic infections. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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 minimisation 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 medications such as paracetamol, an antihistamine, and a corticosteroid. Package Leaflet section 2 and section 4 Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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 minimisation measures:** SmPC Section 4.2 and 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 minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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 hospitalisations are important contributing factors of drug-induced hepatotoxicity.
Risk minimization measures	**Routine risk minimisation measures:** 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 minimisation measures:**

	None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

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.
Risk minimization measures	**Routine risk minimisation measures:** SmPC Section 4.5 and 4.8 SmPC Section 4.3: co-administration of ADCETRIS with bleomycin is contraindicated due to increased pulmonary toxicity. SmPC Section 4.4: contains 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 minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Missing Information: Long term safety	
Evidence for linking the risk to the medicine	It is not known whether it is safe to use brentuximab vedotin for longer than 1 year.
Risk minimization measures	**Routine risk minimisation measures:** None

	Legal status **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C. Post-authorisation development plan

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

None

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

None