

CADTH

pCODR PAN-CANADIAN
ONCOLOGY DRUG REVIEW

**pan-Canadian Oncology Drug Review
Stakeholder Feedback on a pCODR Expert Review
Committee Initial Recommendation
(Manufacturer)**

**Pralatrexate (Folotyn) for Peripheral T-cell
Lymphoma**

April 4, 2019

Feedback on pERC Initial Recommendation

Name of the Drug and Indication(s): Pralatrexate (FOLOTYN®) for the treatment of patients with relapsed or refractory PTCL (rrPTCL)

Eligible Stakeholder Role in Review: Submitter

Organization Providing Feedback: Servier Canada Inc.

Comments on the Initial Recommendation

a) Please indicate if the eligible stakeholder agrees, agrees in part, or disagrees with the Initial Recommendation:

agrees agrees in part disagree

Servier is pleased that the pERC issued a positive recommendation for pralatrexate for the treatment of patients with rrPTCL. Servier agrees with the assessment by pERC and the pCODR CGP that there is a net clinical benefit with pralatrexate. However, Servier believes the wording of the recommendation could be revised to better align with the recognized unmet need for additional therapies, as well as patient values for treatment choice, in such a heterogeneous disease entity. Specifically, Servier disagrees with the following language within the pERC Recommendation:

1) **Within the reimbursement criteria, “Reimbursement should be for patients with relapsed or refractory PTCL who have undergone previous systemic therapy, none of which include romidepsin”**

Servier believes that this does not align with the recognized need for additional treatment choices. Rather, the criteria will create a significant barrier for patients who have failed romidepsin and require additional therapy. Moreover, it will create a difficult choice for doctors when deciding whether to use pralatrexate or romidepsin for a given patient.

2) **Within the condition: “The public drug plan cost of pralatrexate should be lower than the public drug plan cost of romidepsin”**

While there is uncertainty in the comparative effectiveness of pralatrexate versus romidepsin, there is no evidence to suggest that one therapy is more effective than the other. Furthermore, pralatrexate may be associated with savings when considering wastage, and its shorter administration time is an enabler to implementation. As such, Servier proposes that the condition be reworded so that the public drug plan cost of pralatrexate does not exceed the public drug plan cost of romidepsin.

b) Please provide editorial feedback on the Initial Recommendation to aid in clarity. Is the Initial Recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

Page Number	Section Title	Paragraph, Line Number	Comments and Suggested Changes to Improve Clarity
Servier has no editorial feedback on the Initial Recommendation to aid in clarity.			

Comments Related to Eligible Stakeholder Provided Information

Notwithstanding the feedback provided in part a) above, please indicate if the Stakeholder would support this Initial Recommendation proceeding to Final pERC Recommendation (“early

conversion”), which would occur two (2) Business Days after the end of the feedback deadline date.

Support conversion to Final Recommendation.

Do not support conversion to Final Recommendation.

Recommendation does not require reconsideration by pERC.

Recommendation should be reconsidered by pERC.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
1	pERC Reco.	2 nd Paragraph	<p><i>“Reimbursement should be for patients with relapsed or refractory PTCL who have undergone previous systemic therapy, none of which include romidepsin”</i></p> <p>pERC noted that patients in the PROPEL trial did not have previous treatment with romidepsin, and thus pralatrexate should only be considered for patients who have not had romidepsin as one of their previous systemic therapies. However, given the timing of the trials for pralatrexate (PROPEL start August 2006, complete January 2009) and romidepsin (NCT00426764 start June 2007, complete November 2010),^{1,2} it is unlikely that either trial would have enrolled many patients who had been treated with the opposing therapy.</p> <p>Furthermore, romidepsin [histone deacetylase (HDAC) inhibitor] and pralatrexate (antifolate) have two different mechanisms of action with non-over-lapping side-effect profiles.^{3,4} In fact, both these differences support the rationale for studying the combination of romidepsin and pralatrexate for the treatment of patients with relapsed/refractory lymphoid malignancies (NCT01947140).⁵ Thus, the use of one should not preclude the use of another.</p> <p>Importantly, pERC agreed with the pCODR CGR and the registered clinicians that rrPTCL has an aggressive course and there is a need for more effective palliative treatment options. To add to this, a new treatment option may represent an opportunity for some patients to successfully bridge to a potential curative transplant. As well, pERC concluded that pralatrexate aligns with patients values in that it offers a choice of treatment. In limiting reimbursement for patients who have not undergone (or will not undergo) previous systemic therapy with romidepsin, patients who are refractory to or have relapsed following treatment with romidepsin and who could benefit from subsequent systemic therapy would be left with limited options.</p> <p>As noted in the potential next steps for stakeholders, Servier recognizes that the choice between pralatrexate and romidepsin will likely depend on treatment availability, patient values and preferences, clinical factors such as tolerability to adverse events, and the relative overall cost. To build onto this point, the choice between pralatrexate and romidepsin should not limit access to both in sequence for a patient that may benefit from additional lines of therapy in the relapsed/refractory setting. However, if one were to apply the recommended reimbursement criteria for pralatrexate (which is restricted to patients without prior romidepsin therapy) with the existing criteria for romidepsin (which has no restrictions related to a specific prior therapy),⁶ the (lack of) choice is already dictated for clinicians and patients. That is, to gain access to both treatment options for those patients who could benefit, pralatrexate would need to be used first, followed by romidepsin; if romidepsin is used first, only one treatment option would be available.</p> <p>Servier requests that pERC reconsider the reimbursement criteria to remove the restriction for patients who have previously been treated with romidepsin in order to fulfill the need for more effective palliative treatment options and better align with patients values to offer an additional choice of treatment, irrespective of their prior treatment history. Servier further proposes that a note be included within the section titled “No Evidence for Optimal Sequencing of Pralatrexate and</p>

Romidepsin” to clarify that the choice of pralatrexate or romidepsin should not restrict the subsequent use of the other.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
1	pERC Reco.	Bulleted condition	<i>“The public drug plan cost of pralatrexate should be lower than the public drug plan cost of romidepsin”</i>

In the submitted MAIC, there was no statistically significant difference between the treatment effects of pralatrexate and romidepsin, although there was uncertainty associated with the estimates of relative treatment effects. pERC noted that it was unable to draw a firm conclusion concerning the comparative effectiveness of pralatrexate, stating that it is uncertain whether pralatrexate is more costly and less effective than romidepsin or less costly and more effective than romidepsin. While there is uncertainty in the comparative effectiveness of pralatrexate, there is also no evidence to suggest that one therapy is more effective than the other. Based on the submitted MAIC, the CGR noted “pralatrexate provided equivalent control of rrPTCL patients treated with romidepsin”, and as argued above, the ability to choose between the two should not be restricted. It is also important to consider that:

- The cost of the two treatments is equivalent over a common duration when excluding dose intensity, administration, and wastage [cost of \$20,027 per month, as per the pharmacoeconomic (PE) evaluation],
- The cost of pralatrexate is *less* than that of romidepsin over a common duration when considering dose intensity, administration, and wastage (\$16,486 per month vs. \$20,911 per month, as per the submitted PE evaluation), and
- Pralatrexate is administered by intravenous (IV) push and has shorter chair time than current treatments, which pERC considered an enabler to implementation.

Servier proposes that pERC reword the condition so that the public drug plan cost of pralatrexate does not exceed the public drug plan cost of romidepsin.

Page Number	Section Title	Paragraph, Line Number	Comments related to Stakeholder Information
9	Cost-effectiveness estimates	1 st and 2 nd paragraphs	<i>“The EGP’s ICER estimate range for the comparison of pralatrexate to BSC were wide [\$189,133/QALY - \$519,325/QALY] [...] EGP noted that the best estimate would likely be closer to the upper bound ICER estimate...”</i>

The EGR’s upper bound ICER estimate vs. BSC corresponds to a 50% reduction of the clinical benefits after 2y (trial duration) and equal utilities in the pre-progression state over a 5y time horizon. Servier disagrees with this best estimate, namely in reducing the clinical benefit beyond 2y while maintaining an assumed high cost for pralatrexate due to long-term treatment as per the modelled PFS. If assuming that the benefit beyond 2y for pralatrexate is reduced by 50%, then the treatment duration for pralatrexate should not exceed that observed in the clinical trial. Such a scenario was indeed considered by the EGP (using 38 vials, based on median duration of treatment in PROPEL) and the associated ICER vs. BSC was \$240,758/QALY (deterministic) over a 5y time horizon. As such, Servier believes that the best estimate ICER vs. BSC would not be closer to the upper bound estimated by the EGP; rather it would be closer to the mid-point between the upper and lower bounds.

REFERENCES

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- ¹ ClinicalTrials.gov. Study of Pralatrexate With Vitamin B12 and Folic Acid in Patients With Relapsed or Refractory Peripheral T-cell Lymphoma (PROPEL). Accessed at <https://clinicaltrials.gov/ct2/show/NCT00364923>
 - ² ClinicalTrials.gov. A Trial of Romidepsin for Progressive or Relapsed Peripheral T-cell Lymphoma. Accessed at <https://clinicaltrials.gov/ct2/show/NCT00426764>
 - ³ Servier Canada Inc. FOLOTYN® (pralatrexate) Product Monograph. October 19, 2018.
 - ⁴ Celgene Inc. ISTODAX® (romidepsin) Product Monograph. December 13, 2016.
 - ⁵ ClinicalTrials.gov. Pralatrexate + Romidepsin in Relapsed/Refractory Lymphoid Malignancies (PDX+Romi). Accessed at <https://clinicaltrials.gov/ct2/show/NCT01947140>
 - ⁶ pCODR. Provincial Funding Summary: Romidepsin (Istodax) for Peripheral T-Cell Lymphoma. Accessed at https://www.cadth.ca/sites/default/files/pcodr/pcodr-provfund_istodax-ptcl.pdf