CANADIAN RISK MANAGEMENT PLAN SUMMARY

for

POTELIGEO® (mogamulizumab)

RMP version number: 2.0

Data lock point for this RMP: 29 Mar 2025

Date of final sign-off: 02 Jun 2026

Rationale for submitting an updated RMP:
- Update of PASS study milestones in line with PASS protocol

Summary of significant changes in this RMP:
- Part III: Update of PASS status, objectives and study milestones, in line with PASS protocol
- Part VII:
  - Annex 2: PASS details updated in line with PASS protocol
  - Annex 3: Inclusion of latest PASS protocol
- Editorial revisions made to align with regulatory guidance and alignment of content with the updated DLP.

Other RMP versions under evaluation in Canada: Not applicable

Details of the currently approved RMP:
Version number: 1.0
Approved with control number: 269942
Date of approval: 06 Mar 2023

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LIST OF ABBREVIATIONS

ATL	Adult T-cell leukemia-lymphoma
CTCL	Cutaneous T-cell lymphoma
GVHD	Graft versus host disease
HSCT	Hematopoietic stem cell transplantation
IRR	Infusion-related reaction
IV	Intravenous(ly)
MF	Mycosis fungoides
NRM	Non-relapse mortality/non-relapse death without prior relapse or progression
PASS	Post-authorization safety study
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SS	Sézary syndrome

1 INTRODUCTION

This is a summary of the risk management plan (RMP) for POTELIGEO® by Kyowa Kirin, Inc. under submission control number #501327. The RMP describes important risks of mogamulizumab, how these risks can be reduced or prevented and how more information will be obtained about POTELIGEO's risks and uncertainties (missing information). POTELIGEO's product monograph and its patient medication information give essential information to healthcare professionals and patients on how POTELIGEO should be used.

2 THE DRUG AND WHAT IT IS USED FOR

POTELIGEO contains mogamulizumab as an active substance. In Canada, POTELIGEO is indicated for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy. POTELIGEO is administered via intravenous (IV) infusion, and is available as a 4mg/mL concentrate for solution for infusion.

3 ASSOCIATED RISKS AND MINIMIZATION MEASURES

Important risks of POTELIGEO, together with measures to minimize such risks and the proposed studies for learning more about POTELIGEO’s risks, are outlined in Section 5. If important information that may affect the safe use of POTELIGEO is not yet available, it is listed under ‘missing information’.

For the risks associated with POTELIGEO, routine risk minimization measures include the product monograph and patient medication information, which provide essential information to healthcare professionals and patients, including warnings, precautions, and advice on appropriate use. Poteligeo is a prescription medicine, which further supports risk minimization by ensuring that it is prescribed and administered under the supervision of qualified healthcare professionals. No additional risk minimization measures are required beyond routine measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, through signal detection and periodic safety update report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

A post-authorization safety study (PASS) is ongoing to further assess the safety concern of an increased risk of severe graft versus host disease (GVHD) following allogeneic hematopoietic stem cell transplantation (HSCT).

4 LIST OF IMPORTANT RISKS AND MISSING INFORMATION

List of important risks and missing information	
Important identified risks	• Infusion-related reaction
Important potential risks	• Increased risk of severe graft versus host disease (GVHD) after allogeneic hematopoietic stem cell transplant (HSCT) • Autoimmune complications/immune-related reactions
Missing information	• Use in patients with history of autologous or allogeneic transplant

5 SUMMARY OF IMPORTANT RISKS

A summary of the important risks and missing information for POTELIGEO is provided below:

Important identified risk: Infusion-related reaction	
Evidence for linking the risk to the medicine	Infusion-related reaction (IRR) occurred in approximately a third of patients treated with mogamulizumab in hematologic clinical studies at the data pooling of 2016. However, severe (Grade ≥3) IRR occurred infrequently, i.e. in approximately 2.9% of patients treated with mogamulizumab. Nearly all IRRs occurred in the first 4 weeks of treatment. Based on the frequency, the clinical importance, and the potential for severe events, IRR is considered to be an important identified risk for mogamulizumab.
Risk factors and risk groups	Infusion-related reactions have been observed in patients treated with mogamulizumab, with the majority occurring during or shortly after the first infusion (Canadian Product Monograph Section 7).
Risk minimization measures	<u>Routine risk minimization measures:</u> Canadian Product Monograph Sections 4, 7 and 8. Advice to monitor patients during and after infusion for signs and symptoms of IRRs is included in Section 7 of the Canadian Product Monograph. A recommendation that mogamulizumab should be interrupted and treatment of the symptoms initiated for mild to severe (Grades 1 to 3) infusion reactions and that mogamulizumab should be permanently discontinued in the event of life-threatening (Grade 4) reaction is included in Canadian Product Monograph Section 4. It is also noted that the infusion rate should be reduced by at least

	50% when re-starting the infusion after symptoms resolve. If the reaction recurs and is unmanageable, discontinue the infusion. In addition, Section 4 states that pre-medication such as diphenhydramine and acetaminophen is recommended for the first mogamulizumab infusion and if an infusion reaction occurs, premedication for subsequent mogamulizumab infusions is to be administered. <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Important potential risk: Increased risk of severe GVHD after allogeneic HSCT	
Evidence for linking the risk to the medicine	Allogeneic HSCT is a recognized treatment option for advanced refractory cutaneous T-cell lymphoma (CTCL), although experience is limited and not well defined. Retrospective studies of outcomes after allogeneic HSCT (transplant from another person) for adult T-cell leukemia-lymphoma (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 (NRM) 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 hematologic indications was conducted to a data lock point of 20 Jul 2017. Data on 32 of the 35 subjects reported to have undergone transplant were 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 hematologic malignancies are the degree of human leukocyte antigen match, intensity of conditioning (higher risk with total body irradiation), source of graft (higher risk with peripheral blood than bone marrow, and in female human

	leukocyte antigen 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 the product for the treatment of CTCL.
Risk minimization measures	<u>Routine risk minimization measures:</u> Canadian Product Monograph Section 7. A recommendation for patients to be closely followed for early evidence of transplant-related complications is included in Canadian Product Monograph Section 7. Section 7 of the Canadian Product Monograph states that GVHD has been reported in patients who received allogeneic HSCT after mogamulizumab. Section 7 also includes a warning stating that a higher risk of transplant complications has been reported when mogamulizumab is given within a short time frame (approximately 50 days) before HSCT. <u>Additional risk minimization measures:</u> None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorization safety study (PASS) of allogeneic HCT in patients treated with mogamulizumab.

Important potential risk: Autoimmune complications/immune-related reactions	
Evidence for linking the risk to the medicine	<u>Clinical trials</u> During clinical trials, patients with active autoimmune diseases were excluded. Immune-mediated events of interest have been reported in recipients of mogamulizumab in clinical trials, although no clear temporal relationship with initiation of mogamulizumab were identified. In many of these reports, there were confounding factors or alternative explanations for the immune-related events. <u>Post marketing reports</u> Reports of immune-mediated events of interest were also received from post marketing sources. The causal link between these immune-mediated events and mogamulizumab use has not been confirmed with many of these post-marketing reports either containing confounding factors or deemed to be explained by non-immune mediated medical conditions. The other remaining reports contained very limited information for assessment.

Risk factors and risk groups	During clinical trials, patients with active autoimmune diseases were excluded. No consistency was identified in the time of event onset with regards to the start date of mogamulizumab treatment, and some events were reported long after discontinuation of mogamulizumab treatment in clinical trials. In the majority of the clinical trial cases, confounding factors were reported, such as recent viral infections, use of co-suspect medications and/or underlying patient risk factors for the development of those medical conditions. In the remaining reports, the information provided raised possible alternative etiologies for these events (e.g., lung infection rather than immune-mediated interstitial lung disease) or did not clarify the likely etiology of the events (e.g. myositis reports where paraneoplastic syndromes were possible explanations, or encephalitis where infectious etiology could not be excluded). In the review of the post-marketing safety data for suspected immune-mediated conditions did not identify any new information concerning this potential risk. The causal link between these immune-mediated events and mogamulizumab use has not been confirmed with many of these post-marketing reports either containing confounding factors or deemed to be explained by non-immune mediated medical conditions.
Risk minimization measures	Routine risk minimization measures: Canadian Product Monograph Sections 7 and 8. Advice to interrupt or permanently discontinue mogamulizumab for any suspected immune-mediated adverse reactions is included in Section 7 of the Canadian Product Monograph. It is also advised to consider the benefit/risk of mogamulizumab in patients with a history of autoimmune disease. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

Missing information: Use in patients with a history of autologous or allogeneic transplant	
Risk minimization measures	Routine risk minimization measures: Canadian Product Monograph Section 7. Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None