pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Everolimus (Afinitor) for pancreatic neuroendocrine tumours

August 30, 2012

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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.

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1 ECONOMIC GUIDANCE IN BRIEF

1.1 Background

The main economic analysis **submitted to pCODR by Novartis Pharmaceuticals Canada Inc.,** compared everolimus plus best supportive care to placebo plus best supportive care for patients with progressive, unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors (NETs). This patient population reflects patients from the RADIANT-3 trial (Yao et al. 2011). Everolimus is administered orally. Best supportive care included somatostatin analogues, proton-pump inhibitors for gastrinoma, diazoxide, pancrealipase and non-specific anti-diarrheals.

According to the pCODR Clinical Guidance Panel (CGP), this comparison was appropriate at time of submission, but with the recent approval of sunitinib for pNETs, the inclusion of sunitinib as a comparator would have been more appropriate. However, sunitinib was not included in the economic analysis.

Patient advocacy groups considered the following factors important in the review of everolimus, which are relevant to the economic analysis: improvement in a patient's quality of life and survival, treatment that will enable them to continue to work and maintain a normal life, and oral administration of everolimus. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

- The submitted economic analysis explicitly considered improvements in quality of life by applying utility scores and measuring outcomes in quality-adjusted life years. However, the quality of life information was not collected in the clinical trial and was not obtained from patients with pNETs; the quality of life information was based on indirect data from interviews with the UK general public and with UK patients with neuroendocrine tumours.
- The model has not considered whether everolimus will enable patients to return to work – the model adopts the perspective of the publicly funded health care system which is appropriate for pCODR because drug funding recommendations must be considered from a health system perspective.
- The benefits of oral administration could not be explicitly considered in the submitted analysis as it compares everolimus with placebo not an intravenous drug comparator.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for everolimus, and which are relevant to the economic analysis: differences between everolimus and sunitinib with respect to costs, treatment outcomes, side effect profile, and information on the sequential use of everolimus and sunitinib. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- A comparison of everolimus versus sunitinib was not considered by the manufacturer as sunitinib was not approved for this specific indication at the time of submission.
- Oral administration of everolimus was not explicitly considered in the submitted model as everolimus was compared with placebo, not intravenous treatments.
- Drug wastage with everolimus dosage reductions was not explicitly considered in the submitted model.

At the list price, everolimus costs $186.00 per 2.5 mg, 5 mg, or 10 mg tablets. At the recommended dose of 10 mg per day, the average cost per day in a 28-day course of everolimus is $186.00 and the average cost per 28-day course is $5,208. Sunitinib is available as 12.5 mg, 25 mg, and 50 mg capsules at a cost of $63.15, $126.30, and $252.61 respectively. At the recommended dose of 37.5 mg per day, the average cost per day in a 28-day course of sunitinib is $189.45 and the average cost per 28-day course is $5,305.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $165,129/QALY and $273,781/QALY when everolimus plus best supportive care is compared to placebo plus best supportive care. This estimate is based on reanalyses conducted by the Economic Guidance Panel and using the model submitted by Novartis Pharmaceuticals Canada Inc. It should be noted that the above estimates did not account for structural limitations identified in the submitted model; hence, the estimates may potentially be an underestimation of the actual incremental cost-effectiveness ratio.

The incremental cost-effectiveness ratio (ICER) was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔQALY or ΔLY). The Economic Guidance Panel's best estimate of:

- the extra cost (ΔC) of everolimus is between $69,538 and $78,696. Costs included drug costs and healthcare costs associated with routine follow-up for patients receiving active treatment, disease progression, routine health care resources involved in best supportive care and death. Costs associated with management of serious adverse events were also considered.
- the extra clinical effect (ΔQALY or ΔLY) of everolimus is between 0.254 QALYs (13.2 weeks) and 0.477 QALYs (28.4 weeks) or between 0.278 (14.5 weeks) and 0.635 (33.0 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from RADIANT-3 study (Yao et al., 2011), a randomized controlled trial comparing everolimus with placebo. The biggest influence on both QALYs and life years was the estimate of survival following tumour progression.

This range is based on Economic Guidance Panel reanalyses that assumed the model's time horizon to be shorter than the proposed lifetime time horizon modelled by the manufacturer. Given the model's limitation and the heavy reliance on extrapolation it was felt appropriate to consider more conservative options related to shorter time horizons. The assumption that the time horizon should be reduced was suggested by the pCODR Clinical Guidance Panel.

- The upper estimate of the range (ICER of $273,781) assumed that the time horizon of the model was reduced to 3 years (the approximate duration of the clinical trial) versus the 10 years modelled by the manufacturer. The extra costs associated with everolimus were $69,538 and the extra QALYs associated with everolimus were 0.254.
- The lower estimate of the range (ICER of $165,129) assumed that the time horizon of the model was reduced to 5 years (the expected duration of clinical benefit suggested by the pCODR Clinical Guidance Panel) versus the 10 years used by the manufacturer. The extra costs associated with everolimus were $78,696 and the extra QALYs associated with everolimus were 0.477.

- The estimates above represent the EGP's best estimates despite the model's inherent structural limitations that the EGP was incapable of addressing in the reanalyses. The EGP attempted to conduct a reanalysis where the mortality rate from cancer is a function of time and is influenced directly by the increasing proportion of patients in the post-progression state. However, the submitted model did not permit modifications to this risk value and thus it was difficult to assess any possible impact on the Submitter's cost and effect estimates.

The Economic Guidance Panel's estimates differed from the submitted estimates. This is primarily because in the submitted model, progression and survival are modelled independently; there is no direct assessment of a patient's risk of dying before tumour progression and a patient's risk of dying after tumour progression; it is implicitly assumed that a patient's risk for dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state; and that progression-free survival and overall survival were extrapolated using short term data (Yao et al. 2011). Therefore, in the Economic Guidance Panel reanalyses, when the time horizon was shortened to align with clinical data as suggested by the CGP which did not believe a survival benefit could be accrued beyond 5 years with this treatment, extra QALY gains for everolimus are lower and lead to a decrease in the extra healthcare-associated costs for everolimus. This occurs because a significant portion of life expectancy gain (>76%) is derived from extrapolated data not actual data in the model.

According to the economic analysis that was submitted by the manufacturer, when everolimus plus best supportive care was compared to placebo plus best supportive care:

- The extra cost (ΔC) of everolimus is $90,247. Incremental costs for everolimus are based on a model where survival and progression are modelled independently and assuming that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state, which the Clinical Guidance Panel considered as inappropriate.
- The extra clinical effect (ΔE) of everolimus is 0.807 QALYs or 1.174 life years gained (LYG). This was largely driven by the assumption that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state, which the CGP considered as inappropriate.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC/ΔE) was $111,805 per QALY or $76,841 per LYG.

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 key reasons for differences between the submitter's and Economic Guidance Panel's estimates relate to assumptions around model structure. The manufacturer submitted a model where survival and progression are modelled independently and where it is assumed that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state. As a result, a significant proportion of life expectancy gain (>76%) is derived from extrapolated data not actual data, biasing results in favour of everolimus by overestimating increases in the clinical effects for everolimus plus best supportive care versus placebo plus best supportive care. In other words, the model implicitly assumed that patients continued to benefit from the

drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The Clinical Guidance Panel determined that assuming such benefit effect may not be a realistic expectation and that survival benefits would not be anticipated beyond 5 years with this treatment based on the currently available information. The Economic Guidance Panel estimate is based on a reanalysis which assumed that the time horizon of the model was reduced to align with the short term data for progression free survival and overall survival. The manufacturer forecasts PFS and overall survival using 31 months (2.7 years) and 42 month (3.7 years) data.

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

Yes. Based on patient advocacy group input, patients considered the following factors important in the review of everolimus and which were relevant to the economic analysis: improvement in a patient's quality of life, treatment that will enable them to continue to work and maintain a normal life, and oral administration of everolimus. These factors were addressed in the economic analysis when possible and appropriate.

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

No. The manufacturer submitted a partitioned-survival analysis in which patients transitioned between four health states: stable disease, stable disease with adverse events; disease progression; and death. Transition rates between these health states were determined by progression-free survival and overall survival estimates from RADIANT- 3 study (Yao et al., 2011). However, in the submitted economic model, survival and progression are modelled independently and it is assumed that a patient's risk of dying is a function of time and is not influenced directly by the increasing proportion of patients in the post-progression state. As a result, a significant proportion of life expectancy gain (>76%) in the 10-year model is derived from extrapolated data not actual data, biasing results in favour of everolimus by overestimating increases in QALY gains.

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

In the submitted economic model, because survival and progression are modelled independently, there is no direct assessment of a patient's risk of dying before tumour progression and a patient's risk of dying after tumour progression. The pCODR Clinical Guidance Panel supported that these risks may differ. The submitter assumes that over a 10-year period a patient's risk of dying following tumour progression would be improved with everolimus even though treatment with everolimus would have been stopped early in the 10-year time period. The model implicitly assumed that patients continued to benefit from the drug as if there was carry-over beneficial effect of the drug even after tumour progression has occurred and the drug has been stopped. The time horizon of the data from the clinical trial, RADIANT-3 study is short (3.7 yrs) in comparison with the 10 year time horizon of the model. Based on the clinical data currently available and expected estimates of biological plausibility, the Clinical Guidance Panel suggested that it was unlikely there would be any survival benefit accrued beyond five years with this treatment. Therefore, assumptions around extrapolation using short term data could have a pronounced effect on clinical effect estimates. Overall, this has an impact on the cost-effectiveness estimates and the Economic Guidance Panel conducted reanalyses to address these limitations, which led to higher estimates of the ICER.

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 cost and utility data used were adequate and the EGP would have used similar data. However, estimates of the long term survival gains with treatment were uncertain due to an assumption relating to improved survival post progression and the Economic Guidance Panel would have used different clinical data which accounted for differences in risk of death before and after tumour progression. It is also worth noting that according to clinical trial data collected until February 2010, the ITT overall survival did not statistically significantly differ between everolimus and placebo [HR 1.05 (95% CI 0.71, 1.55)]. The median survival was not reached in either group at the time of the first interim analysis (February 2010), and it was reached only for the placebo group at the second interim analysis (February 2011); the median overall survival was 36.6 months among patients assigned to the placebo group. Estimates of overall survival might be confounded by the crossover of placebo patients, after disease progression, to open-label everolimus. Therefore, the rank-preserving structural failure time (RPSFT) method was introduced to adjust for the crossover which may have led to increase in survival benefit of everolimus. The RPSFT analysis estimated that survival time while receiving everolimus is lengthened by a factor of [redacted] (95% CI [redacted] to [redacted]). This cross-over adjustment results in a correction of the study HR from [redacted] (95% CI [redacted],[redacted]) to [redacted]([redacted] to [redacted]). *(Non-disclosable economic information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).* While the RPSFT corrections produced a greater signal for benefit in overall survival as seen in lower point estimate in the HR, this result was still not statistically significant.

1.4 Summary of Budget Impact Analysis Assessment

What factors most strongly influence the budget impact analysis estimates?

The manufacturer submitted a budget impact analysis that was not specific to any Canadian public drug plan which estimates of the increased costs for the three years subsequent to the listing of everolimus for pancreatic NETs. The key variables included in the manufacturer's budget impact analysis are: total population of Canada, prevalence of pancreatic NETs, proportion of cases that are unresectable or metastatic with well-differentiated disease, treatment cost, proportion of population covered by a provincial public drug plan, and the market share for those who are covered. The factors which most heavily influenced the budget impact analysis are the proportion of pancreatic NET patients eligible for public coverage, the proportion of these patients who would use everolimus if available rather than best supportive care, and the availability and displacement of sunitinib as a comparator for the same indication.

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

The model structure of the budget impact analysis was appropriate. The key limitations of the submitted budget impact analysis relate to the limited data to support the assumptions relating to the proportion of eligible patients who would be covered by a drug plan, the proportion of these patients who would take everolimus if available rather than best

supportive care, and the market share of everolimus if sunitinib was offered as a comparator for the same indication.

1.5 Future Research

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

An economic model which provides the opportunity to adjust the movement of patients from pre-tumour progression to post-tumour progression to death would have enabled more accurate estimation of cost-effectiveness estimates.

An analysis of survival following tumour progression would be necessary to populate the new model; however, the provided survival information by the manufacturer was incomplete and thus no analysis was available for this review. The uncertainty around model inputs in the new model could be addressed using standard health economic modeling methodologies such as deterministic or probabilistic sensitivity analysis (PSA). The results of the manufacturer-submitted PSA should be viewed with caution because of the noted inherent structural model limitations.

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

If everolimus becomes a standard treatment option for patients with pancreatic NETs, an assessment of effectiveness and cost-effectiveness of treatment sequences of everolimus including sunitinib in the treatment of unresectable locally advanced or metastatic would provide a more accurate reflection of real-world cost-effectiveness and may improve estimates of budget impact.

An indirect comparison of everolimus, sunitinib, and placebo was presented at the 2012 Gastrointestinal Cancers Symposium and is summarized in the pCODR Clinical Guidance Report. This could be used to inform future cost-effectiveness analyses.

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 Gastrointestinal 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 everolimus for pNETs. The Economic Guidance Report is one source of information that is considered in the pERC Deliberative Framework. The pERC Deliberative Framework is available on the pCODR website (www.pcodr.ca). A full assessment of the clinical evidence of everolimus for pNET 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*. Novartis Canada Inc., as the primary data owner, did not agree to the disclosure of some economic information, which was provided to pERC for their deliberations, and this information has been redacted in this 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. The Final Economic Guidance Report reflects revisions made to the Initial Economic Guidance Report following feedback from stakeholders on the Initial Recommendation.

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.

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