PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Pemetrexed (Alimta) for Non-Squamous Non-Small Cell Lung Cancer

November 19, 2013

DISCLAIMER

Not a Substitute for Professional Advice

This report is primarily intended to help Canadian health systems leaders and policymakers make well-informed decisions and thereby improve the quality of health care services. While patients and others may use this report, they are made available for informational and educational purposes only. This report should not be used as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision making process, or as a substitute for professional medical advice.

Liability

pCODR does not assume any legal liability or responsibility for the accuracy, completeness or usefulness of any information, drugs, therapies, treatments, products, processes, or services disclosed. The information is provided "as is" and you are urged to verify it for yourself and consult with medical experts before you rely on it. You shall not hold pCODR responsible for how you use any information provided in this report.

Reports generated by pCODR are composed of interpretation, analysis, and opinion on the basis of information provided by pharmaceutical manufacturers, tumour groups, and other sources. pCODR is not responsible for the use of such interpretation, analysis, and opinion. Pursuant to the foundational documents of pCODR, any findings provided by pCODR are not binding on any organizations, including funding bodies. pCODR hereby disclaims any and all liability for the use of any reports generated by pCODR (for greater certainty, "use" includes but is not limited to a decision by a funding body or other organization to follow or ignore any interpretation, analysis, or opinion provided in a pCODR report).

FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

INQUIRIES

Inquiries and correspondence about the pan-Canadian Oncology Drug Review (pCODR) should be directed to:

pan-Canadian Oncology Drug Review
1 University Avenue, suite 300
Toronto, ON
M5J 2P1

Telephone: 416-673-8381
Fax: 416-915-9224
Email: info@pcodr.ca
Website: www.pcodr.ca

TABLE OF CONTENTS

1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The economic analysis **submitted to pCODR by Eli Lilly Canada Inc.** compared pemetrexed plus best supportive care (BSC) to placebo plus BSC as maintenance therapy following induction chemotherapy with four cycles of pemetrexed and cisplatin for patients with advanced or metastatic (Stage IIIb or IV) 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). Pemetrexed is administered intravenously. Current standard of care for maintenance therapy in Canada includes BSC.

According to the pCODR Clinical Guidance Panel (CGP), this comparison was appropriate.

Patient advocacy groups considered the following factors important in the review of pemetrexed, which are relevant to the economic analysis: improvement in patient quality of life and survival, a better side effects profile, convenience of use, and fewer treatment visits.

- The submitted economic evaluation explicitly considered quality of life by applying utility scores. The data on quality of life were collected directly from the patients who participated in the clinical trial. Survival data were also obtained from the clinical trial, and post-trial survival was estimated.
- Side effects were considered in the model.
- The model did not consider the impact of ease of use.
- The model did not consider patient time costs as it adopted the perspective of the publicly funded health care system, as is appropriate for pCODR, which must consider funding decision from this viewpoint.

The Provincial Advisory Group (PAG) considered that the following factors would be important to consider if implementing a funding recommendation for pemetrexed, and which are relevant to the economic analysis: the size of the eligible patient population and accessibility to treatment.

- The PAG believed that a funding recommendation for pemetrexed maintenance therapy would likely lead to an increase in the eligible patient population for 1st line therapy with pemetrexed as well. This scenario was considered in the budget impact analysis.
- The cost per mg of the 100mg vial is higher than that of the 500 mg vial, which may present barriers to implementation. This was not considered in the economic evaluation, nor was the difference in price of the two vial sizes.
- The PAG also noted that based on the treatment regimen used in the pivotal study (cisplatin + pemetrexed) it may be difficult to assess the use of pemetrexed in selected patients that are not able to receive cisplatin as the combination therapy. This was not accounted for in the model.

At the list price, pemetrexed cost $514.80 and $2145 per 100mg and 500mg vial, respectively. Assuming use of the 500mg vial, at the recommended dose of 500mg/m^2 on day 1 of every 21 day cycle, the average daily cost is $174 and the average cost per 28-day course is $4862. Assuming use of the 100mg vial, at the recommended dose of 500mg/m^2 on day 1 of every 21 day cycle, the average daily cost is $208 and the average cost per 28-day course is $5834. If wastage based on EGP estimates is taken into consideration, the average daily cost with the 500mg vial is $189 and the cost of a 28 day course is $3968,

and with the 100mg vial, the average daily cost and the cost of a 28 day course are $214 and $4505, respectively.

1.2 Summary of Results

The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $170,272 per QALY and $173,864/QALY when maintenance therapy with pemetrexed is compared to standard of care. This estimate is based on reanalyses conducted by the Economic Guidance Panel using the price for pemetrexed submitted by the manufacturer, the model submitted by Eli Lilly, as well as some additional analyses conducted by the manufacturer at the request of the Economic Guidance Panel. The ICER is likely even higher than the EGP's best estimates because the EGP best estimates were influenced by additional calculations obtained from the manufacturer that were based on a longer time horizon than that recommended by EGP (i.e. 5-year time horizon).

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The EGP's best estimate of:

- the extra cost of pemetrexed is between $37,460 and $38,250. Factors affecting costs included modelling assumptions, the price of pemetrexed, and assumptions regarding post-progression therapy.
- the extra clinical effect of pemetrexed is between 0.21 and 0.22 QALYs. The estimate of clinical effect is based on progression-free survival, overall survival, and utility values obtained from the PARAMOUNT trial (Paz-Ares et al. 2012; Paz-Arez et al. 2013)

The EGP based these estimates on the model submitted by Eli Lilly Canada Inc. and reanalyses conducted by the EGP as well as by the manufacturer. The assumption that the time horizon should be reduced was supported by the pCODR Clinical Guidance Panel. The reanalysis conducted by the EGP using the submitted model showed that when:

- the half-cycle correction for pemetrexed was removed, the extra cost of pemetrexed increases to $37,487, which increases the estimated incremental cost-effectiveness ratio.
- Post-progression therapy is assumed to be equal in the two groups, the extra cost of pemetrexed is $36,424, which increases the estimated incremental cost-effectiveness ratio.
- the time horizon is decreased from 9 years to 5 years, the extra clinical effect of pemetrexed is 0.22 QALYs, which increases the estimated incremental cost-effectiveness ratio.
- the price of the 100mg vial of pemetrexed is increased to $514.80 per unit, the extra cost of pemetrexed is $39,116, which increases the estimated incremental cost-effectiveness ratio. When a five-year time-horizon is also applied, the extra cost of pemetrexed is $38,342 and the extra clinical effect of pemetrexed is 0.22 QALYs, which increases the estimated incremental cost-effectiveness ratio.
- pCODR and EGP criteria for estimating drug costs as well as a five-year time horizon are applied, the extra cost of pemetrexed is between $36,486 and $36,881 and the extra clinical effect of pemetrexed is 0.22 QALYs, which increases the estimated incremental cost-effectiveness ratio.

The EGPs estimates differed from the submitted estimates. This was primarily due to different assumptions regarding time horizon, the use of the half-cycle correction for pemetrexed, the price of the 100mg vial of pemetrexed, and assumptions regarding the manner in which pemetrexed may be used (costing and wastage).

According to the economic analysis that was submitted by Eli Lilly Canada Inc., when pemetrexed is compared with placebo:

- the extra cost of pemetrexed is $36,396. Costs considered in the analysis included: drug and drug administration, adverse events, follow-up care, home care, and palliative care.
- the extra clinical effect of pemetrexed is 0.25 QALYs (0.33 Life-Years (Lys)). The clinical effect considered in the analysis was based on progression-free survival, overall survival, and utility estimates obtained from the PARAMOUNT trial (Paz-Ares et al. 2012; Paz-Arez et al. 2013)
- So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $143,261/QALY ($110,734/LY).

1.3 Summary of Economic Guidance Panel Evaluation

If the EGP estimates of ΔC, ΔE and the ICER differ from the Submitter's, what are the key reasons?

The manufacturer's submitted model assumed a 9-year time horizon. Based on reported estimates of survival in this population as well as opinion from the Clinical Guidance Panel, this time horizon was unlikely. A time horizon of 5 years was considered although thought to still be optimistic in this patient population. There were also differences in the pricing and costing of pemetrexed. In addition, the manufacturer's base case used a half-cycle correction for the cost of pemetrexed, which underestimated the cost of treatment.

Were factors that are important to patients adequately addressed in the submitted economic analysis?

Yes. Based on patient advocacy group input, patients considered survival, quality of life, and side-effects to be important factors in treatment, and these factors were considered in the economic model.

Is the design and structure of the submitted economic model adequate for summarizing the evidence and answering the relevant question?

Yes, the model structure was adequate.

For key variables in the economic model, what assumptions were made by the Submitter in their analysis that have an important effect on the results?

Key factors that have an important impact on results include the model time horizon, the half-cycle correction on the cost of pemetrexed, and the price and costing of pemetrexed. The estimated time horizon was not considered to be consistent with the prognosis of this patient group. The half-cycle correction made assumptions regarding the administration of

pemetrexed that did not reflect the way in which it is used in practice. The price of the 100mg vial of pemetrexed was underestimated. The ways in which the vials might be combined due to availability was not accounted for, and the potential wastage of pemetrexed was likely underestimated,

Were the estimates of clinical effect and costs that were used in the submitted economic model similar to the ones that the EGP would have chosen and were they adequate for answering the relevant question?

The utility data used were adequate and the EGP would have used similar data. Estimated survival was optimistic and greater than what would have been used by the EGP. Reanalysis by the EGP would have considered shorter time horizons that were more consistent with the prognosis for this patient group. Estimations of expected post-trial survival would have also considered different assumptions regarding the selection of time points for projection, as well as between-group differences in post-progression survival rates (NICE 2013), which likely overestimated the estimated lifetime horizon of nine years. There was an error in the pricing of pemetrexed in the manufacturer's model, as well as an underestimation in expected wastage of medication.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

Key variables in the budget impact analysis included British Columbia population data, the age-standardized incidence of NSCLC, the proportion of NSCLC being non-squamous metastatic disease, disease-specific mortality, the percentage of patients receiving chemotherapy as initial treatment, second-line regimens, current and projected estimated market share of pemetrexed and other chemotherapeutic agents, and drug costs (including wastage). One-way sensitivity analyses included varying the size of the eligible population, a lower percentage of patients surviving past first-line to receive maintenance therapy, the number of cycles for all maintenance therapies, the exclusion of wastage costs, and pessimistic and optimistic market share scenarios.

The manufacturer's model was most sensitive to the assumed market share of pemetrexed.

What are the key limitations in the submitted budget impact analysis?

A key limitation of the submitted budget impact analysis was an underestimate of the cost of pemetrexed 100mg, as well as an underestimate of potential wastage of the medication in actual use. The unit cost of a 100 mg vial of pemetrexed is given as $429.00 in the BIA. This price appears to be based on an estimated one-fifth of the cost of a 500 mg vial ($2145.00). The price of the 100 mg vial has been reported by the manufacturer to be $514.80 per unit. Furthermore, wastage is likely to be higher than that considered in the analysis, given pCODR's standard for BSA ($1.7m^2$ versus $1.79m^2$), assumptions regarding vial dosage combinations (two 500mg vials or nine 100mg vials versus one 500mg vial and four 100 mg vials), and utilization patterns in more remote areas where vial sharing is less likely. Given the higher unit cost of the 100mg vial and potential for greater wastage than that reported, the budget impact of the additional pemetrexed indication has likely been underestimated in this analysis.

1.5 Future Research

What are ways in which the submitted economic evaluation could be improved?

- Long-term clinical data to validate the projections and assumptions regarding post-trial survival
- Better flexibility in the model for estimating alternative drug utilization assumptions.

Is there economic research that could be conducted in the future that would provide valuable information related to pemetrexed?

Real-world Canadian data on the actual utilization of pemetrexed dosage formats and wastage, as well as on the factors that might influence usage patterns would be informative (e.g. availability, regional variations). In addition, given the large impact that assumptions regarding survival have on the estimates, longer or post-trial follow-up of patients on pemetrexed maintenance therapy would be useful.

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 Final Economic Guidance Report was prepared by the pCODR Economic Guidance Panel and supported by the pCODR Lung 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-effectiveness of pemetrexed (Alimta) for non-squamous non small cell lung cancer. A full assessment of the clinical evidence of pemetrexed (Alimta) for non-squamous non small cell lung cancer 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.pcodr.ca).

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 Final Economic Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Economic Guidance Report supersedes the Initial Economic Guidance Report. Note that no revisions were made in between posting of the Initial and Final Guidance Reports.

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.pcodr.ca). 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

Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009; 374:1432-1440

Greenhalgh J, McLeod C, Bagust A, Boland A, Fleeman N, Dundar Y, Oyee J, Dickson R, Davis H, Green J, McKenna E, Pearson M. Pemetrexed for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer. Health Technol Assess. 2010 Oct;14(Suppl. 2):33-9.

Klein R, Wielage R, Muehlenbein C, Liepa AM, Babineaux S, Lawson A, Schwartzberg L. Cost-effectiveness of pemetrexed for advanced nonsquamous non-small cell lung cancer. J Thorac Oncol. 2010;5:1263-1272.

Matter-Walstra K, Joerger M, Kühnel U, Szucs T, Pestalozzi B, Schwenkglenks M. Cost-effectiveness of maintenance pemetrexed in patients with advanced nonsquamous-cell lung cancer from the perspective of the Swiss health care system. Value Health. 2012 Jan;15(1):65-71.

National Institute for Health and Clinical Excellence. Lung Cancer (non small cell, non squamous) – pemetrexed (maintenance following pemetrexed and ciplastin) [ID489]: appraisal consultation 2 document. Avaialble at: http://www.nice.org.uk/guidance/index.jsp?action=article&o=64921. (Accessed September 29th, 2013).

Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012; 13:247-255

Paz-Ares L, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival resultsof the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus ciplastin for advanced nonsquamous non-small cell lung cancer. J Clin Oncol 2013;31:1-10.

Zeng X, Peng L, Li J, Chen G, Tan C, Wang S, Wan X, Ouyang L, Zhao Z. Cost-effectiveness of continuation maintenance pemetrexed after cisplatin and pemetrexed chemotherapy for advanced nonsquamous non-small-cell lung cancer: estimates from the perspective of the Chinese health care system. Clin Ther. 2013 Jan;35(1):54-65.