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CADTH Reimbursement Recommendation

Mogamulizumab (Poteligeo)

Indication: Relapsed or refractory mycosis fungoides or Sézary syndrome after at least 1 prior systemic therapy

Sponsor: Kyowa Kirin Canada, Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Poteligeo?

CADTH recommends that Poteligeo should be reimbursed by public drug plans for the treatment of relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) if certain conditions are met.

Which Patients Are Eligible for Coverage?

Poteligeo should only be covered to treat adult patients with MF or SS who have already tried at least 1 treatment that did not work or in whom the disease has come back. Patients receiving Poteligeo should be in relatively good health (i.e., have a good performance status, as determined by a specialist).

What Are the Conditions for Reimbursement?

Poteligeo should only be reimbursed if prescribed by a specialist and if the price of Poteligeo is reduced.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial showed that treatment with Poteligeo prevented MF and SS from spreading further and was found to have response in areas of the body where MF and SS was already present.
- Poteligeo meets some of the unmet needs identified by patients including prevention of MF and SS from spreading further and improved response rates, as well as a need for additional treatment options.
- Poteligeo is not considered cost-effective compared to established clinical management. Economic evidence suggests that a price reduction is required to ensure Poteligeo is cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) in the indicated population. The estimates of cost-effectiveness and price reduction are highly uncertain due to the quality of the evidence.
- Based on public list prices, Poteligeo will cost the public drug plans $7,015,623 over 3 years.

Additional Information

What Is MF or SS?

MF and SS are the most common forms of a rare type of cancer in the blood called cutaneous T-cell lymphoma. In MF, a type of cancerous white blood cell (lymphocyte) affects the skin, resulting in a red, scaly rash that can be itchy, painful, and become infected. In SS, these cancerous white blood cells are also found in the blood and lymph nodes. MF typically spreads slowly while SS spreads much faster. In Canada, there were 2,510 cases of MF and 110 cases of SS between 1992 and 2010.

Unmet Needs in MF or SS

Though there are several treatment options available in Canada, most treatments are not publicly funded, which reduces the treatment options available to all patients. Additionally, current treatment options do not work well, and most patients then require additional treatment.

How Much Does Poteligeo Cost?

Treatment with Poteligeo is expected to cost approximately $35,258 in the first treatment cycle, and $17,629 for subsequent cycles.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that mogamulizumab be reimbursed for the treatment of adult patients with relapsed or refractory MF or SS after at least 1 prior systemic therapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One open-label, multicenter, 1-way crossover, phase III randomized controlled trial (RCT) (MAVORIC) in adult patients with MF or SS who had failed at least 1 prior course of systemic therapy demonstrated that compared with vorinostat, treatment with mogamulizumab resulted in added clinical benefit with clinically meaningful and statistically significant prolonged progression-free survival [PFS] (hazard ratio (HR): 0.53 [95% CI, 0.41, 0.69]), overall response rate (28.0% versus 4.8%; risk difference: 23.1 [95% CI, 21.8 to 33.1], P < 0.0001), and was associated with a manageable toxicity profile. pERC noted that there were some improvements in measures of health-related quality of life (HRQoL) in the MAVORIC trial; however, pERC was unable to draw any conclusions on the effect of mogamulizumab on HRQoL based on the available evidence due to high attrition rates, short duration of follow-up, and crossover and open-label study design.

pERC acknowledged the unmet need for this rare patient population in this setting given the severe nature of this disease with substantial morbidity and lack of effective available therapies. Patients identified a need for longer survival, more treatment options, better quality of life, fewer side effects, longer treatment-free periods, and easier application. Given the totality of the evidence, pERC concluded that mogamulizumab meets some of the needs identified by patients, including a need for additional treatment options and prolonged PFS.

It was not possible to determine the cost-effectiveness of mogamulizumab owing to structural limitations of the sponsor's model, immature and confounded overall survival (OS) data, the lack of comparative evidence for mogamulizumab relative to established clinical management (ECM; consisting of methotrexate, bexarotene, interferon alpha-2a, gemcitabine, CHOP, liposomal doxorubicin, etoposide, prednisolone, vorinostat, PUVA, extracorporeal phototherapy, total skin electron beam therapy, chlorambucil, purine analogues, pralatrexate, romidepsin, and alemtuzumab), and an estimate of ECM cost that does not reflect current clinical practice. As such, a base-case cost-effectiveness estimate could not be determined in patients with MF or SS who have previously received at least 1 lines of systemic therapy. Based on the sponsor's submission, a price reduction of at least 51% would be required for mogamulizumab to achieve an incremental cost-effectiveness ratio (ICER) of $50,000 per QALY. CADTH notes that this estimate likely underestimates the true price reduction that would be required for mogamulizumab to be considered cost-effective at a $50,000 per QALY threshold.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Mogamulizumab should be reimbursed for adult patients who have all of the following: 1.1. Histologically confirmed MF or SS 1.2. Stage IB, IIA, IIB, III or IV disease 1.3. Failed at least one prior course of systemic therapy	Evidence from the MAVORIC trial demonstrated that mogamulizumab resulted in improvements in PFS, and ORR in adult patients who have histologically confirmed MF or SS of stage IB-IV disease and have failed at least one prior systemic therapy.	pERC noted that brentuximab vedotin is available in some jurisdictions and that patients with MF are required to have CD30+ immunohistochemical expression for treatment with brentuximab vedotin. As a result, pERC agreed with the clinical experts that brentuximab vedotin would be sequenced ahead of mogamulizumab in patients with CD30+ MF in jurisdictions where brentuximab vedotin is available for patients with CD30+ MF.
2. Patients should have a good performance status	The MAVORIC trial included patients with ECOG performance status of 0 to 1. Patients with an ECOG performance status of 2 were not eligible for inclusion in MAVORIC trial. The CADTH review identified no evidence to demonstrate the benefit of MF or SS with mogamulizumab in patients with ECOG performance status greater than 1. pERC agreed with the clinical experts that treatment of mogamulizumab in these patients should be left to the discretion of the treating clinician.	—
3. Treatment with mogamulizumab should not be used in patients with active or untreated CNS metastases	Patients with clinical evidence of CNS metastasis were excluded from the MAVORIC trial. The CADTH review did not identify any evidence to demonstrate the safety and potential benefits in patients with active or untreated CNS metastases.	—
Renewal		
4. To be eligible for renewal of mogamulizumab, patients should be assessed by the treating physician for all of the following: 4.1. disease progression with: 4.1.1. skin and blood assessment conducted every 4 weeks 4.1.2. lymph nodes and visceral involvement imaging conducted	In the MAVORIC trial, response in skin and blood was evaluated every 4 weeks during treatment. In the first year of treatment, response in lymph nodes and viscera was documented 4 weeks after the start of study treatment (end of cycle 1) and every 8 weeks thereafter. After the first year, response in the lymph nodes and viscera was documented every 16 weeks.	—

Reimbursement condition	Reason	Implementation guidance
every 3 to 4 months 4.2. acceptable toxicity.		
Prescribing		
5. Mogamulizumab should only be prescribed by a clinician with experience and expertise in treating MF or SS. The treatment should be supervised and delivered in outpatient specialized oncology clinics or infusion centers with expertise in systemic therapy delivery.	To ensure that mogamulizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
Pricing		
6. A reduction in price	The cost-effectiveness of mogamulizumab is unknown. Based on the sponsor's submitted pharmacoeconomic model at least a 51% reduction in price is required to achieve an ICER of $50,000 per QALY; the true price reduction required is likely greater.	—

CNS = central nervous system; CR = complete response; CTCL = cutaneous T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; GVHD = graft vs. host disease; ICER = incremental cost-effectiveness ratio; MF = mycosis fungoides; ORR = overall response rate; pERC = pCODR Expert Review Committee; PFS = progression-free survival; QALY = quality-adjusted life-year; SCT = stem cell transplantation; SS = Sézary syndrome.

Discussion Points

- pERC considered the limitations in accessing funded treatments for MF and SS and availability of funded treatment options across jurisdictions in Canada. pERC acknowledged the clinical experts' statement that in Canada, treatment selection for MF or SS is often guided by what drug is funded and available rather than necessarily the 1 with best chances of response and fewest side effects.
- pERC noted that vorinostat was the comparator in the MAVORIC trial; while it is approved for use in Canada, it is not reimbursed by public drug plans and is therefore not accessible to all patients in Canada. pERC considered vorinostat to be an appropriate clinical comparator. Though mogamulizumab demonstrated meaningful improvements in important outcomes compared to vorinostat, the magnitude of clinical benefit of mogamulizumab compared to comparators currently reimbursed by public drug plans remains unknown.
- pERC discussed the sponsor-submitted matching-adjusted indirect comparison (MAIC), in particular the comparison between mogamulizumab (MAVORIC trial) and the 2 arms of the ALCANZA trial (brentuximab vedotin and physician's choice [methotrexate and bexarotene]) and noted considerable differences between the populations in the 2 studies. pERC concluded that results of the MAIC were uncertain and likely not generalizable to the Canadian setting.

- pERC noted that OS was an exploratory end point, considered immature and confounded by the 1-way crossover design. pERC acknowledged that although the sponsor conducted a separate analysis of OS for Health Canada to account for crossover, no information on the methodology used for these tests or how the most suitable crossover adjustment method was chosen was provide. As a result, pERC felt the effect of mogamulizumab compared to vorinostat on OS remained uncertain.
- While pERC acknowledged that the results of the MAVORIC trial suggest that mogamulizumab may appear to demonstrate a greater benefit in patients with more advanced disease, SS, and skin and blood involvement, pERC agreed that clinical benefit was demonstrated in the overall study population. Furthermore, pERC acknowledged that there was no robust evidence demonstrating a difference in the treatment effect of mogamulizumab by disease stage. Aside from patients with stage IA, who were not eligible for the MAVORIC trial, mogamulizumab demonstrated improved PFS across all included stages (IB-IV) and the trial was not powered to detect differences by stage.
- The cost-effectiveness of mogamulizumab is highly sensitive to crossover adjustment within the MAVORIC trial and assumptions about long-term survival beyond the observed data. Scenario analyses conducted by CADTH found ICERs between $128,138 and $332,667 per QALY based on plausible single-variable changes in the pharmacoeconomic model. Given the high degree of uncertainty within the MAVORIC trial data, an additional price reduction is likely warranted.

Background

MF and Sézary syndrome (SS) are the 2 most common types of cutaneous T-cell lymphomas (CTCL), accounting for approximately half to two-thirds of CTCL cases. Both MF and SS result from infiltration of malignant T-lymphocytes preferentially to skin. MF is usually associated with an indolent clinical course and intermittent, stable, or slow progression, while SS is a rare leukemic subtype of CTCL characterized by a more aggressive course of disease and shorter survival. Clinical experts noted that diagnosis often takes upwards of 3 years, with misdiagnosis occurring early on. The clinical presentation of MF is highly variable ranging from non-specific erythematous scaly patches to thin plaques or papulonodular eruptions. In approximately 30% of cases, the patches or plaques evolve to tumours. Patients with SS present with a triad of skin redness (erythroderma), enlarged lymph nodes (lymphadenopathy), and a large number of circulating atypical lymphocytes (Sézary cells) in the skin, lymph nodes, and peripheral blood. Both MF and SS are considered rare diseases. The incidence of MF increases with age and is approximately 5.6 per million persons. In Canada, 2,510 cases of MF, and 110 cases of SS were documented from 1992 through 2010.

Mogamulizumab has received a Notice of Compliance from Health Canada for the treatment of adult patients with relapsed or refractory MF or SS after at least 1 prior systemic therapy. Mogamulizumab is a defucosylated, humanized IgG1 kappa monoclonal antibody that binds to CCR4 on the surface of some T-cell malignancies and is expressed on regulatory T-cells and a subset of T-helper 2 T-cells. It is available as a 20 mg/5 mL vial for IV infusion and the target Health Canada–approved dose is 1.0 mg/kg on days 1, 8, 15, and 22 of the first 28-day cycle, then on days 1 and 15 of each subsequent 28-day cycle.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase III, open-label RCT in adults with Stage IB, II-A, II-B, III and IV MF or Sézary syndrome.
- Patients' perspectives gathered by patient groups, Lymphoma Canada (LC) in collaboration with the Canadian Skin Patient Alliance (CPSA) and Cutaneous Lymphoma Foundation (CLF).
- Input from public drug plans and cancer agencies that participate in the CADTH review process.
- 2 clinical specialists with expertise diagnosing and treating patients with Mycosis Fungoides and Sézary Syndrome.
- Input from 2 clinician groups, including the Canadian Cutaneous Lymphoma Providers, and the Ontario Health (Cancer Care Ontario; OH-CCO) Hematology Cancer Drug Advisory Committee.
- A review of the pharmacoeconomic model and report, and indirect treatment comparison submitted by the sponsor.

Stakeholder Perspectives

Patient Input

LC in collaboration with the CPSA and CLF, conducted an anonymous online survey of CTCL patients, primarily MF and SS patients, between March 8, 2021 and September 21, 2021. A total of 449 patients that responded to the survey that were diagnosed with either MF or SS, of which 46 (14%) were Canadian. The majority of respondents were at least 60 years old (69%), and more than half were female (54%).

MF can be difficult to diagnose, with symptoms that can occur for many years before a diagnosis is achieved and can masquerade as other more common skin conditions such as eczema or psoriasis. The majority of patient's participating in this survey were diagnosed between 1 and 5 years ago (41%), with a portion of patients diagnosed over 10 years ago (26%). Only 23% of patients had their condition correctly diagnosed as MF or SS at presentation. Symptoms of MF or SS that have the most impact on patients' quality of life (QoL) at diagnosis included visual patches or lesions (78%), and itchiness of skin or lesions (57%). Symptoms that most commonly affected respondents' current QoL were similar to those at diagnosis, with the stress of diagnosis, and the addition of fear or worry of disease progression and anxiety impacting their current wellbeing.

A total of 327 patients provided information about their experience with MF or SS CTCL treatments. Of the 211 patients treated with systemic treatments, 27% received interferon, 26% received methotrexate, 24% received oral bexarotene, 23% received mogamulizumab, and 10% were treated with romidepsin. The most common side effects respondents experienced by patients during their MF or SS CTCL treatments included fatigue (41%), skin pain or burning (34%), skin irritation or rash (33%), and moderate to severe itching (30%). A total of 27% of survey respondents indicated that the number of clinic visits had the most

significant impact on their QoL, while 21% indicated that treatment-related fatigue had the most significant impact on their QoL, citing additional negative impacts due to treatment on ability to work (21%), travel (21%), and have intimate relationships (19%).

Access to treatment within the patient's community is an important consideration, as certain treatments may only be available at specific tertiary cancer centers. A sub-analysis of Canadian patients revealed that 32% of Canadians could not access treatment locally. Most patients responding to this survey were within the US where more treatment options are approved for use, including mogamulizumab; however, 81% of all respondents cited the importance of having an increased number of treatment options available. Patients indicated that longer survival (82%) and better QoL (76%) are extremely important for new therapies to address, followed by longer treatment-free periods (70%), easier treatment application (68%), and fewer side effects (64%).

Of all patients that responded to the survey, 52 (12%) had experience with mogamulizumab, largely accessed through private insurance (42%), public drug programs (29%), compassionate access (17%), or clinical trial (8%). Only 2 patients had their disease progress during treatment, while 25% were in remission. A total of 36% of patients had all of their symptoms managed by mogamulizumab, with major symptom management in skin itchiness (62%), red skin patches or rash (56%), and skin pain (25%) (52 respondents). When asked to describe their experience with mogamulizumab, 69% of patients responded they had a good to excellent experience with the therapy.

Clinician Input

Input from Clinical Experts Consulted by CADTH

According to advice obtained from a clinical expert consulted by CADTH for this review, treatment selection in Canada is often guided by what drug is funded and available rather than the 1 with best chances of response, and fewest side effects. They noted that most currently available treatment options demonstrate suboptimal response rates (< 30% to < 50%), or responses of limited duration (< 4 months) and acknowledged that these responses are primarily in the context of skin; however when used in SS, they are in the context of blood component as well.

Per the clinical experts, in Canada, systemic therapy is generally limited to interferon, isotretinoin (off-label use for MF), or oral methotrexate. Bexarotene was noted by the experts as a superior retinoid to isotretinoin; however, it is not approved by Health Canada. Other options include local radiotherapy, extracorporeal photopheresis, chemotherapy (gemcitabine, or liposomal doxorubicin), vorinostat, romidepsin, and pralatrexate, though many of these are not funded in Canada. Brentuximab was recently approved for use in CD30+ expressing MF, limited, or advanced stage, which has relapsed following 1 of these systemic approaches. Experts stated that some patients derive benefit from existing therapies, before ultimately progressing and requiring an alternate, thus agreed that other systemic treatments including interferon, retinoids, with or without extracorporeal photopheresis (as available) should be attempted before mogamulizumab based on availability.

Experts noted that diagnosis often takes upwards of 3 years, with misdiagnosis occurring early on. There are no pre-symptomatic tests to identify patients best suited for treatment with mogamulizumab. The experts identified patients most suitable for mogamulizumab are those with advanced stage MF and/or with blood involvement (stage IIIB, IVA, IVB), or SS that have failed front line systemic therapy. Conversely, clinical experts believed that patients with

stage IA MF should not be treated with mogamulizumab as they were not included in the pivotal clinical trial, and patients with stage IB or IIA/B (as evidence by the response outcomes demonstrated on study) are less likely to derive benefit, possibly due to the mechanism of action of mogamulizumab. Overall, the clinical experts felt that aside from patients with stage IA, who were not eligible for the MAVORIC trial, funding criteria should not include staging information, as the primary outcome of the MAVORIC trial demonstrated improved PFS across all included stages (IB-IV) and was not powered to detect differences by stage.

The experts expressed that the goals of treatment in MF/SS consist of prolonged survival, improved response rate, improvement in skin related symptoms, and QoL. They noted that these outcomes are reflective of what is measured in clinical trials, with existing defined response criteria for MF/SS in any of each disease compartments (skin, nodal, and blood). These also include criteria to define progressive disease, and they noted that intolerable adverse events (AEs), notably mogamulizumab-associated rash that does not respond to management algorithms, or other AEs would be reason to discontinue.

Clinician Group Input

Clinician group input was provided by 2 clinician groups: the Canadian Cutaneous Lymphoma Providers and the Ontario Health (Cancer Care Ontario [OH-CCO]) Hematology Cancer Drug Advisory Committee. Clinician groups noted the individualized approach to treatment, as well as the lack of a defined standard of care in MF or SS. Along with suboptimal response rates and limited duration with current treatments, access issues were cited as a major unmet need in this population. The clinician groups expressed the lack of publicly funded treatments in Canada and noted that treatment selection is guided more by what drug is funded and available rather than necessarily the 1 with best chances of response, and fewest side effects. The clinician groups expressed that patients should be offered mogamulizumab if they meet the eligibility of the clinical trial, with 1 clinician group highlighting its use in advanced stage MF and/or with blood involvement, or Sézary syndrome, and mogamulizumab would likely be used in second-line following chemotherapy, brentuximab vedotin (if CD30+), or interferon. One clinician group considered the potential for mogamulizumab's concurrent use with extracorporeal photopheresis, particularly for patients with SS. Important goals of treatment, as well as factors considered clinically meaningful outcomes of treatment include disease control through reduction in frequency or severity of symptoms, improvement in symptoms, or stabilization of disease, prolonged survival, and improvement in QoL. Lastly, the clinician groups noted that mogamulizumab would be received in an outpatient setting, and also highlighted that disease progression, AEs, and treatment-related toxicity should be considered when deciding to discontinue treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for mogamulizumab:

- Considerations for initiation of therapy.
- Considerations for prescribing of therapy.
- Generalizability of trial populations to the broader populations in the jurisdictions.
- Care provision issues.
- System and economic issues.

- Potential need for a provisional funding algorithm (oncology only).

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
The comparator in the pivotal trial, MAVORIC, is vorinostat which is not publicly funded in Canada. It is noted the pERC conditionally recommended brentuximab vedotin for the treatment of adult patients with CD30+ mycosis fungoides who have had one prior systemic therapy in December 2020. This treatment is funded in some provinces. There is no standard of care for the treatment of MF or SS in patients who progress after one prior systemic therapy. Public funding of treatments varies across provinces.	pERC acknowledged that vorinostat is not publicly funded in Canada and that there is no standard of care for the treatment of MF or SS in patients who progress after one prior systemic therapy. pERC noted that public funding of treatments varies across provinces and discussed the availability of brentuximab vedotin for the treatment of adult patients with CD30+ mycosis fungoides who have had one prior systemic therapy which is available only is some provinces.
How does mogamulizumab compare to brentuximab vedotin for patients with CD30+ MF? Should these drugs be sequenced and if so, is there a preferred order?	pERC noted that brentuximab vedotin is available in some jurisdictions and that patients are required to have CD30+ immunohistochemical expression for treatment with brentuximab vedotin. As a result, pERC agreed with the clinical experts that brentuximab vedotin would be sequenced ahead of mogamulizumab in patients with CD30+ MF in jurisdictions where brentuximab vedotin. pERC also noted that CD30+ is seldomly expressed in SS, and patients with SS are not eligible for brentuximab under Canadian funding models.
Considerations for initiation of therapy	
The MAVORIC trial enrolled patients with stage IB-IV previously treated with systemic therapy. Should funding criteria include staging information?	pERC agreed with the clinical experts that aside from patients with stage IA, who were not eligible for the MAVORIC trial, funding criteria should not include staging information, as the primary outcome of the MAVORIC trial demonstrated improved PFS across all included stages (IB-IV) and was not powered to detect differences by stage. However, the clinical experts noted that there was a clearer benefit observed in the MAVORIC trial for advanced stages (III-IV).
MAVORIC enrolled patients with ECOG 0 to 1. Is it reasonable to treat patients with ECOG 2 or greater with mogamulizumab?	pERC noted that patients with ECOG 2 were not eligible for the MAVORIC trial and agreed with the clinical experts that this may not be reflective of Canadian clinical practice for MF/SS particularly for those with advanced stage, and multiply relapsed disease. pERC agreed with the clinical experts that treatment of mogamulizumab in these patients should be left to the discretion of the treating clinician.
MAVORIC excluded patients with CNS metastasis, significant cardiac disease (class III or IV NYHA) and large cell transformation. Should these patients be eligible for mogamulizumab?	pERC acknowledged the clinical expert's statement that it is currently unclear whether patients with CNS metastases or significant cardiac disease should be excluded from using mogamulizumab. pERC agreed with the clinical experts that due to safety concerns, prescribing for advanced heart failure is a concern and that physicians should use discretion in this population. The clinical experts stated that mogamulizumab would not be

Implementation issues	Response
	prescribed in the absence of future or additional data supporting use in patients with CNS metastases. Ultimately, pERC felt that mogamulizumab should not be initiated in patients with active (untreated or uncontrolled) CNS metastases. pERC acknowledged the clinical expert's statement that large cell transformation is a clinical challenge in the management of MF, with no standard of care, and a generally poor prognosis. pERC noted that the MAVORIC trial was amended to allow patients who developed large cell transformation while on vorinostat to cross over to mogamulizumab, provided they met all other eligibility criteria. As a result, pERC agreed with the clinical experts that patients with large cell transformation should be considered for mogamulizumab provided they meet other eligibility criteria.
The majority of patients in the MAVORIC trial failed more than 1 prior systemic therapy. Should patients be required to have failed more than one prior systemic therapy to be eligible for mogamulizumab?	pERC agreed with the clinical experts that in line with the MAVORIC trial, patients in Canada are likely to have received multiple prior systemic therapies. There is no concern surrounding the use of mogamulizumab in patients that have failed multiple systemic therapies.
In MAVORIC, patients with a global complete response could continue treatment for up to 12 months or until progression, whichever came first. Upon relapse, would these patients be eligible for retreatment and if so, if there a reasonable time frame (i.e., patients must have been off therapy for a minimum time frame to be eligible for retreatment)?	pERC noted that there is currently no evidence to support retreatment with mogamulizumab in patients who relapse and noted that only 4 patients in the MAVORIC trial achieved a complete response. However, the clinical experts noted that patients with cutaneous lymphoma can be retreated with prior therapies and still achieve a response. As a result, pERC felt that retreatment may be reasonable on a case-by-case review by province.
Considerations for prescribing of therapy	
Mogamulizumab 1 mg/kg IV over 60 minutes on days 1, 8, 15 and 22 of the first 28 days cycle and then days 1 and 15 q28 days thereafter. Treatment continued until disease progression, unacceptable toxicity. Mogamulizumab is supplied as 20 mg vials with potential for wastage.	pERC acknowledged the potential for wastage.
Generalizability	
Should patients currently receiving a second-line systemic therapy be eligible to switch to mogamulizumab?	pERC agreed with the clinical experts that if current treatment is effective and well tolerated, switching to mogamulizumab is not required. In line with the clinical trial, patients would be eligible to switch following failure of systemic therapy.
Funding algorithm (oncology only)	
Drug may change place in therapy of comparator drugs. Brentuximab vedotin for the treatment of adult patients with CD30+ mycosis fungoides who have had 1 prior systemic therapy.	pERC agreed with the clinical experts that brentuximab vedotin would be sequenced ahead of mogamulizumab in patients with CD30+ MF in jurisdictions where brentuximab vedotin is available for patients with CD30+ MF.
Care provision issues	
Potential for infusion reactions (grade 1 to 2 incidence 32%, grade 3 incidence 2%). Drug rashes are common and must be monitored for.	pERC acknowledged the potential for infusion reactions and that drug rashes common. pERC noted that as per Health Canada Product Monograph, mogamulizumab should be discontinued for life-threatening (Grade 4) rash or (Grade 4) infusion reactions.

Implementation issues	Response
Preparation of mogamulizumab requires a sterile compounding pharmacy and has limited final product stability. As such, administration of mogamulizumab is likely to be restricted to facilities/locations with access to a sterile compounding pharmacy on site.	The storage, stability, and disposal guidance of mogamulizumab is stated in the Health Canada product monograph.
System and economic issues	
Brentuximab vedotin for previously treated CD30+ MF has confidential pricing (pCPA).	pERC noted that brentuximab vedotin is available for patients with CD30+ MF in some jurisdictions.

CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; MF = mycosis fungoides; NYHA = New York Heart Association; pCPA = pan-Canadian Pharmaceutical Alliance; pERC = pCODR Expert Review Committee; PFS = progression-free survival; SS = Sézary syndrome.

Clinical Evidence

Description of Studies

One study (MAVORIC) was included in the review. MAVORIC is an open-label, multicenter, 1-way crossover, phase III RCT evaluating the effectiveness of mogamulizumab compared to vorinostat in patients with CTCL who had failed at least 1 prior course of systemic therapy. Patients in the MAVORIC trial were required to have a histologically confirmed diagnosis of MF or SS, of any stages IB, II-A, II-B, III and IV, as well as an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. A total of 372 patients were randomized 1:1 to either mogamulizumab 1.0 mg/kg IV infusion on days 1, 8, 15 and 22 of the first cycle and on days 1 and 15 of subsequent cycles (n = 186) or vorinostat 400 mg by mouth once daily on day 1 of each 28-day cycle (n = 186). The primary outcome of the MAVORIC trial was PFS, with key secondary end points of overall response rate (ORR), and HRQoL as assessed by the Skindex-29, FACT-G, and EQ-5D-3L. Other secondary and outcomes included best overall response (BOR), and duration of response (DOR). Overall survival (OS) was an exploratory outcome of the MAVORIC trial. MAVORIC was conducted in 11 countries; however, no Canadian investigative sites were included. The clinical data cut off for the final analysis of the MAVORIC study was December 31, 2016. No interim analyses were conducted.

Demographic and baseline characteristics of the MAVORIC trial were well balanced, with a median age of 64 years, 58.1% male, and 69.9% white. Most patients had an ECOG performance status of 0 (56.5%). Most patients had MF (54.8%), with the remaining patients diagnosed with SS (45.2%). The population in the MAVORIC trial was heavily pre-treated, with a median of 3 prior systemic therapies in each treatment group.

Efficacy Results

Overall response rate was higher in the mogamulizumab group compared to the vorinostat group; 52 (28.0%) of patients treated with mogamulizumab achieved an ORR compared to 9 (4.8%) with vorinostat. The results of subgroup and post-hoc analyses also suggested that mogamulizumab provided superior response rates in patients with SS (37.0% versus 2.3%), advanced stage disease (30.0% versus 2.9%), and B2 blood involvement (37.4% versus 3.2%). Additionally, 83 (66.9%) patients treated with mogamulizumab versus 23 (18.4%) patients

treated with vorinostat achieved an ORR in the blood compartment, and 78 (41.9%) and 29 (15.6%) achieved ORR in the skin compartment.

At the time of the data cutoff (December 31, 2016), the median efficacy follow-up was 17.0 months. The median PFS was 7.70 months (95% CI, 5.67 to 10.33) in the mogamulizumab group, compared to 3.10 months (95% CI, 2.87 to 4.07) in the vorinostat group (P < 0.0001). The HR for mogamulizumab versus vorinostat was 0.53 (95% CI, 0.41 to 0.69), in favour of mogamulizumab. Results of sensitivity analyses varying the definition of PFS were consistent with the primary analysis. Multiple subgroup and post-hoc analyses of PFS were conducted, demonstrating an improved survival with mogamulizumab in patients with SS (13.30 versus 3.13 months), advanced stage disease (9.40 versus 3.07 months), stage III/IV disease (10.90 versus 3.00 months), and B1 (8.63 versus 2.53 months) and B2 blood involvement (11.17 versus 3.30 months).

HRQoL was assessed by the Skindex-29, FACT-G, and EQ-5D-3L. In general, the magnitude of improvement from baseline to cycle 5 was greater with mogamulizumab compared to vorinostat. Across all scale domains for the Skindex-29, mogamulizumab and vorinostat reduced scores from baseline to cycle 5, with mean symptom scale scores demonstrating the greatest improvement (−18.0 versus −8.2). Results were consistent across HRQoL measures, with both mogamulizumab and vorinostat demonstrating an increase in FACT-G total score at cycle 5. With the EQ-5D Visual Analogue Scale, mean baseline scores increased from 60.9 (SD: 22.10) to 69.0 (SD: 20.30) at cycle 5 for mogamulizumab compared to 60.8 (SD: 20.02) to 63.5 (SD: 20.08) with vorinostat.

Other secondary outcomes evaluated also favoured mogamulizumab, with a BOR of 34.9% versus 6.5%, and a median DOR of 14.07 months with mogamulizumab compared to 9.13 months with vorinostat. At a median efficacy follow-up of 17.0 months, there was no difference in median OS between mogamulizumab (median OS not estimable [NE]) and vorinostat (43.93 months).

Harms Results

The overall incidence of treatment-emergent adverse events (TEAEs) was consistent between mogamulizumab (97.3%) and vorinostat (99.5%) arms. AEs were reported for randomized treatment. Incidence of specific TEAEs in patients who crossed over were not reported. The most frequently reported TEAEs with mogamulizumab were infusion-related reactions (33.2%), drug eruption (23.9%), diarrhea (23.4%), and fatigue (23.4%). The most frequently reported TEAEs with vorinostat were diarrhea (61.8%), nausea (42.5%), fatigue (37.6%), and thrombocytopenia (30.6%). The incidence of serious adverse events (SAEs) was higher in the mogamulizumab group compared to vorinostat (37.5% versus 24.7%). The most frequently occurring SAEs by system organ class were infections and infestations (16.3% versus 10.8%). Withdrawal due to AEs were similar between treatment groups during the randomized treatment period, with 19.0% of patients in the mogamulizumab group and 23.1% of patients in the vorinostat group discontinued treatment due to AEs, most frequently due to drug eruption for mogamulizumab (7.1%). A total of 5 (2.7%) and 9 (4.8%) patients died due to AEs during the randomized treatment period.

Notable harms including infusion-related reactions (IRRs) and infections were generally more frequent in the mogamulizumab group. In the randomized treatment phase, IRRs occurred in 33.2% of patients with mogamulizumab compared to 0.5% of patients for vorinostat, while infections and infestations occurred in 64.1% and 50% of patients, respectively. Though not

expressly reported as a group in the MAVORIC trial, the most frequently occurring immune-related TEAEs with mogamulizumab were drug eruption (23.9% versus 0.5%), and fatigue (23.4% versus 37.6%).

Critical Appraisal

The MAVORIC trial was an open-label, phase III RCT. In general, patients did not differ with regards to baseline characteristics, indicating that randomization was successful. There were no notable differences between mogamulizumab and vorinostat patients discontinuing randomized treatment, with most patients in both groups discontinuing due to disease progression. The reviewers and the clinical experts consulted by CADTH agreed that the open-label design used was appropriate; however, noted that this could potentially increase the risk of bias in the reporting of outcomes that are subjective in measurement and interpretation, such as response, HRQoL and AEs; however, the blinded independent review was instituted to assess for any potential investigator bias. The MAVORIC trial also included a one-way crossover design, where patients who failed treatment with vorinostat were able to crossover to the mogamulizumab group, which may have confounded the results for OS.As an exploratory end point, results for OS are considered descriptive The end points considered in the study were clinically appropriate for this population per the clinical experts consulted by CADTH and have been recommended by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of EORTC. Acceptable methods to account for multiplicity were used in the MAVORIC trial to adjust for the overall study-wise type 1 error rate for the key secondary end points. All subgroup analyses of the MAVORIC trial including disease type, stage, blood involvement, region, age, gender, race, and lactate dehydrogenase levels were prespecified; however, they were not controlled for multiplicity.

In discussion with the clinical experts consulted by CADTH, the inclusion and exclusion criteria for the MAVORIC trial were generally appropriate to enroll patients with a rare disease. There were, however, no Canadian sites in the MAVORIC trial. The MAVORIC trial enrolled patients with MF/SS of stages IB, IIA, IIB, III or IV, which was considered by the CADTH review team and clinical experts to be broad given the differences in disease behaviour and prognosis at each stage. The clinical experts also noted that the trial included a high proportion of patient with SS compared with the overall incidence of SS in Canada. The clinical experts also expected more patients with ECOG performance status of 2 in Canadian clinical practice, who were not eligible for the MAVORIC trial. Though approved by Health Canada for the treatment of CTCL, vorinostat is not widely accessible in Canada; thus, the comparative efficacy of mogamulizumab relative to vorinostat in patients with MF/SS in Canada may not be generalizable.

Results for HRQoL demonstrated improvements in HRQoL domains at various time points in the analysis; however, per the definitions of these populations, HRQoL results were only presented as observed data, and not for the entire intent-to-treat (ITT) population. As such, these patients can be considered responders to treatment, which may bias the results. Moreover, high attrition rates were observed for all HRQoL measures ranging from 42.2% to 44.8% of mogamulizumab-treated patients, and 66.3% to 67.03% of patients treated with vorinostat failing to complete the assessments at 6 months compared to baseline, resulting in uncertainty in the results, and thus may impact the generalizability of the results.

Indirect Comparisons

Description of Studies

The sponsor submitted an indirect treatment comparison (ITC) that compared individual patient data of the MAVORIC trial to the populations of relevant trial reports for comparators of interest in the treatment of CTCL, including the subtypes MF or SS. The objective of the sponsor-submitted report was to assess the feasibility of performing ITCs to compare mogamulizumab versus relevant comparators of interest for the outcomes of PFS, OS, time to treatment failure (TTF), ORR, and Skindex-29. Of specific focus was the comparison between mogamulizumab (MAVORIC trial) and the 2 arms of the ALCANZA study (brentuximab vedotin and physician's choice [methotrexate and bexarotene]), given that they were expected to be the main comparators in the cost-effectiveness model.

An initial feasibility assessment was conducted based on the findings of a clinical systematic literature review (SLR). The SLR review extracted evidence from 39 publications detailing 26 different studies: 14 parallel trials and 12 single-arm studies. The feasibility assessment to determine whether a network meta-analysis was possible by evaluating the network connectivity of included trials through comparators, the trial inclusion and exclusion criteria (i.e., population), demographic and disease characteristics, and study end points.

Based on the comparators of interest considered in the feasibility assessment, no connected networks were able to be formed with mogamulizumab. As such, an unanchored MAIC was used as an alternative analytical method to compare treatment from the ALCANZA trial with mogamulizumab. Multiple MAICs were conducted including the comparison of the mogamulizumab arm with the brentuximab vedotin arm for the entire ITT population of MAVORIC and ALCANZA trials, as well as the MF-only population of the MAVORIC trial. Additional comparisons included the vorinostat arm of the MAVORIC trial with the physicians' choice (methotrexate or bexarotene) arm in the ITT and MF-only populations. Outcomes evaluated included PFS, OS, and response in skin.

Efficacy Results

Two studies were included in the sponsor-submitted MAIC: MAVORIC and ALCANZA. For PFS, results of the MAIC comparing mogamulizumab to brentuximab after weighting demonstrated a greater probability of PFS events with mogamulizumab over brentuximab using both the ITT (HR: 2.21 [95% CI, 1.68, 3.19]) and MF only (HR: 2.52 [95% CI, 1.78, 3.75]) populations, while there was no difference between vorinostat and physicians' choice. For OS, there was no difference between mogamulizumab and brentuximab after matching patients to the ALCANZA population in the MAVORIC ITT (HR: 0.90 [95% CI, 0.62, 1.27]) or MF only populations (HR: 0.79 [95% CI, 0.45, 1.18]). The comparison between vorinostat and physicians' choice was unable to be conducted due to the crossover in the trials. [redacted]

Critical Appraisal

The choice to conduct an MAIC between MAVORIC and ALCANZA was justified considering the lack of common comparator. Moreover, no rationale or justification for brentuximab and physicians' choice from the ALCANZA trial as the primary comparator in the MAIC was provided. The main comparator for the MAIC, brentuximab vedotin, is indicated for adult patients with primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-

expressing MF who have received prior systemic therapy. This population was different from that of the MAVORIC trial, as no SS patients were included, and CD30-positivity was not assessed in MAVORIC, increasing the uncertainty in the analyses. The MAIC also provided a naïve comparison between vorinostat in the MAVORIC trial and physicians choice consisting of methotrexate or bexarotene in the ALCANZA trial, both of which, including vorinostat are rarely used in Canadian clinical practice according to the clinical experts consulted by CADTH; therefore, further limiting the generalizability of these results.

There were many key differences between the MAVORIC and ALCANZA trials that have an impact on the comparability of populations within these studies, particularly the inclusion criteria of the studies (i.e., the eligible population), the specific diagnosis, as well as differences in various baseline characteristics such as CD30 status, disease stage, blood involvement, prior treatments, and treatments in the study. The heterogeneity in population was accounted for by conducting matched analyses with the ITT population of MAVORIC, as well as the MF-only population of MAVORIC to the ALCANZA population, resulting in an effective sample size (ESS) that was reduced by 50.5% for the ITT population and 25.7% for the MF-only population. There were also considerable differences in baseline age, ECOG performance status, disease stage, and blood involvement; however, it was uncertain what direction this may impact results. A comprehensive list of prognostic factors and treatment-effect modifiers for weighting was provided (including these baseline characteristics); however, the method of identification, justification, and validation of prognostic factors and treatment effect modifiers was unclear, and it was uncertain whether all key factors were included in weighting; thus the risk of bias on the relative treatment effects for unanchored MAICs is considered substantial and must be considered.

Overall, given the differences between MAVORIC and ALCANZA in inclusion and exclusion criteria, the diagnosed population and the populations included in the analyses, the baseline characteristics, the differences in study design, and the significant reduction in ESS, the results of the MAIC are uncertain and may not be generalizable.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model (PSM)
Target population	Adult patients with mycosis fungoides or Sézary syndrome who have previously received ≥ 1 systemic therapy
Treatment	Mogamulizumab (Cycle 1: 1 mg/kg on days 1, 8, 15, and 22; Cycle 2+: 1 mg/kg on days 1 and 15)
Submitted price	Mogamulizumab, 20 mg, IV infusion: $2,203.60

Component	Description
Treatment cost	Cycle 1: $35,258; cycle 2+: $17,629
Comparator	ECM; consisting of methotrexate, bexarotene, interferon alpha-2a, gemcitabine, CHOP, liposomal doxorubicin, etoposide, prednisolone, vorinostat, PUVA, extracorporeal phototherapy, total skin electron beam therapy, chlorambucil, purine analogues, pralatrexate, romidepsin, and alemtuzumab)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, Lys
Time horizon	Lifetime (30 years)
Key data source	MAVORIC
Key limitations	• The comparative impact of mogamulizumab on OS is highly uncertain due to lack of head-to-head evidence for mogamulizumab compared to ECM and the high degree of uncertainty in the sponsor's MAIC. The sponsor assumed that the effectiveness of ECM would be equivalent to that observed for vorinostat in the MAVORIC trial, which may not be appropriate and adds additional uncertainty to estimates of incremental survival. • OS data from MAVORIC are confounded by cross over between treatment arms. The sponsor employed multiple statistical techniques to attempt to address this issue, and the predicted OS varied considerably according to the method chosen. • The choice of a PSM to evaluate the cost-effectiveness of mogamulizumab is inappropriate given the high level of uncertainty associated with the OS data from the MAVORIC trial. The sponsor's model predicts that the majority of gains in LYs and QALYs with mogamulizumab are obtained after disease progression by patients who are receiving subsequent treatment, which lacks face validity. • The long-term extrapolation of the clinical effects of mogamulizumab are highly uncertain. Clinical experts consulted by CADTH indicated that the OS predicted by the sponsor's model for mogamulizumab is likely overestimated. • The ECM basket of therapies does not reflect clinical practice in Canada. The composition of the ECM basket and the frequency of use of each included therapy was assumed by the sponsor to be the same regardless of whether patients had mycosis fungoides or Sézary syndrome, which lacks face validity according to clinical experts consulted by CADTH. Incremental costs are therefore unknown. • The sponsor employed poor modelling practices in their pharmacoeconomic model, preventing CADTH from fully validating the model and its findings.
CADTH reanalysis results	• Due to the identified limitations (including structural limitations of the model, immature and confounded OS data, the lack of comparative evidence for mogamulizumab relative to ECM, and an estimate of ECM cost that does not reflect current clinical practice), the cost-effectiveness of mogamulizumab could not be estimated from the sponsor's submitted evidence, and the cost-effectiveness of mogamulizumab is unknown. Consequently, a price reduction analysis could not be conducted. • CADTH undertook an exploratory analysis of the sponsor's base case to explore the impact of alternative assumptions related to OS. Results of this analysis suggest that the ICER is highly sensitive to uncertainty in the OS data and the method used to reflect the effect of crossover in the MAVORIC trial. • Using the sponsor's base case (which is subject to the limitations detailed above), a 51% price reduction would be required for mogamulizumab to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY. This estimate is based on estimates of incremental OS that are likely not representative of the true incremental effect of mogamulizumab. Consequently, the true price reduction that would be needed for mogamulizumab to be cost-effective is unknown but is likely greater than 51%.

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; ECM = established clinical management; ICER = incremental cost-effectiveness ratio; LY = life-year; MAIC = matching-adjusted indirect comparison; OS = overall survival; PSM = partitioned survival model; PUVA = phototherapy UV-A; QALY = quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of patients eligible for mogamulizumab is uncertain; the ECM basket of treatments does not reflect clinical practice; the market uptake of mogamulizumab is uncertain; the duration of treatment is uncertain; and the cost of mogamulizumab treatment was underestimated. CADTH reanalyses included: adopting a higher proportion of patients with prior systemic treatment and assuming that patients receive subsequent treatment after discontinuation of mogamulizumab.

Based on the CADTH reanalyses, the budget impact from the introduction of mogamulizumab for the full Health Canada–approved indication is expected to be $5,534,655 in year 1, $637,681 in year 2, and $843,287 in year 3, with a 3-year total budget impact of $7,015,623. The 3-year budget impact of reimbursing mogamulizumab among the MF estimated to be $3,280,852 and $3,734,771 among the Sézary syndrome subgroup. The estimated budget impact is sensitive to the prevalence of MF and Sézary syndrome, the proportion of patients with prior treatment experience, mogamulizumab uptake, and treatment duration.

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: February 9, 2022

Regrets: None

Conflicts of interest: None