pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug-funding decisions. The pCODR process brings consistency and clarity to the cancer drug assessment process by looking at clinical evidence, cost-effectiveness and patient perspectives.

pERC Final Recommendation
Upon consideration of feedback from eligible stakeholders, pERC members considered that criteria for early conversion of an Initial Recommendation to a Final Recommendation were met and reconsideration by pERC was not required.

Drug: Romidepsin (Istodax)

Submitted Funding Request:
For patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are not eligible for transplant and have received at least one prior systemic therapy

Submitted By: Celgene Inc.	**Manufactured By:** Celgene Inc.
NOC Date: October 16, 2013	**Submission Date:** December 1, 2014
Initial Recommendation: April 30, 2015	**Final Recommendation:** May 19, 2015

pERC RECOMMENDATION

The pCODR Expert Review Committee (pERC) recommends funding romidepsin (Istodax) conditional on the cost effectiveness being improved to an acceptable level. Funding should be for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are ineligible for transplant and who have undergone previous systemic therapy. Additionally, patients should have an ECOG PS of 0-2 and romidepsin treatment should be continued until disease progression or unacceptable toxicity. pERC made this recommendation because the Committee considered that there may be a net clinical benefit of romidepsin based on the meaningful and durable nature of response in the proportion of patients that achieved a response. pERC also considered that the clinical course of PTCL is aggressive, there are no other effective therapeutic options, the side effect profile of the drug is manageable and it aligns with patient values. Additionally, the patient population to whom this recommendation applies is small. However, pERC acknowledged that because of the non-randomized, non-comparative phase two study design, there was considerable uncertainty in the magnitude of the benefit and, therefore, in the incremental cost-utility of romidepsin. This led to a wide range of incremental cost-utility estimates, all of which pERC considered unacceptable. Therefore, romidepsin could not be considered cost-effective at the submitted price.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC concluded that there may be a net clinical benefit of romidepsin in patients with relapsed/refractory PTCL who are ineligible for transplant and who have undergone previous systemic therapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of romidepsin to an acceptable level. pERC noted that there is no clear mechanism to determine which patients will respond to treatment with romidepsin. pERC also noted that there is no clear way to determine what the duration of treatment in these patients will be, as treatment continues until disease progression or unacceptable toxicity. Additionally, pERC agreed that the cost of romidepsin is very high. Therefore, due to the high cost of the drug, the considerable uncertainty in the duration of treatment and number of patients that may be treated with romidepsin, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness.

Collecting Prospective Evidence to Reduce Uncertainty in the Magnitude of Benefit and Cost-Effectiveness
Given the considerable uncertainty in the magnitude of clinical benefit of romidepsin in patients with relapsed/refractory PTCL who are ineligible for transplant and who have undergone previous systemic therapy, pERC concluded that any additional prospective evidence that could be collected would better inform the true cost-effectiveness of romidepsin.

SUMMARY OF pERC DELIBERATIONS

pERC noted that peripheral T-cell lymphoma (PTCL) is an uncommon but aggressive malignancy and that the number of patients with relapsed/refractory PTCL is relatively small. While there is no standard treatment regimen in Canada for patients with relapsed/refractory PTCL, pERC noted that available treatments can include conventional doses of anti-cancer drugs as single agents or combination therapies or regimens used to treat B-cell lymphomas. Results with these regimens have generally been disappointing with relatively low response rates, short duration of response and poor survival. pERC, however, noted that for a small subset of patients who have the systemic CD30+ anaplastic large cell lymphoma (ALCL) subtype of PTCL, brentuximab vedotin monotherapy is currently available in most jurisdictions for relapsed/refractory disease. Therefore, pERC agreed with the pCODR Clinical Guidance Panel (CGP) that PTCL has an aggressive clinical course and there is a need for effective treatment options given the limited efficacy of currently available treatments.

pERC's Deliberative Framework for drug funding recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

Two single arm phase II studies of romidepsin in patients with relapsed/refractory PTCL were included in the pCODR systematic review (Piekarz et al 2011 and Coiffier et al 2012, 2014). pERC deliberated upon the results of these studies and concluded that there may be a net clinical benefit from treatment with romidepsin. pERC noted that a meaningful and durable nature of response (DoR) was observed in a small proportion of patients who responded to treatment with romidepsin. Members discussed if this duration was clinically meaningful and differing opinions were expressed. Most members agreed that the observed DoR was impressive and meaningful while a minority disagreed with using DoR as an indicator for net clinical benefit. The majority of pERC members considered that, in a population of patients with an aggressive disease and who have relapsed or are refractory to several lines of therapy, it is uncommon to observe long durations of response. Additionally, pERC considered a systematic review provided by the manufacturer which compared responses to other therapies used to treat PTCL. That review demonstrated that the DoR with romidepsin was substantially longer than what has been observed with other therapies. pERC, therefore, concluded that the unexpectedly long DoR observed with romidepsin suggests that there may be a net clinical benefit in the small proportion of patients who respond to treatment.

pERC noted that a small subset of patients with the systemic CD30+ anaplastic large cell lymphoma (ALCL) subtype of PTCL currently qualify for treatment with brentuximab vedotin. While comparative data between the two agents are not available, pERC agreed with the CGP's conclusion that these patients should qualify for treatment with both romidepsin and brentuximab as the mechanisms of action of the two drugs are different and most patients will experience relapse and become refractory to one or both agents. As there is no evidence to inform the optimal sequencing of these therapies, pERC agreed that the choice in therapy should be made in consultation with the treating oncologist and based on the patient's treatment goals.

pERC acknowledged that because of the non-randomized, non-comparative phase two study design of the two included studies, there was considerable uncertainty around the magnitude of the clinical benefit with romidepsin. pERC considered the feasibility of conducting a randomized controlled trial (RCT) to reduce uncertainty in this setting. pERC noted that although the CGP felt that an RCT was not feasible, the pCODR Methods Team had identified a completed RCT in relapsed/refractory PTCL with as yet unpublished efficacy and toxicity data. As such, pERC considered that a RCT was feasible in this patient population. Whether the results of the identified RCT will help inform the clinical value of romidepsin is unclear as the trial design allows romidepsin to be one of three investigator-selected treatments in the control arm of the trial. Nevertheless, pERC accepted the results of the Coiffier et al and Piekarz et al studies in concluding that there may be a net clinical benefit with the use of romidepsin based upon the meaningful and durable DoR observed in the small proportion of patients with response. pERC also concluded that prospective data collection to provide additional information on the magnitude of clinical benefit in this setting would be useful. Quality of life was not measured in the two included studies and this was seen as a limitation.

pERC also discussed the safety of romidepsin in patients with PTCL based on the toxicity profile observed in Coiffier et al and Piekarz et al studies and concluded that the toxicity of romidepsin was manageable. pERC noted that the most common adverse events were hematological and gastrointestinal events whose frequency and severity were considered to be familiar enough for hematologists and oncologists to effectively manage. While the prolongation of the QT interval is considered a potentially serious cardiac adverse event, pERC agreed with the CGP that the frequency of QT prolongation was low; the amount of prolongation was usually small; and evidence suggested that this prolongation is mainly attributable to the anti-emetics used with the treatment, and not due to romidepsin itself.

pERC noted that patient advocacy groups did not provide input on the romidepsin submission by the posted deadline. Instead, the Committee discussed a summary provided by pCODR compiling information on patient experiences and perspectives regarding PTCL and romidepsin. pERC agreed that romidepsin aligned with patient values as it provided patients with a treatment option that offered the potential of long lasting DoR in patients who respond to treatment with a manageable toxicity profile. Additionally, patient information indicated that patients would be willing to tolerate side effects if they could achieve longer survival, have durable remissions with control of their PTCL-related symptoms, and improved quality of life. Although patients valued having treatment options that improved their quality of life, pERC was unable to determine the impact of romidepsin on the quality of life of patients as these data were not available from the clinical trials.

pERC deliberated on the cost-effectiveness of romidepsin compared with available therapies in patients with relapsed/refractory PTCL. It was noted that due to the limitations of relying on non-comparative, non-randomized evidence and the heavy reliance on extrapolation of overall survival data, there was substantial uncertainty in the magnitude of the net clinical benefit associated with romidepsin. In addition, there was considerable uncertainty surrounding the proportion of patients who may respond to treatment with romidepsin as there is no biomarker available to help identify or guide which subsets of PTCL patients will respond to this treatment. Additionally, the duration of therapy for these patients is unknown as patients who responded to treatment were treated until disease progression or they experienced an unacceptable toxicity. pERC also noted that assumptions of a constant utility over time did not reflect the real life clinical setting since patients' quality of life generally worsen as their disease progresses and they enter the terminal phase of their illness. The multitude of unquantifiable factors made it challenging for the Economic Guidance Panel (EGP) to estimate the incremental cost and effect of treatment with romidepsin and led to a wide range of incremental cost-effectiveness estimates, all of which pERC considered to be too high to be acceptable. Therefore, romidepsin could not be considered cost-effective at the submitted price.

pERC noted that the price of romidepsin was a key driver of cost-effectiveness and that the cost for a 28-day cycle of romidepsin was $23, 238.00 when assuming drug wastage and $18,435.48 assuming vial sharing. pERC considered this absolute cost to be very high relative to other new high cost cancer drug treatments and that it is well above typical new cancer drug costs. The Committee noted that in order to improve the cost-effectiveness of romidepsin and offset the considerable uncertainty in the incremental effect, a substantial reduction in drug price would be required. pERC also considered that additional prospective evidence regarding the magnitude of the clinical benefit of romidepsin, which could inform the understanding of the true cost-effectiveness of romidepsin, would be useful to collect.

pERC discussed the feasibility of implementing a funding recommendation for romidepsin in PTCL and noted that drug wastage is a substantial concern. pERC noted that only one vial size is available while patients will typically need a third partial vial to achieve a full dose. pERC acknowledged this may result in a substantial cost to the hospitals/treatment centers and if it is not covered, it may cause some centers to decide not to provide the treatment. pERC also noted that the patient population that would qualify for romidepsin is small, the re-constituted drug has a short stability period and vial sharing between patients would be unlikely. Additionally pERC acknowledged a substantial uncertainty regarding duration of treatment as patients are treated until disease progression or unacceptable toxicity.

EVIDENCE IN BRIEF

pERC deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report providing clinical context
- an evaluation of the manufacturer's economic model and budget impact analysis
- guidance from pCODR clinical and economic review panels
- Patient advocacy group input was not received for this review; however, pERC used a summary provided by pCODR through a comprehensive search of published and grey literature on patient experiences and perspectives regarding PTCL and romidepsin to inform its deliberations.
- input from pCODR's Provincial Advisory Group.

Feedback on the pERC Initial Recommendation was also provided by:

- input from pCODR's Provincial Advisory Group.
- the Submitter (Celgene Inc.)

The pERC initial recommendation was to fund romidepsin (Istodax) conditional on the cost effectiveness being improved to an acceptable level. Funding should be for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) who are ineligible for transplant and who have undergone previous systemic therapy. Feedback on the pERC Initial Recommendation indicated that the manufacturer and pCODR's Provincial Advisory Group agreed with the initial recommendation. The pERC Chair and pERC members reviewed the feedback and it was determined that the pERC Initial recommendation was eligible for early conversion to a pERC Final Recommendation without reconsideration by pERC because there was unanimous consensus from stakeholders on the recommended clinical population outlined in the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of romidepsin (Istodax) when used in the relapsed/refractory setting for patients with peripheral T-cell lymphoma (PTCL) who are ineligible for transplant and who have undergone systemic therapy.

Studies included: Two single arm phase II studies

The pCODR systematic review included two single arm, multicenter, phase II studies of romidepsin in relapsed/refractory PTCL patients (Piekarz et al 2011 and Coiffier et al 2012, 2014).

No randomized trials were identified that met the eligibility criteria for the systematic review. pERC noted that PTCL is a relatively uncommon malignancy and that the number of patients with PTCL who are in the relapsed/refractory setting is very small. pERC discussed the feasibility of conducting a randomized controlled trial in this population and noted that the pCODR Methods Team had identified a completed randomized controlled trial (RCT) in relapsed/refractory PTCL which demonstrates that a RCT is feasible in this setting. This study evaluated the comparative efficacy of another new therapy, alisertib, vs. physician's choice (romidepsin, gemcitabine or pralatrexate) in patients with relapsed/ refractory PTCL. As romidepsin is only one potential treatment of choice in the comparator arm of this trial, pERC agreed that it was uncertain whether the results of this RCT will help inform the clinical value of romidepsin in this patient population. Although the Committee concluded that a RCT in the relapsed/refractory setting is indeed feasible, the Committee accepted the results of the Coiffier et al and Piekarz et al studies in reaching a conclusion that there may be a net clinical benefit of romidepsin based upon the meaningfully long DoR observed in the small proportion of patients achieving a response.

The pCODR review also provided contextual information on currently available treatment options for patients with relapsed/refractory PTCL in the form of a systematic review of thirty-three studies assessing treatment options for PTCL. pERC considered this information and agreed that the responses observed with a multitude of therapies used to treat PTCL are generally low. While response rates with romidepsin were also in line with those observed within other therapies, the DoR with romidepsin was substantially longer and led pERC to conclude that there may be a net clinical benefit in the small minority of patients who respond to treatment.

Patient populations: Similar in both studies

pERC noted that the two studies included in the systematic review were similarly designed. The Coiffier et al study included 130 patients with PTCL. The majority of patients in this study were male (68%), had an ECOG PS of 0 (43%), 1(49%) and 2(9%), had a primary diagnosis of PTCL of the following subtypes: unspecified or NOS (57%), angioimmunoblastic T-cell lymphoma (15%) or ALK-1-negative ALCL (4%). Patients treated with romidepsin had received a median of 2 prior systemic therapies. An independent review committee was used to assess tumour response. The Piekarz et al study included 47 patients with PTCL. Patients in this study had an ECOG PS of 0 (35%), 1(51%) and 2(13%). The majority of patients in this study were male (53%), had a primary diagnosis of PTCL with the following subtypes: unspecified or NOS (53%), angioimmunoblastic T-cell lymphoma (21%) or ALK-1-negative ALCL (16%). In this study, patients treated with romidepsin had received a median of 3 prior systemic therapies. Results from the Piekarz et al study are based on an interim analysis.

Patients in both studies received romidepsin 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle for 6 cycles. pERC noted that among the minority of patients who responded to therapy, treatment was continued beyond the 6 cycles until disease progression or an unacceptable treatment toxicity occurred.

Key efficacy results: Meaningfully long duration of response

The key efficacy outcome deliberated on by pERC was response rate. The primary outcomes of the two included studies were complete response (CR) and unconfirmed complete response (CRu). In the Coiffier et al study among all patients, 15% (n=19) achieved CR/CRu, the primary outcome. For the secondary outcomes in this study, the median durability of response (DoR) among 33 (25%) patients that achieved objective disease response (ORR: CR/CRu + PR) was 28 months (range, < 1-48+). The median durability of response had not been reached for those patients who achieved CR/CRu (n = 19). Response and DoR rates were similar in the Piekarz et al study. While response rates observed with romidepsin are comparable to those with other conventional treatments, pERC agreed that the substantially longer DoR observed with romidepsin was clinically meaningful and longer than what has been previously reported for other treatments in this disease. pERC noted that the durability of response was not significantly different based upon the number of prior therapies (1, 2 or $\geq$3). pERC concluded that this unexpectedly long DoR in a patient population with an aggressive disease and who have had several lines of therapy is uncommon. pERC, however, acknowledged that there is no clear mechanism (e.g. predictive biomarker) to distinguish which patients will respond to treatment with romidepsin.

In the Piekarz et al study, among all patients, 18% achieved CR and 38% (95%CI, 24% - 53%) achieved ORR. In the 8 patients who had a complete response, the median duration of response was 29.7 months (range 3-74).

Quality of life: Not measured

Quality of life was not measured in either study. pERC did note that improvements in ECOG status was observed in a proportion of patients responding to romidepsin. pERC was however unable to comment on the impact of romidepsin on quality of life.

Safety: Manageable toxicity profile

pERC discussed the safety profile of romidepsin based on the adverse events reported in Coiffier et al and Piekarz et al studies. The most common categories of adverse events with romidepsin from these studies were hematological and gastrointestinal. The nature, frequency and severity of the categories of adverse events were considered by the CGP to be familiar and manageable for hematologists and oncologists. pERC noted that ECG abnormalities were uncommon and observed in 8 (6%) of patients in the Coiffier et al study while one patient in the Piekarz et al study had an asymptomatic, non-recurrent, 12-beat run of ventricular tachycardia during an ECG; this patient was found to have abnormal magnesium, and potassium levels during this event. pERC noted the CGP's discussion with regard to the prolongation of the QT interval. The CPG felt the evidence supported the view that the QT prolongation was mainly attributable to the anti-emetics used with the treatment, and not due to the romidepsin itself. Although pERC considered it challenging to assess the safety of romidepsin in the absence of randomized comparative data, pERC concluded, based on the available data and the CGP's conclusion, that the toxicity of romidepsin is manageable.

Need: Aggressive disease with no effective treatment

pERC noted that PTCL is an uncommon but aggressive malignancy and that the number of patients with relapsed/refractory disease is relatively small. From among about 600 new diagnoses of PTCL in Canada annually, approximately 70% will experience relapsed/refractory disease and potentially be candidates for further therapy. For these patients, conventional doses of anti-cancer drugs are frequently used, as single agents or in combination, largely based on phase II data or regimens used to treat B-cell lymphomas. Clinical results have generally been disappointing, with most regimens giving relatively low response rates, typically less than 50%, short response durations and poor survival rates. pERC noted that PTCL tends to be rapidly progressive and those patients who do not respond to therapy, or who are not given any therapy, do poorly with survival typically measured in months.pERC, therefore, agreed thatpatients are in need of effective therapies that will prolong their survival and with a manageable toxicity profile.

PATIENT-BASED VALUES

Values of patients with peripheral T-cell lymphoma: Treatment choice, proven efficacy, longer remission, manageable toxicity profile

pERC noted that no patient advocacy groups provided input on the review of romidepsin by the posted deadline. The Committee discussed a summary provided by pCODR which compiled information to illustrate patient experiences and perspectives on PTCL and romidepsin.

pERC noted that the summary suggests that patients with PTCL want the opportunity to have a choice of treatments with proven efficacy, including for those patients who have the poorest prognostic disease features. The summary also suggests a need for access to therapies that will offer disease control, longer lasting remissions and an improved quality of life while offering increased efficacy, minimal toxicity and manageable side effect profiles relative to other treatments. pERC noted that caregiving can have a large impact on day-to-day life, such as, ability to travel, volunteer, spend time with family and friends, work, concentrate, exercise, attend to household chores and fulfill family obligations. It was also noted that caregivers of patients with PTCL had difficulties with managing “side effects” of the treatment, as well as difficulties with accessibility of treatment.Therefore, pERC concluded that providing access to romidepsin would align with patient values.

Patient values on treatment: Survival, longer remission, manageable toxicity profile, quality of life

pERC noted the importance of new drugs to patients that are able to control specific symptoms associated with their disease. The summary indicated the importance of longer survival, achievement of remission, disease control and improvements in quality of life as a tradeoff for drug related side effects. pERC noted that while romidepsin offered response rates similar to other conventional therapies, the duration of response was substantially longer that what has been observed with other therapies and would be consistent with longer and lasting remission. Romidepsin also had a manageable toxicity profile. pERC was, however, unable to determine the impact of romidepsin on quality of life due to lack of data.

Input from three patients with experience using romidepsin was captured in the pCODR summary. Two of three patients reported having been heavily pre-treated. One patient had been on treatment for 33 months and was disease free. The second patient reported side effects with romidepsin including rigors, night sweats, interrupted sleep, anorexia and extreme fatigue but indicated feeling much better with a lessening of side effects after cycle 2. This patient had completed 7 cycles. The third patient had only received 2 cycles of treatment and reported experiencing fever and chills with romidepsin that appeared to get progressively better in the days following treatment. pERC noted that for the most part these patients considered side-effects to be tolerable and short-lived which would permit patients to regain a satisfactory quality of life.

ECONOMIC EVALUATION

Economic model submitted: Cost-utility

The pCODR Economic Guidance Panel (EGP) assessed a cost-utility analysis of romidepsin compared to currently available treatments for patients with relapsed/refractory PTCL who are not eligible for transplant and have received at least one prior systemic therapy.

pERC noted that a subset of patients with the systemic CD30+ anaplastic large cell lymphoma (ALCL) subtype of PTCL currently qualify for treatment with brentuximab vedotin. Brentuximab was considered to be a relevant treatment option by the CGP but was not included as a modification to the main economic analysis. pERC agreed that patients with this specific subtype of PTCL should qualify for treatment with both romidepsin and brentuximab but was unable to comment on the comparative efficacy and cost effectiveness of the two drugs. While pERC noted that this subset of patients is very small, the Committee agreed that jurisdictions need to consider the impact of making both these drugs available to this subset of PTCL patients.

Basis of the economic model: Clinical and economic inputs

Costs considered in the analysis included drug costs, administration costs and ongoing medical care costs.

The clinical effect considered in the analysis was based on projected overall survival, time on treatment and utilities values.

Drug costs: High absolute drug cost and wastage as cost drivers; unknown treatment duration or number of patients to be treated

Romidepsin costs $2,582.00 per 10 mg vial. At the recommended dose of 14 mg/m^2 on days 1, 8 and 15 of a 28-day cycle, assuming vial sharing, romidepsin costs $658.41 per day and $18,435.48 per 28 day cycle. Assuming no vial sharing and wastage of excess drug, romidepsin costs $829.9286 per day and $23,238.00 per 28 day cycle. pERC noted that patients who had response to therapy had the option to continue treatment beyond the recommended 6 cycles of therapy until progression or unacceptable toxicity. pERC noted this created uncertainty in the duration of therapy and is likely to have an impact on the cost-effectiveness of romidepsin.

pERC noted that the price of romidepsin was a key driver of cost-effectiveness and that the cost per 28-day cycle of romidepsin was $$23,238.00 when assuming wastage of drug and $18,435.48 with vial sharing. pERC considered this cost to be extremely high relative to other new cost cancer drug treatments. pERC also noted that drug wastage is a substantial concern due to the dosing which is weight based and will require the use of a third partial vial for most patients with a considerable amount of the third vial being wasted. Additionally, the full dose cannot be extracted out of a vial because of the viscosity of the reconstituted drug and there is limited potential for vial sharing with a small patient population and the short-term stability of the reconstituted drug. The Committee, therefore, agreed that in order to improve the cost-effectiveness of romidepsin and offset the considerable uncertainty in the incremental cost and effect, a substantial reduction in drug price would likely be required. pERC further considered that additional prospective evidence regarding the magnitude of the clinical benefit of romidepsin, could inform the understanding of the true cost-effectiveness of romidepsin, and would be useful to collect.

Cost-effectiveness estimates: Substantial uncertainty in incremental cost

pERC deliberated on the cost-effectiveness of romidepsin compared with available therapies in patients with relapsed/refractory PTCL. It was noted that due to the limitations of relying on non-comparative, non-randomized evidence and the heavy reliance on extrapolation of overall survival data, there was substantial uncertainty in the magnitude of the net clinical benefit associated with romidepsin. In addition, there was considerable uncertainty surrounding the proportion of patients who might respond to treatment with romidepsin as there is no biomarker available to help identify what subsets of patients who are most likely to respond to this treatment. The duration of therapy for these patients is also unknown as study patients who responded to treatment were treated until disease progression or unacceptable toxicity. pERC also noted that assumptions of a constant utility over time did not reflect the clinical setting since patients quality of life generally worsens as their disease progresses and they approach death. This multitude of unknown factors made it challenging for the Economic Guidance Panel (EGP) to estimate the incremental cost and effect of treatment with romidepsin and led to a wide range of incremental cost-utility estimates, all of which pERC considered to be unacceptable. Finally, based on input from the Clinical Guidance Panel, pERC also noted that the EGP revised the economic model's time horizon from 20 to 10 years to reflect the more plausible clinical scenario. While pERC noted that a shortened time horizon was included as part of the EGP's re-analysis estimates, the committee agreed that it had minimal impact on the re-analysis estimates. Therefore, romidepsin could not be considered cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Wastage, treatment duration

pERC discussed input from pCODR's Provincial Advisory Group on the feasibility of implementing a positive funding recommendation for romidepsin. pERC acknowledged a number of issues related to the cost of romidepsin and subsequent budget impact. Due to the small number of patients with relapsed/refractory PTCL, pERC noted that the budget impact could be relatively small. However, because of the small patient population, vial sharing would be unlikely and, therefore, drug wastage could be a significant issue. Additionally, due to the weight based dosing of romidepsin requiring a third additional partial vial in most patients, a substantial amount of the third vial may be wasted. pERC noted that while only a small proportion of treated patients respond to romidepsin, it is unable to give guidance on who will respond to therapy as there is no evidence to inform this. Additionally, patients that respond to therapy should be treated until disease progression or unacceptable toxicity. This unknown duration of therapy will need to be considered by jurisdictions during implementation.

pERC agreed with the CGP's guidance indicating that patients with mycosis fungoides type of cutaneous T-cell lymphoma, which was not the subject of this review, should not qualify for treatment with romidepsin. However, individuals with mycosis fungoides that has transformed to an aggressive histology T-cell lymphoma should qualify for treatment, as these patients were included in the reviewed trials. pERC anticipates that QT prolongation may not be a significant concern attributed to romidepsin as the evidence seems to indicate that it is mainly attributable to the anti-emetics used with treatment, and not due to the romidepsin itself. pERC noted that patients with a specific subtype of PTCL (eg. anaplastic large cell lymphoma) should qualify for treatment with either romidepsin and brentuximab but was unable to comment on the comparative efficacy and cost effectiveness of the two drugs. At present there are no data available to guide sequencing of romidepsin or brentuximab. While pERC agreed that the number of patients with the anaplastic large cell lymphoma subset of PTCL is exceedingly small, the Committee agreed that jurisdictions need to consider the impact of making both these drugs available to these patients. Additional implementation impacts are also expected as a result of the 4 to 4.5 hours infusion time which will increase chemotherapy chair utilization and require additional nursing resources. Increase pharmacy preparation time will also be required due to the time needed to prepare the drug for administration due to its high viscosity.

DRUG AND CONDITION INFORMATION

Drug Information	• histone deacetylase (HDAC) inhibitor • 10 mg vial • Recommended dosage of 14 mg/m^2 intravenously over 4 hours on days 1, 8 and 15 of each 28-day cycle
Cancer Treated	• Peripheral T-Cell Lymphoma
Burden of Illness	• Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group, collectively comprising 5-10% of all non-Hodgkin lymphomas in Canada • it is estimated that approximately 400 patients per year would be candidates for romidepsin therapy in Canada for relapsed/refractory PTCL
Current Standard Treatment	• No standard of care in the relapsed/refractory patient population
Limitations of Current Therapy	• No standard effective treatment options for relapsed/refractory PTCL

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee (pERC)

Recommendations are made by the pCODR Expert Review Committee following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Anthony Fields, Oncologist (Chair)
Dr. Maureen Trudeau, Oncologist (Vice-Chair)
Dr. Scott Berry, Oncologist
Bryson Brown, Patient Member
Dr. Matthew Cheung, Oncologist
Mario de Lemos, Pharmacist
Dr. Sunil Desai, Oncologist
Mike Doyle, Economist
Dr. Bill Evans, Oncologist
Dr. Allan Grill, Family Physician
Dr. Paul Hoskins, Oncologist
Danica Wasney, Pharmacist
Carole McMahon, Patient Member Alternate
Jo Nanson, Patient Member
Dr. Tallal Younis, Oncologist
Dr. Kelvin Chan, Oncologist

All members participated in deliberations and voting on the initial recommendation except:

- Drs. Paul Hoskins and Sunil Desai who were not present for the meeting
- Mike Doyle who was present for the deliberations but was absent for the voting
- Carole McMahon who did not vote due to her role as a patient member alternate

Because the pERC Initial Recommendation met the criteria for early conversion to a pERC Final Recommendation, reconsideration by pERC was not required and deliberations and voting on the pERC Final Recommendation did not occur.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of romidepsin (Istodax) for Peripheral T-Cell Lymphoma, through their declarations, three members had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, none of these members were excluded from voting.

Information sources used

The pCODR Expert Review Committee is provided with a *pCODR Clinical Guidance Report* and a *pCODR Economic Guidance Report*, which include a summary of patient advocacy group and Provincial Advisory Group input, as well as original patient advocacy group input submissions to inform their deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this recommendation.

Use of this recommendation

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