Summary of the risk management plan for POTELIGEO (Mogamulizumab)

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

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

This summary of the RMP for POTELIGEO 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 POTELIGEO's RMP.

I. The medicine and what it is used for

POTELIGEO is authorised for the treatment of mycosis fungoides (MF) or Sézary syndrome (SS) in adults who have received at least one prior systemic therapy (see SmPC for the full indication). It contains mogamulizumab as the active substance and it is given by infusion.

Further information about the evaluation of POTELIGEO's benefits can be found in POTELIGEO's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/human/medicines/004232/human_med_002323.jsp&mid=WC0b01ac058001d124

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

Important risks of POTELIGEO, together with measures to minimise such risks and the proposed studies for learning more about POTELIGEO'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 continuously and regularly analysed 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 POTELIGEO is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of POTELIGEO 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 POTELIGEO. 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	Infusion-related reaction
Important potential risks	Hepatitis B reactivation Increase in the risk of severe Graft Versus Host Disease (GVHD) after allogeneic Haematopoietic Stem Cell Transplant (HSCT)
Missing information	Use in patients with history of transplant (autologous or allogeneic)

II.B Summary of important risks

Important identified risk: Infusion-related reaction	
Evidence for linking the risk to the medicine	Infusion-related reaction occurred in approximately a third of patients treated with mogamulizumab in haematologic clinical studies. However, severe (Grade ≥3) infusion-related reaction occurred infrequently, i.e. in approximately 2.9% of patients treated with mogamulizumab. Nearly all infusion-related reaction occurred in the first 4 weeks of treatment. Based on the frequency, the clinical importance, and the potential for severe events, infusion-related reaction is considered to be an important identified risk for mogamulizumab.
Risk factors and risk groups	Infusion-related reactions occur in approximately a third of patients treated with mogamulizumab with the majority occurring during the first infusion with the incidence decreasing over time.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Package leaflet Section 2 & 4 SmPC Section 4.2 & 4.4, where advice is given on interrupting mogamulizumab treatment and initiating medical management for infusion reactions of any severity; reducing the infusion rate by at least 50% when re-starting the infusion after mild, moderate or severe reactions; and permanently discontinuing mogamulizumab following life-threatening reactions. Pre-medication with anti-pyretic and anti-histamine is recommended for the first mogamulizumab infusion. If an infusion reaction occurs, pre-medication for subsequent mogamulizumab infusions is also recommended. In addition, infusion of POTELIGEO should only be administered when staff trained to evaluate and manage anaphylactic reactions is immediately available, in an environment where full resuscitation facilities can be assured. Additional risk minimisation measures: None.

Important potential risk: Hepatitis B reactivation	
Evidence for linking the risk to the medicine	Patients with cutaneous T-cell lymphoma (CTCL) are at increased risk of infection, particularly with advanced disease and when using combination therapies; patients frequently display evidence of immunosuppression, in particular at the later stages of the lymphoma and the risk is also increased by compromised skin integrity. A retrospective study of 356 patients with CTCL in the era predating monoclonal antibodies, and identified 478 infective episodes. Cutaneous bacterial infection was most common (17.0 infections per 100 patient-years [PY]), followed by cutaneous herpes simplex virus and herpes zoster virus infection (3.8 infections per 100 PY), bacteraemia (2.1 infections per 100 PY), bacterial pneumonia (1.7 infections per 100 PY), and urinary tract infection (1.4 infections per 100 PY). Viral reactivation is a known complication of chemotherapy, especially for malignant lymphoma, and the increased risk in lymphoma patients parallels the potency of the immunosuppressive treatments. Review of available data for mogamulizumab revealed no evidence of increased hepatitis B reactivation in the CTCL setting, although the data are limited due to exclusion of subjects with a history of acute or chronic hepatitis from most of the clinical development studies). Reported cases of hepatitis B occurred in the adult T cell leukaemia-lymphoma (ATL) setting against a confounding immunosuppressive background of prior/concomitant ablative cytotoxic therapy.
Risk factors and risk groups	Patients with CTCL are at increased risk of serious infections. No risk factors for increased susceptibility to hepatitis B reactivation subsequent to mogamulizumab administration have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.8 Package leaflet Section 2 & 4 SmPC Section 4.4, where testing of patients for hepatitis B infection before initiation of treatment with mogamulizumab is advised, and prompt treatment recommended. Additional risk minimisation measures: None.

Important potential risk: Increased risk of severe GVHD after allogeneic HSCT	
Evidence for linking the risk to the medicine	Allogeneic HSCT is a recognised treatment option for advanced refractory CTCL, although experience is limited and not well defined. Retrospective studies of outcomes after allogeneic HSCT (transplant from another person) for ATL suggest that prior treatment with mogamulizumab may increase the risk of moderate to severe acute GVHD and be associated with increased non-relapse mortality and reduced overall survival. However, a prolonged interval between mogamulizumab treatment and allogeneic HSCT may reduce the risk of moderate to severe acute GVHD. The retrospective nature of these reports, possible confounding factors, and the inherent risks of allogeneic HSCT mean that this potential risk requires further evaluation before a definitive assessment is possible. Whilst the same potential risk that prior treatment with mogamulizumab may increase the risk of moderate to severe GVHD after allogeneic HSCT for advanced refractory CTCL, very limited data are currently available, and a definitive assessment is not possible. A review of the 456 patients who had received mogamulizumab (as initial or cross-over therapy) in Western clinical trials for haematologic indications was conducted after the data lock point of this RMP, to a data lock point of 20 Jul 2017. Data on 32 of the 35 subjects reported to have undergone transplant are available, including 24 CTCL subjects. Twelve of 32 subjects developed acute GVHD after transplant (10 CTCL; 2 non-CTCL subjects). Due to the small subject numbers, no conclusions could be drawn concerning the effect of mogamulizumab treatment on the eventual outcome of HSCT as a treatment for T-cell lymphoma. Review of post-marketing data pertaining to this risk showed findings consistent with those recorded from clinical studies.
Risk factors and risk groups	The predominant determinants of acute GVHD risk after allogeneic HSCT for haematologic malignancies are the degree of human leukocyte antigen (HLA) match, intensity of conditioning (higher risk with total body irradiation), source of graft (higher risk with peripheral blood than bone marrow, and in female HLA identical sibling donors to male recipients) and GVHD prophylaxis regimen (higher risk with cyclosporine than tacrolimus). It is currently unclear whether the same risk factors of acute GVHD after allogeneic HSCT are applicable for CTCL, due to the limited

	experience of this treatment option. The risk of moderate to severe acute GVHD after allogeneic HSCT for ATL may be increased after prior mogamulizumab administration, although longer periods between mogamulizumab administration to allogeneic HSCT may reduce the risk. However, this requires confirmation, particularly regarding use of POTELIGEO for the treatment of CTCL.
Risk minimisation measures	Routine risk minimisation measures: Package leaflet Section 2 & 4 SmPC Section 4.4, where a recommendation for patients to be closely followed for early evidence of transplant-related complications is included. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: A post-authorisation safety study to characterise the safety of allogeneic HSCT in patients with CTCL treated with mogamulizumab.

Missing information: Use in patients with a history of autologous or allogeneic transplant	
Risk minimisation measures	Routine risk minimisation measures: Package leaflet Section 2, notes that patients should talk to their doctor or nurse if they have undergone stem cell transplant and Section 4 notes that they should tell their doctor immediately if they experience GVHD symptoms. Additional risk minimisation measures: None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorization or specific obligation of POTELIGEO.

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

One Category 3 post-authorisation safety study has been proposed to further investigate the potential risk of increased risk of severe GVHD after allogeneic HSCT.

Study title:

Post-Authorisation Safety Study to Characterise the Safety of Allogeneic Haematopoietic Stem Cell Transplantation (HSCT) in Patients with Cutaneous T-Cell Lymphoma (CTCL) treated with Mogamulizumab.

Objectives:

To include treatment-related mortality, non-relapse mortality and cause, and incidence and characterisation of GVHD and graft failure.