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.

The pCODR Expert Review Committee (pERC) recommends funding pemetrexed (Alimta) as a maintenance treatment following first-line treatment with pemetrexed plus cisplatin in patients with advanced or metastatic non-squamous non-small cell lung cancer (NS-NSCLC) conditional on its cost-effectiveness being improved to an acceptable level. Funding should be for patients who achieved stable disease or better with 4 cycles of induction pemetrexed plus cisplatin and with an ECOG performance status of 0 or 1 after induction therapy. The Committee made this recommendation because it was satisfied that there is a net clinical benefit of pemetrexed in this setting based on an improvement in progression-free survival and overall survival. However, at the submitted price, pemetrexed could not be considered cost-effective compared with no maintenance therapy.

Pricing Arrangements to Improve Cost-Effectiveness
Given pERC was satisfied there is a net clinical benefit of pemetrexed plus cisplatin as a maintenance treatment following first-line treatment with pemetrexed plus cisplatin in patients with advanced or metastatic NS-NSCLC, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of pemetrexed to an acceptable level. pERC noted that jurisdictions need to consider the impact of vial size and wastage since pemetrexed is priced per vial, not per milligram and as such, actual use in clinical practice may significantly increase costs.
SUMMARY OF pERC DELIBERATIONS

pERC noted that the burden of lung cancer is large. Most patients with lung cancer will have non-small cell lung cancer (NSCLC) and a large proportion of these will be non-squamous. pERC noted that options for maintenance treatment following first-line induction with pemetrexed plus cisplatin include erlotinib or close monitoring until disease progression occurs and second-line treatment is started. pERC further discussed that the scope of the pCODR review was limited to the requested funding for the use of pemetrexed maintenance therapy after first-line induction with pemetrexed plus cisplatin. While platinum-based doublets are considered the standard first-line induction treatment, pERC noted that doublets other than pemetrexed plus cisplatin exist and are more widely accessible. This recommendation does not address the issue of maintenance therapy in jurisdictions where pemetrexed plus cisplatin is not used as the first-line induction therapy. The pCODR systematic review included one randomized controlled trial, the PARAMOUNT study (Paz-Ares 2012 and 2013), which compared pemetrexed maintenance therapy with no maintenance therapy, after all patients received induction with pemetrexed plus cisplatin. pERC considered this to be an appropriate comparison as the pCODR Clinical Guidance Panel indicated that observation until disease progression and second-line treatment is an acceptable treatment strategy.

pERC deliberated on the net clinical benefit of maintenance pemetrexed following first-line pemetrexed plus cisplatin and concluded that there is a net clinical benefit. pERC noted that there was a statistically significant benefit in progression-free survival and overall survival favouring pemetrexed in the PARAMOUNT study. However, pERC noted that the magnitude of progression-free survival benefit observed was modest. pERC also noted that although the study was well-conducted, few patients in the placebo group crossed-over to receive subsequent pemetrexed after they had progressed. Therefore, pERC could not determine the benefit of using pemetrexed as a second-line treatment strategy rather than as a maintenance treatment strategy. Despite these factors, pERC considered pemetrexed to be an effective treatment in this setting.

pERC reviewed information on adverse events from the PARAMOUNT study and concluded that they were consistent with the known toxicity profile of pemetrexed and that the safety of pemetrexed was acceptable for these patients. However, pERC noted that to receive maintenance therapy in the PARAMOUNT study, patients must have had an ECOG performance status of 0 or 1 following induction with four cycles of pemetrexed plus cisplatin and there may not be a large proportion of patients meeting these eligibility criteria due to the toxicities of first-line therapy.

pERC reviewed input from patient advocacy groups and determined that maintenance pemetrexed aligns with patient values when used after first-line pemetrexed plus cisplatin. pERC noted that patients were seeking tolerable treatments that provide longer and better symptom and disease control. Therefore, pERC determined that based on the efficacy and safety of pemetrexed observed in the PARAMOUNT study, pemetrexed aligns with these patient values.

pERC deliberated on the cost-effectiveness of maintenance pemetrexed following first-line pemetrexed plus cisplatin. pERC noted that the cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were higher than the manufacturer’s estimates primarily due to modeling a shorter time horizon (5 years versus 9 years), using a more accurate price of pemetrexed and removal of the half-cycle correction from the model as described in the Economic Guidance Report. The EGP noted that the manufacturer assumed that the price of the 100 mg vial of pemetrexed is one-fifth the price of the 500 mg vial; however, the actual cost of the 100 mg vial is higher. Overall, pERC considered that the structure of the submitted economic model to be reasonable and was satisfied that the EGP was generally able to adjust the time horizon and drug costs. Therefore, pERC accepted the EGP’s best estimates and concluded that pemetrexed was not cost-effective at the submitted price.
pERC considered the feasibility of implementing a recommendation for maintenance pemetrexed following first-line pemetrexed plus cisplatin. pERC noted that the current funding recommendation would be most relevant for provinces that already fund pemetrexed plus cisplatin in the first-line setting. pERC considered that the budget impact of funding maintenance pemetrexed could be high in other provinces, if additional funding were required for pemetrexed plus cisplatin as a first-line treatment. pERC further noted that an assessment of pemetrexed as a first-line treatment was outside the scope of this pCODR review and because pERC did not review the evidence for pemetrexed as a first-line treatment, pERC was unable to comment further. pERC also noted that this recommendation is not generalizable to settings where other first-line therapies such as gemcitabine plus cisplatin are used. Furthermore, the budget impact of pemetrexed is influenced by potential wastage and the choice of vial size as pemetrexed is not priced per milligram.

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
- input from two patient advocacy groups (Canadian Cancer Survivor Network and Lung Cancer Canada)
- 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 (Eli Lilly Canada)

The pERC initial recommendation was to fund pemetrexed (Alimta) as a maintenance treatment following first-line treatment with pemetrexed plus cisplatin in patients with advanced or metastatic non-squamous non-small cell lung cancer (NS-NSCLC) conditional on its cost-effectiveness being improved to an acceptable level. 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 pCODR review evaluated the safety and efficacy of pemetrexed for patient outcomes compared to standard therapies or placebo in the continuation of maintenance treatment for patients with locally advanced or metastatic non-squamous, non-small cell lung cancer who received pemetrexed and cisplatin as first-line treatment.

Studies included: one randomized controlled trial

The pCODR systematic review included one double-blind randomized controlled trial (RCT), PARAMOUNT (Paz-Ares 2012 and 2013) which compared pemetrexed plus best supportive care to placebo plus best supportive care for the maintenance treatment of patients with advanced (locally advanced or metastatic) non-squamous, non-small cell lung cancer (NSNSCLC). pERC considered this to be an appropriate comparison as the pCODR Clinical Guidance Panel indicated that observation until disease progression and the introduction of second-line treatment is an acceptable treatment strategy.

All patients in the PARAMOUNT study received induction treatment with four cycles of pemetrexed plus cisplatin. For patients randomized to receive maintenance therapy following induction, pemetrexed was administered at a dose of 500 mg/m² IV every three weeks until disease progression.
Patient populations: ECOG performance status 0 or 1 following induction
The PARAMOUNT study included patients who had an ECOG performance status 0 or 1 prior to the start of first-line induction treatment with pemetrexed plus cisplatin. However, pERC also noted that only those who achieved at least stable disease and had an ECOG performance status of 0 or 1 following induction with four cycles of pemetrexed plus cisplatin received maintenance therapy and there may not be a large proportion of patients meeting these criteria due to toxicities of first-line therapy. Upon review of feedback from pCODR’s Provincial Advisory Group on the practical implications of only using pemetrexed in patients with an ECOG status greater than 1 following induction, it was noted that in the absence of data to support use of pemetrexed in patients with ECOG performance status greater than 1 following induction, pERC was unable to extend the recommendation to use in a broader patient population.

Key efficacy results: improvement in progression-free survival and overall survival
Key efficacy outcomes deliberated on by pERC included investigator assessed progression free survival (PFS), the primary outcome of the PARAMOUNT study, and overall survival. At the March 2012 analysis, the median PFS was 4.1 months versus 2.8 months (HR: 0.62, 95% CI, 0.49 to 0.79) in the pemetrexed maintenance arm compared to the no maintenance arm, respectively. pERC considered that the magnitude of the observed progression-free survival benefit was modest. However, an improvement in overall survival favouring pemetrexed maintenance was also observed. The median overall survival was 13.9 months versus 11.0 months (HR: 0.78, 95% CI, 0.64 to 0.96, P = 0.0199) in the pemetrexed maintenance group and no maintenance group, respectively. pERC discussed that although a 3 month survival benefit favouring the pemetrexed group was observed, this may have been due to differences in the use of subsequent therapies. pERC noted that few patients in the placebo group crossed-over to receive subsequent pemetrexed after they had progressed. Therefore, pERC could not determine the benefit of using pemetrexed as a second-line treatment strategy rather than as a maintenance treatment strategy. Despite this, pERC considered pemetrexed to be an effective maintenance treatment following first-line pemetrexed plus cisplatin.

Quality of life: similar between pemetrexed maintenance and no treatment
In the PARAMOUNT study, quality of life was measured using the EuroQol 5-dimensional scale (EQ-5D). When measured at end of treatment, similar declines in quality of life were observed in both the pemetrexed maintenance and no maintenance groups, indicating that pemetrexed does not appear to have a negative impact on quality of life.

Safety: acceptable toxicity and consistent with known adverse events
pERC reviewed information on adverse events from the PARAMOUNT study. Serious adverse events (25% vs. 14%, respectively), adverse events (82% vs. 67%, respectively) and withdrawals due to adverse events (18% vs. 7%) were higher for pemetrexed maintenance compared with no maintenance. At the cut-off date March 5, 2013, more patients receiving pemetrexed maintenance compared with no maintenance reported serious adverse events including anemia (2.5% vs. 0%, respectively), fatigue (0.8% vs. 0.6%, respectively) and febrile neutropenia (1.7% vs. 0%, respectively). Common possible drug-related adverse events in the pemetrexed maintenance versus no maintenance groups included fatigue (22% vs. 12%, respectively), anemia (18.1% vs. 5%, respectively), and neutropenia (11% vs. 0.6%, respectively). pERC noted that the adverse events observed were consistent with the known toxicity profile of pemetrexed and concluded that the safety of pemetrexed was acceptable for these patients.

Need: limited need if first-line pemetrexed plus cisplatin is not available
Lung cancer remains the leading cause of cancer-related deaths globally. It is estimated that in 2013 there will be 25,500 new cases and 20,200 lung cancer associated deaths in Canada. pERC noted that the burden of lung cancer is large. Most patients with lung cancer will have non-small cell lung cancer (NSCLC) and a large proportion of these will be non-squamous.

Maintenance therapy following induction with four cycles of a platinum-based doublet has been shown to improve progression-free survival. However, the benefit of maintenance erlotinib and pemetrexed appears to be restricted to those with a good performance status following induction chemotherapy, and a best response of stable disease or better. pERC noted that options for maintenance treatment following first-line induction with pemetrexed plus cisplatin include erlotinib or close monitoring until disease progression occurs and second-line treatment is started. pERC further discussed that the scope of the pCODR review was limited to the requested funding for the use of pemetrexed maintenance therapy after first-line induction with pemetrexed plus cisplatin. While platinum-based doublets are standard first-line
induction treatment, pERC noted that doublets other than pemetrexed plus cisplatin exist and are more widely accessible. This recommendation does not address the issue of maintenance therapy in jurisdictions where pemetrexed plus cisplatin is not used as the first-line induction therapy.

PATIENT-BASED VALUES

Values of patients with NS-NSCLC: improvements of a few months meaningful
pERC reviewed input from patient advocacy groups. Input indicated that patients have significant symptom burdens including cough, shortness of breath, pain and fatigue, which adversely affect their daily functioning. Patients also indicated that modest improvements of a couple of months are generally considered to be important gains to patients due to the relatively short survival of patients with advanced NS-NSCLC. Therefore, although pERC noted that the improvement in median progression-free survival observed in the PARAMOUNT study was modest (approximately 1.3 months), this gain may be meaningful for patients. In addition, a 2.9 month improvement in median overall survival was observed, which patients consider meaningful. Therefore, based on the improved efficacy observed in the PARAMOUNT study, pERC considered that pemetrexed maintenance therapy aligns with patient values when used after first-line pemetrexed plus cisplatin.

Patient values on treatment: minimizing side effects of treatment
Patient advocacy group input indicated that patients expect new treatments to be better able to control symptoms, stop disease progression, minimize side effects and reduce hospital visits. pERC discussed that there were only a small number of patients providing input who had experience with pemetrexed and it is unknown how many of these patients would have received pemetrexed as a maintenance therapy. pERC noted that pemetrexed is a tolerable treatment with a known side effect profile and the adverse events observed in the PARAMOUNT study were consistent with this. Patient input also noted that most of the adverse events with pemetrexed were considered acceptable because the drug delayed disease progression. Therefore, pERC considered that pemetrexed aligns with the patient value of minimizing side effects. Patient input noted that the use of pemetrexed plus cisplatin as a first-line therapy may require fewer hospital visits than the use of gemcitabine plus cisplatin as a first-line therapy; however, a review of first-line therapies was outside the scope of this pCODR review.

ECONOMIC EVALUATION

Economic model submitted: cost-effectiveness and cost-utility
The pCODR Economic Guidance Panel assessed a cost-effectiveness analysis and cost-utility analysis that compared pemetrexed plus best supportive care to placebo plus best supportive care as maintenance therapy following induction chemotherapy with four cycles of pemetrexed and cisplatin for patients with advanced or metastatic non-squamous, non-small-cell lung cancer (NS-NSCLC). The patient population reflects patients from the PARAMOUNT trial (Paz-Ares et al. 2012 and 2013).

Basis of the economic model: clinical and economic inputs
Costs considered in the analysis included drug and drug administration costs, the costs of managing adverse events and costs associated with follow-up care, home care, and palliative care.

Key clinical effects considered in the analysis included drug and drug administration costs, the costs of managing adverse events and costs associated with follow-up care, home care, and palliative care.

Drug costs: choice of vial size and potential wastage may increase drug costs
At the list price, pemetrexed costs $514.80 and $2,145 per 100mg and 500mg vial, respectively. It was noted pemetrexed is not priced per milligram and the cost of 100 mg pemetrexed differs depending on whether the 100 mg vial or the 500 mg vial is used. Therefore, pERC considered that provinces will need to consider the impact of vial size and potential wastage since actual use in clinical practice could significantly increase costs.

Assuming use of the 500mg vial and no wastage, at the recommended dose of 500mg/m² on day 1 of every 21 day cycle, the average daily cost is $174 and the average cost per 28-day course is $4,862. Assuming use of the 100mg vial and no wastage, at the recommended dose of 500mg/m² on day 1 of every 21 day cycle, the average daily cost is $208 and the average cost per 28-day course is $5,834. Depending on how
much wastage occurs and if different combinations of vial sizes are used to try to minimize wastage, actual costs may differ in clinical practice.

Cost-effectiveness estimates: not cost-effective at the submitted price
pERC deliberated on the cost-effectiveness of maintenance pemetrexed following first-line pemetrexed plus cisplatin. pERC noted that the cost-effectiveness estimates provided by the pCODR Economic Guidance Panel (EGP) were higher than the manufacturer’s estimates primarily due to the use of a shorter time horizon, a more accurate price of pemetrexed and removing the half-cycle correction in their reanalysis, as described in the Economic Guidance Report. pERC noted that the EGP used a time horizon of 5 years based on input from the pCODR Clinical Guidance Panel compared with the manufacturer’s time horizon of 9 years. pERC agreed with the Panels that, based on the expected period of clinical benefits and the need to extrapolate short-term trial data over an extended period of time, a 5 year time horizon was reasonable. The EGP also noted that the manufacturer assumed that the price of the 100 mg vial of pemetrexed is one-fifth the price of the 500 mg vial; however, the actual cost of the 100 mg vial is higher. In addition, the EGP conducted the re-analysis by estimating wastage of 25mg to 75mg of pemetrexed as opposed to 5mg assumed by the manufacturer.

Overall, pERC considered that the structure of the submitted economic model was reasonable and that the EGP was generally able to make adjustments for the time horizon and drug costs. Therefore, pERC accepted the EGPs best estimates, which were between $170,272 per QALY and $173,864 per QALY when maintenance therapy with pemetrexed was compared to best supportive care. Consequently, pERC concluded that pemetrexed was not cost-effective at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: funding of first-line pemetrexed plus cisplatin
pERC considered the feasibility of implementing a recommendation for maintenance pemetrexed following first-line pemetrexed plus cisplatin. pERC noted that the current funding recommendation would be most relevant in those provinces that already fund pemetrexed plus cisplatin in the first-line treatment of locally advanced and metastatic non-squamous non-small cell lung cancer. pERC considered that the budget impact of funding maintenance pemetrexed could be higher in other provinces, if additional funding were required for pemetrexed plus cisplatin as a first-line treatment. pERC further noted that reviewing pemetrexed as a first-line treatment was outside the scope of this pCODR review and because pERC did not review the evidence for pemetrexed as a first-line treatment, pERC was unable to comment further. pERC also discussed that this recommendation could not be generalized to other first-line therapies, such as gemcitabine plus cisplatin.

In addition, for many patients receiving first-line pemetrexed plus cisplatin, close observation is an accepted clinical approach. Therefore, the introduction of pemetrexed maintenance may not replace another treatment for all patients and would be an add-on therapy for patients who previously would have received no treatment until disease progression.

pERC also noted that the budget impact of pemetrexed is influenced by wastage and the vial size used, as pemetrexed is not priced per milligram. It was noted that the budget impact analysis provided by the manufacturer underestimated the actual cost of the pemetrexed 100mg vial and potential wastage. Therefore, the budget impact is likely to be higher than the manufacturer’s estimate.
**DRUG AND CONDITION INFORMATION**

**Drug Information**
- Multi-targeted anti-folate drug
- 100mg and 500mg vials
- 500 mg/m² IV on day 1 every 21 days

**Cancer Treated**
- Maintenance treatment of patients with locally advanced or metastatic non-squamous, non-small cell lung cancer following first-line pemetrexed plus cisplatin

**Burden of Illness**
- Lung cancer remains the leading cause of cancer-related deaths globally.
- It is estimated that in 2013 there will be 25,500 new cases and 20,200 deaths associated with lung cancer in Canada.

**Current Standard Treatment**
- Best supportive care until disease progression
- Erlotinib

**Limitations of Current Therapy**
- Overall effectiveness of maintenance strategies uncertain

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**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. Bill Evans, Oncologist
Dr. Maureen Trudeau, Oncologist (Vice-Chair)  Dr. Allan Grill, Family Physician
Dr. Chaim Bell, Economist  Dr. Paul Hoskins, Oncologist
Dr. Scott Berry, Oncologist  Danica Lister, Pharmacist
Bryson Brown, Patient Member  Carole McMahon, Patient Member Alternate
Mario de Lemos, Pharmacist  Jo Nanson, Patient Member
Dr. Sunil Desai, Oncologist  Dr. Peter Yenner, Oncologist
Mike Doyle, Economist  Dr. Tallal Younis, Oncologist

All members participated in deliberations and voting on the initial recommendation except:
- Dr. Bill Evans who was not present for the meeting
- Carol 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 pemetrexed (Alimta) for non-squamous non-small cell lung cancer, through their declarations, seven 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 document.

Use of this recommendation
This recommendation from the pCODR Expert Review Committee (pERC) is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policymakers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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