pan-Canadian Oncology Drug Review
Final Economic Guidance Report

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

April 4, 2019

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by **Servier Canada Inc,** compared FOLOTYN® (pralatrexate) to an historical control population, for the treatment of patients with relapsed or refractory PTCL. Pralatrexate is indicated for the treatment of patients with relapsed or refractory PTCL. It has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit.

A Case Match Control Analysis (CMCA) matching patients from a single-arm study 1:1 with a historical control population was used to estimate the survival advantage of pralatrexate in patients with R/R PTCL.

An indirect treatment comparison (ITC) of pralatrexate versus romidepsin was performed. This followed feedback from the Provincial Advisory Group that requested a comparison of pralatrexate versus romidepsin.

Table 1. Submitted Economic Model

Patient Population Modelled	**Servier Canada Inc** is requesting Pralatrexate to be reimbursed for the treatment of patients with relapsed or refractory PTCL. This aligns with the patient population that the economic model is built on.				
Type of Analysis	Cost effectiveness and cost utility analysis				
Type of Model	Partitioned-survival model				
Comparator	Base-case analysis was performed with an historical control population in order to estimate clinical outcomes, and best supportive care (BSC), such as a combination of monotherapy and combination chemotherapies as a proxy for BSC, in order to estimate costs. A scenario analysis was performed with romidepsin group.				
Year of Costs	2018				
Time Horizon	10 years				
Discount Rate	1.5%				
Perspective	Publicly funded health care system in Canada				
Cost of pralatrexate	Single dose vial of 20 mg costs $2,108.63. At the recommended of 30 mg/m^2 IV once weekly for 6 weeks in 7-week cycles and a dose intensity of 80% as per PROPEL trial, pralatrexate costs:$16,486.33 per month (excluding wastage)				
Cost of best supportive care (BSC)	Cost per monthly cycle of $1,625.59/cycle Combination of monotherapy and combination therapy chemotherapy agents				
				Daily dose	Cost/month
	Gemcitabine	200mg	$43.72	1000	$1,076.52
	Dexamethasone	4mg	$0.30	40	$17.65

	Cisplatin	100mg	$2.70	75	$4.99
	Etoposide	20mg	$15.00	100	$355.29
	Gemcitabine	200mg	$43.72	1200	$1,520.38
Cost of romidepsin	Romidepsin costs $2,582.00 per 10mg vial. The monthly cost of romidepsin excluding wastage is $20,910.64.				
Model Structure	The model was comprised of 3 health states: pre-progression, progression (or post-progression), and death. Transitions between these health states were driven by the PROPEL trial[1] and Case Match Control Analysis (CMCA)[2]; For PFS, in the absence of a comparator arm in the PROPEL trial, the non-responder arm was used as a proxy for extrapolating PFS for BSC; For OS, in addition to data from the PROPEL trial, OS estimates were informed by CMCA conducted by O'Connor et al and submitted to Health Canada. The KM curves for OS based on the case match control were reconstructed using the algorithms developed by Guyot et al. An indirect treatment comparison (ITC) – a matching adjusted indirect comparison (MAIC), of pralatrexate versus romidepsin was performed. This followed feedback from the Provincial Advisory Group that requested an understanding of the efficacy and safety of pralatrexate versus romidepsin. Only parametric functions were used to estimate survival benefits. These were fitted independently to both treatment arms.				
Key Data Sources	The efficacy and safety parameters for the pralatrexate group were based on the PROPEL trial.[1] The PFS and OS were extrapolated using parametric functions fitted to the patient-level trial data. A Case match control analysis (CMCA) encompassing a multi-cohort retrospective analysis of multiple registries of data, was used to inform OS in BSC arm[2]. The non-responders group from pralatrexate arm was used as a proxy for extrapolating PFS for BSC. The monthly probabilities of being in a given model health state (progression-free, progressive disease, or death) were modelled from the parametric models selected using statistical tests.				
*Drug costs in this table are based on costing information provided by the Submitter, Servier Canada Inc., and are used in the economic model.					

1.2 Clinical Considerations

- According to the Clinical Guidance Panel (CGP), the comparison to BSC is appropriate. However, the most clinically relevant comparison is to romidepsin.The CGP concluded that there is a net overall clinical benefit from the use of pralatrexate in the treatment of patients with symptomatic patients whose peripheral T cell lymphoma has proven refractory to or relapsed after primary systemic treatment.

- This conclusion is based on data from one phase 2 clinical trial of pralatrexate for patients whose peripheral T cell lymphoma has proven refractory to or relapsed after primary systemic treatment (rrPTCL). The overall response rate was 29% with a median duration of response of approximately 10 months. The median progression free survival was 3.5 months and the median overall survival was 14.5 months.

- In the absence of a direct-head to-head trial evaluating the efficacy of pralatrexate, two ITCs were submitted: CMCA comparing pralatrexate to historical controls and a MAIC analysis comparing pralatrexate to romidepsin. The CMCA analysis demonstrated pralatrexate provided superior control of rrPTCL when compared with a matched set of historical control patients treated with a variety of systemic agents. The MAIC analysis demonstrated that pralatrexate provided equivalent control of rrPTCL patients treated with romidepsin.

- The pCODR Methods Team identified a number of limitations of the CMCA that should be considered when interpreting the results; the most significant of these included the high risk of selection bias owing to the retrospective nature of the historical comparator data, and the omission of important variables from the matching process, which may confound the treatment effect estimates obtained.
- The pCODR Methods Team considered a MAIC of the two trials appropriate based on their similarity but noted some limitations that should be considered when interpreting the results; these included limitations in the OS data of both trials, and possible bias introduced by unknown cross-trial differences.

Summary of patient input relevant to the economic analysis

Lymphoma Canada (LC) provided input on pralatrexate as treatment for PTCL and their input is summarized below.

LC conducted two anonymous online surveys—one for patients with PTCL and one for patients with PTCL who have experience with pralatrexate—from May 15 to June 10, 2018.

LC expressed that patient respondents were willing to tolerate significant side effects in new drug therapies. All respondents answered with '9' or '10' when asked if they would be willing to tolerate side effects with a new drug approved by Health Canada for the treatment of PTCL on a scale of 1 (Will Not Tolerate Any Side Effects) to 10 (Will Tolerate Significant Side Effects).

When patients were asked to rate how important it is for a new drug to be "able to control" specific aspects associated with their disease on a scale of 1 (Not important To Control) to 10 (Very Important To Control), all of the results were highly rated, with more importance assigned to bringing about remission and living longer (rated 10/10). According to LC, these results suggest that patient respondents prioritize longevity and disease control over other considerations.

LC highlighted the following from the five patient respondents with experience with pralatrexate.

In terms of side effects, LC noted that mouth sores and mucositis were the most commonly reported side effects, followed by anemia as well as low white blood cell and blood platelet counts. When asked about the tolerability of the side effects associated with pralatrexate on a scale of 1 (completely tolerable) to 10 (completely tolerable), patient respondents gave an average score of 5.

Respondents were asked if they would recommend pralatrexate to other patients with PTCL based on their personal experiences. All three patient respondents who responded to this question responded 'Yes'.

LC expressed that the majority of PTCL patients will die from their disease within two years of diagnosis. LC highlighted that there has been little improvement in PTCL outcomes in the last two decades and that patients are in need of additional treatment options to prolong their life.

Summary of registered clinician input relevant to the economic analysis

Clinicians indicated that the major benefits from pralatrexate are high response rates and durable responses in a heavily pre-treated patient population, as demonstrated in the PROPEL trial. Referring to this trial, clinicians stated that pralatrexate induced durable responses irrespective of age, histologic subtype, amount of prior therapy, prior methotrexate, and prior autologous stem-cell transplant, making it an option worth considering for any patient with relapsed or refractory PTCL. It was also reported that toxicities seem to be manageable with pralatrexate. Clinicians providing input also noted that pralatrexate has a quick infusion time. The need for new treatments in this patient population was emphasized as most patients undergoing treatment for PTCL do not achieve complete remission, or will ultimately relapse. The clinicians providing input reported that pralatrexate would provide an additional option to patients in the relapsed and refractory PTCL setting. No companion diagnostic testing is required.

Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation of pralatrexate for PTCL:

Clinical factors:

- Clarity of eligible patient population
- Place in therapy
- Comparison to romidepsin

Economic factors:

- Weekly dosing administration
- Drug wastage

Specifically:

PAG noted that the current standard of care for relapsed or refractory PTCL is romidepsin and that the PROPEL trial being submitted for review is a phase 2 non comparative trial and is seeking information on the comparison of pralatrexate with romidepsin.

PAG is seeking clarity on the eligible patient population as the funding request is broad for relapsed or refractory patients. PTCL is a heterogeneous group of aggressive lymphomas with many subtypes. It will be important to clearly specify which subtypes of PTCL are eligible for treatment with pralatrexate. PAG is seeking information on the number of previous treatment patients in the trial had received and whether there is information on the pervious treatments used.

PAG has concerns for drug wastage as vial sharing may be difficult with a very small number of eligible patients. PAG also noted that pralatrexate is administered by intravenous push, which has shorter chair time and enables pralatrexate to be administered in smaller clinics.

Pralatrexate is administered once weekly for six weeks out of seven weeks. PAG noted that the administration schedule is not convenient for patients. PAG also noted that Vitamin B12 injections also need to be administered intramuscularly and folic acid would need to be taken concomitantly.

PAG is also seeking clarify on the treatment duration.

PAG noted that there are different therapies available for different histologic subtypes of T cell lymphoma. PAG is seeking clarity on the place in therapy of pralatrexate among the different treatments available and the possible sequencing of treatments.

1.3 Submitted and EGP Reanalysis Estimates

The main assumptions and limitations with the submitted economic evaluation were:

In summary, the key assumption that has the most impact on the results of the economic evaluation is the difference in OS between pralatrexate and the BSC group. Mainly, the PROPEL trial is a phase II, single-arm, non-randomized, open-label trial, and because of this, the comparator group was absent.

First, a Case Match Control Analysis (CMCA) matching patients from a single-arm study 1:1 with a historical control population was used to estimate clinical benefit of pralatrexate compared to BSC. Only the OS was estimated from CMCA, and not the PFS. The full CMCA was published by O'Conner et al in the JNCI Cancer Spectrum. Kaplan-Meier estimates of OS were calculated based on combinations of the following characteristics: histology, number of prior therapy, age, and gender. In total, 81 patients treated in the PROPEL study were matched with the historical control population. The last line of treatment in this historical control population (BSC arm) is unknown, but since the standard of care in this population didn't change much in the last 20 years, the CGP considered that these should be similar to the current BSC in this population. In the absence of comparable PFS data for the BSC arm, its PFS curve was based on the non-responder group of the PROPEL trial PFS curve.

Second, a scenario analysis was provided by the submitter comparing pralatrexate with romidepsin. An ITC of pralatrexate versus romidepsin was undertaken. This followed feedback from the Provincial Advisory Group that requested an understanding of the efficacy and safety of pralatrexate versus romidepsin. In the absence of head-to-head data to compare pralatrexate versus romidepsin, as well as the inability to connect pralatrexate in a network to romidepsin due to the single-arm nature of the studies for both therapies, an unanchored ITC in the form of a MAIC analysis was conducted. An unadjusted (naïve) and adjusted relative effects were performed to estimate the OS and PFS hazard ratios (HRs) of pralatrexate versus romidepsin.

To extrapolate the PFS and OS outcomes beyond the trial follow-up available, the following parametric models were fitted independently to both treatment arms: Weibull, exponential, lognormal, log logistic, and Gompertz.

A second key assumption that has the most impact on the results of the economic evaluation is the cost. For the 1st comparison with the BSC arm estimated by CMCA a mixture of chemotherapies, administered both as a combination or monotherapy, were selected as the best supportive care. Time on treatment in pralatrexate arm was estimated by PFS curve, and two other scenarios were run with 38.1, and 30.3 vials expected to be consumed by a patient during their course of therapy; these were based on median total dose consumed in the PROPEL CSR, and mean total dose consumed in the PROPEL CSR, respectively. The duration of treatment in BSC arm was based on PFS curve. The model allowed the EGP to perform several re-analyses, which had a high impact on ICER.

For the 2nd comparison the cost of romidepsin was based on the PFS as a function of HR estimated in MAIC analysis and the PFS observed for pralatrexate in PROPEL trial. Both HRs for OS and PFS were non statistically significant, yet there was a trend of decreased PFS (HR: 1.28 (85% CI 0.94 – 1.73)) but with an increased OS (HR: 0.88 (95% CI 0.63 – 1.23)) in pralatrexate group compared to romidepsin group. The scenario presented by the submitter took into account these HRs, which produced an increase of the romidepsin cost (time spent in PFS state is longer) whereas the OS was reduced. As such, the submitted ICER of romidepsin versus pralatrexate is overestimated. The model allowed the EGP to perform several re-analyses. HRs of PFS and OS had a high impact on ICER. Additionally, only parametric curves have been used to estimate PFS and OS of pralatrexate. The EGP noted that the graphical representation provided by the submitter showed that all these parametric models overestimate the KM curve from PROPEL trial, and none of these were really good fits. The EGP considered that the extrapolation of clinical benefits using these parametric curves is highly uncertain. For this reason the EGP conducted several re-analyses on the extrapolation parametric curves (log-logistic and Gompertz, which have the 2nd and 3rd smallest value of AIC criteria), as well as on reducing the clinical benefit of pralatrexate. These have a high impact on the total cost of pralatrexate, and respectively the cost difference between pralatrexate and romidepsin. The EGP noted that as the model is built on the HRs of PFS and OS equal to 1, the survival difference (QALYs and LYs) was not impacted by these scenarios.

A third key assumption that has the most impact on the results of the economic evaluation is the time horizon. Considering the natural history of disease and the fact that the maximum period of observation from the PROPEL trial was two years, and all the uncertainties related with the survival benefits of pralatrexate compared to BSC and romidepsin, the 10-year time horizon was considered excessive by both CGP and EGP. The model allowed EGP to perform several re-analyses. Time-horizon had a high impact on ICER.

Finally, another key assumption that has an important impact of the economic evaluation is the drug wastage. Since the number of patients receiving this treatment during the same day will be very small, vial sharing is unlikely to happen. The EGP conducted several re-analyses including pralatrexate wastage, which has an important impact on the incremental cost of pralatrexate compared to both BSC and romidepsin groups, and the ICER, respectively.

The following re-analyses have been performed by varying components of the model that were significant drivers of either the incremental effect or the incremental cost, such as clinical benefit after the 2-year trial period, clinical benefit of pralatrexate compared to romidepsin, time-horizon, duration of treatment, drug wastage and survival extrapolation method.

1. The EGP noted that in the submitted model the time horizon of 10 years was considered excessive for this population with a median survival of approximately 10 months. In addition, because of the main assumption of this model, such as the observed survival benefit maintained after the trial period and in an absence of a comparator group evaluated over the PROPEL trial, a shorter time horizon periods were assessed to decrease the impact of this assumption.
2. An important uncertainty was identified by the EGP in relation with the actual clinical benefit between pralatrexate and BSC, several re-analyses were performed with a reduced clinical benefit of 15%, 25% and 50% applicable after the 2-year trial period. These are equivalent to a HR of the pralatrexate compared to BSC of 0.5, 0.58 and 0.85. The base case was based on a HR of 0.43 which was maintained after the 2-year trial period.
3. A re-analysis was performed to assess impact of OS and PFS extrapolation methods.
4. The scenario submitted in relation to romidepsin was based on HRs of OS and PFS which were non statistically significant. The EGP performed two re-analyses using HR for OS and

PFS equal to 1. As expected no difference was observed in term of clinical benefit, with a slight difference in terms of overall costs, which favors either pralatrexate or romidepsin depending on the parametric model used. This difference in cost can be negligible and considered random error, as such pralatrexate and romidepsin can be considered equivalent in term of both survival and costs.

5. Fixed consumption of pralatrexate as well as drug wastage were tested in re-analyses.
6. As utilities were derived from the literature, and not observed within the PROPEL trial, a re-analysis was performed to test the impact of utility values on ICER.
7. Finally, both CGP and EGP agreed that the most relevant comparator is romidepsin as it is currently the standard of care. Based on the submitted ITC both pralatrexate and romidepsin demonstrated equivalent clinical benefits. The submitted model presents the option of HRs of PFS and OS equal to 1. This option was considered by the EGP in all re-analyses of this comparator. As such some re-analyses were conducted by the EGP in relation with the parametric curves used to extrapolate pralatrexate clinical benefits and a reduction of clinical benefit of pralatrexate. Parametric curves used to estimate OS and PFS of pralatrexate were log-logistic and Gompertz which have the 2nd and 3rd smallest value of AIC criteria.

The Submitter provided feedback in response to the pERC Initial Recommendation noting that they disagree with the EGP's best estimate in reducing the clinical benefit beyond 2 years while maintaining an assumed high cost for pralatrexate due to long-term treatment as per the modelled PFS. The Submitter noted that if the assumption that the benefit beyond 2 years for pralatrexate is reduced by 50%, then the treatment duration for pralatrexate should not exceed that observed in the clinical trial. This scenario was considered by the EGP (using 38 vials based on the median duration of treatment in the PROPEL trial) and the associated ICER (pralatrexate versus BSC was $240,758/ QALY (deterministic) over a 5 year time horizon. Therefore, the Submitter suggested that the best estimate ICER would not be closer to the upper bound estimated by the EGP; rather it would be closer to the mid-point between the lower and upper bounds.

In response to the feedback provided the by the Submitter, the EGP agreed with the Submitter's comment regarding the cost of pralatrexate in the scenario analysis with a reduced clinical benefit of 50% beyond 2 years (trial duration). The EGP notes that the PE model provided has the option to assume that patients will receive treatment with pralatrexate for a maximum of 2 years. As such, the EGP used this option when conducting the re-analysis on the clinical benefits decreased by 50% after the 2 year trial period. The EGP re-analysis estimates are in Tables 2a and 2b. However, the EGP disagreed with the Submitter's suggestion that the estimate of the cost of pralatrexate should be based on the median duration of treatment in the PROPEL trial (i.e., 38 vials), as this does not correlate with the PFS modeled by the parametric models. However, the EGP notes that this option was considered in the EGP's lower bound ICER estimate.

Table 2a. Submitted Base Case and EGP Reanalysis Estimates pralatrexate versus BSC (Deterministic)

Estimates	Submitted Comparator: BSC	EGP Reanalysis: Lower bound	EGP Reanalysis: Upper Bound
ICER estimate ($/QALY), range/point	$254,022/QALY	$200,514/QALY	$394,302/QALY
ΔE (QALY), range/point	0.49	0.40	0.26
ΔE (LY), range/point	0.74	0.47	0.37
ΔC ($), range/point	$124,836	$79,320	$102,239

*Submitter's estimates are based on probabilistic analyses

Table 2b. Submitted Base Case and EGP Reanalysis Estimates pralatrexate versus BSC (Probabilistic, 5000 iterations)

Estimates	Submitted Comparator: BSC	EGP Reanalysis: Lower bound	EGP Reanalysis: Upper Bound
ICER estimate ($/QALY), range/point	$254,022/QALY	$189,133/QALY	$479,307/QALY
ΔE (QALY), range/point	0.49	0.42	0.21
ΔC ($), range/point	$124,836	$80,116	$101,866

Table 3a: Submitted Scenario Analysis and EGP Reanalysis pralatrexate versus romidepsin Estimates (Deterministic)

Estimates	Submitted Comparator: Romidepsin	EGP Reanalysis
ICER estimate ($/QALY), range/point	Dominant	Dominated
ΔE (QALY), range/point	0.06 and 0.22	-0.01
ΔE (LY), range/point	0.25 and 0.48	0
ΔC ($), range/point	-$40,779 and -$24,496	-$9,526 to $81,683

*Submitter's estimates are based on probabilistic analyses

Table 3b: Submitted Scenario Analysis and EGP Reanalysis pralatrexate versus romidepsin Estimates (Probabilistic, 5000 iterations)

Estimates	Submitted Comparator: Romidepsin	EGP Reanalysis
ICER estimate ($/QALY), range/point	Dominant	Dominated
ΔE (QALY), range/point	0.06 and 0.22	-0.01
ΔC ($), range/point	-$40,779 and -$24,496	-$8,968 to $152,694

Table [4a]: Detailed Description of EGP Reanalysis (Deterministic)				
	ΔC	ΔE	ICER /QALY	Δ from baseline submitted ICER
Baseline (Submitter's best case) comparator BSC*	$124,836	0.49	$254,022	--
LOWER BOUND (BSC comparator)				
5y time horizon	$117,185	0.44	$263,400	$9,378
15% reduction of the clinical benefit after 2y (trial duration)	$120,394	0.43	$281,779	$27,757
Fixed duration of Pralatrexate of 38.1 vials	$80,343	0.51	$158,951	-$5,071
Best case estimate of above 3 parameters	$79,320	0.40	$200,514	-$53,508
UPPER BOUND (BSC comparator)				
5y time horizon	$117,185	0.44	$263,400	$9,378
*50% reduction of the clinical benefit after 2y (trial duration)^*	$112,854	0.24	$460,994	$206,971
Equal utilities in pre-progression state (0.746)	$123,626	0.48	$256,562	$2,540
Best case estimate of above 3 parameters	$102,239	0.26	$394,302	$140,280
Romidepsin comparator				
Baseline (Submitter's best case) comparator romidepsin (MAIC HRs)	-$40,779	0.06	Dominant	--

Baseline (Submitter's best case) comparator romidepsin (naïve HRs)	-$24,496	0.22	Dominant	--
LOWER BOUND (romidepsin comparator)				
HRs for both PFS and OS equal to 1	-$5,495	-0.01	-	
HRs for both PFS and OS equal to 1 and parametric PFS and OS curves log-logistic	$6,160	-0.01	Dominated	
HRs for both PFS and OS equal to 1 and 50% reduction of clinical benefits of pralatrexate	-$15,828	-0.01	-	
Best case estimate of above 3 parameters	-$9,526	-0.01	-	
UPPER BOUND (romidepsin comparator)				
HRs for both PFS and OS equal to 1 and parametric PFS and OS curves Gompertz	$81,683	-0.01	Dominated	
HRs for both PFS and OS equal to 1 and 15% reduction of clinical benefits of pralatrexate	-$8,595	-0.01	-	
Best case estimate of above 2 parameters	$65,300	-0.01	Dominated	

*Submitter's estimates are based on probabilistic analyses
^Under the option that all patients will stop treatment with pralatrexate after 2 years.

Table [4b]: Detailed Description of EGP Reanalysis (Probabilistic, 5000 iterations)				
	ΔC	ΔE	ICER /QALY	Δ from baseline submitted ICER
Baseline (Submitter's best case) comparator BSC	$124,836	0.49	$254,022	--
LOWER BOUND (BSC comparator)				
5y time horizon	$125,678	0.50	$252,081	-$1,941
15% reduction of the clinical benefit after 2y (trial duration)	$122,365	0.42	$294,083	$40,061
Fixed duration of Pralatrexate of 38.1 vials	$80,318	0.50	$161,739	-$92,283
Best case estimate of above 3 parameters	$80,116	0.42	$189,133	-$64,889
UPPER BOUND (BSC comparator)				
5y time horizon	$125,678	0.50	$252,081	-$1,941
*50% reduction of the clinical benefit after 2y (trial duration)^*	$102,051	0.23	$439,112	$185,090
Equal utilities in pre-progression state (0.746)	$125,028	0.48	$259,482	$5,460
Best case estimate of above 3 parameters	$101, 866	0.21	$479, 307	$225,285
Romidepsin comparator				

Table [4b]: Detailed Description of EGP Reanalysis (Probabilistic, 5000 iterations)				
	ΔC	ΔE	ICER /QALY	Δ from baseline submitted ICER
Baseline (Submitter's best case) comparator romidepsin (MAIC HRs)	-$40,779	0.06	Dominant	--
Baseline (Submitter's best case) comparator romidepsin (naïve HRs)	-$24,496	0.22	Dominant	--
LOWER BOUND (romidepsin comparator)				
HRs for both PFS and OS equal to 1	-$3,875	-0.01	-	
HRs for both PFS and OS equal to 1 and parametric PFS and OS curves log-logistic	$7,213	-0.01	Dominated	
HRs for both PFS and OS equal to 1 and 50% reduction of clinical benefits of pralatrexate	-$15,154	-0.01	-	
Best case estimate of above 3 parameters	-$8,968	-0.01	-	
UPPER BOUND (romidepsin comparator)				
HRs for both PFS and OS equal to 1 and parametric PFS and OS curves Gompertz	$187,827	-0.01	Dominated	
HRs for both PFS and OS equal to 1 and 15% reduction of clinical benefits of pralatrexate	-$7,412	-0.01	-	
Best case estimate of above 2 parameters	$152,694	-0.04	Dominated	

^Under the option that all patients will stop treatment with pralatrexate after 2 years.

1.4 Evaluation of Submitted Budget Impact Analysis

The budget impact analysis (BIA) was based on the projected number of patients in Ontario who would be expected to start pralatrexate for the treatment of relapsed or refractory PTCL. The factors that most influence the BIA include: number of patients eligible to be treated with pralatrexate and the extent of market expansion.

In conclusion, the submitted BIA is 4 to 5 times lower than the EGP's BIA reanalysis estimates and is mainly due to the underestimation of the projected market share of pralatrexate. It should be noted that no source of data was referred to support the submitter's market share distribution. Finally, the submitter conducted several one-way sensitivity analyses, which demonstrated similar results as in the submitted BIA base-case analysis.

1.5 Conclusions

The EGP's best estimate of ICUR for Pralatrexate when compared to BSC is:

- Between $200,514/QALY and $394,302/QALY (deterministic) or $189,133/QALY and $479,307/QALY (probabilistic). The EGP further notes that this range is due to the uncertainty in the magnitude of long term benefit.

- Within this range of ICUR, the best estimate would likely be $394,302/QALY (upper bound deterministic) or $479,307/QALY (probabilistic), corresponding to the scenario of 50% reduction of the clinical benefits after 2 years (trial duration) and equal utilities in pre-progression state, over a 5-year time horizon. This estimate is obtained under the assumption that no patients will receive pralatrexate after 2 years.

- The EGP anticipates that the ICER is likely to be higher because of the wastage that will be probably incurred, as vials sharing is unlikely, since the number of patients receiving this treatment during the same day will be very small.

- The extra cost of pralatrexate is between $79,320 and $102,239 (deterministic) or $80,116 and $101,866 (probabilistic). The factor that most influences the costs is fixed duration of pralatrexate versus until disease progression.

- The extra clinical effect of pralatrexate is between 0.26 QALY to 0.40 QALY (deterministic) or 0.21 QALY to 0.42 QALY (probabilistic). The factors that most influence the incremental clinical benefit is the maintenance or not of the clinical benefit after the 2-year trial duration, the time horizon and the survival extrapolation methods used.

The EGP's best estimate of the economic analysis of Pralatrexate when compared to romidepsin is:

- The clinical benefits are equivalent at slightly different costs.

- In several re-analyses, pralatrexate was dominated by romidepsin, yet these results should be interpreted with caution as many of the assumptions present great uncertainty.

- The EGP anticipates that if a higher wastage will occur for pralatrexate, pralatrexate will most probably be dominated by romidepsin.

Overall conclusions of the submitted model:

Due to the nature of the PROPEL trial, which is a phase II, single-arm, non-randomized, open-label trial, the comparator group was absent. The main analysis was conducted using a historical control cohort of the comparator group (BSC group). Following the Provincial Advisory Group's request for a comparison of pralatrexate to romidepsin, the submitter performed a scenario analysis using romidepsin as a comparator group. Both CGP and EGP agreed on the fact that the most appropriate comparator group is romidepsin, as this represents the current standard of care for this population. Despite the fact that the submitted model included many appropriate assumptions and an extensive set of sensitivity analysis on BSC group comparator, it included only a limited number of scenarios that could be applicable to romidepsin. As such the EGP was limited in term of the re-analyses that could be performed.

An important driver in this economic evaluation was the comparator group. Mainly, the long-term benefit of pralatrexate relative to the BSC comparator group is uncertain and cannot reasonably be estimated. However, the submitted model allowed the EGP to evaluate the impact of the factors (time horizon, projected clinical benefits and extrapolation parametric curves) contributing to long term benefit. Other important factors related with the cost of pralatrexate were the duration of pralatrexate treatment and drug wastage. The submitted model allowed the EGP to explore their impact on ICER.

2 DETAILED TECHNICAL REPORT

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in Section 1. Pursuant to the pCODR Disclosure of Information Guidelines, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.

3 ABOUT THIS DOCUMENT

This Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lymphoma/Myeloma Clinical Guidance Panel and the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding resource implications and the cost-utility of Pralatrexate for patients with recurrent or metastatic, squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum therapy. A full assessment of the clinical evidence of pralatrexate compared with alternative treatments is beyond the scope of this report and is addressed by the relevant pCODR Clinical Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Economic Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no information redacted from this publicly available Guidance Report.

This Initial Economic Guidance Report is publicly posted at the same time that a pERC Initial Recommendation is issued. A Final Economic Guidance Report will be publicly posted when a pERC Final Recommendation is issued. The Final Economic Guidance Report will supersede this Initial Economic Guidance Report.

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.cadth.ca/pcodr). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

REFERENCES

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