pCODR PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Economic Guidance Report

Sunitinib (Sutent) for pancreatic neuroendocrine tumours

May 3, 2012

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, it is 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 main economic analysis **submitted to pCODR by Pfizer Canada Inc.** compared sunitinib 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 Study A61811111 (Raymond et al., 2011). Sunitinib is administered orally. Best supportive care included analgesics, antidiarrheal agents, beta blockers, emmolients or protectives; concomitant use of somatostatin analogues was also considered a component of best supportive care for some patients.

According to the pCODR Clinical Guidance Panel (CGP), this comparison is appropriate, since there is currently no single standard of care for patients with pancreatic NETs.

Patient advocacy groups considered the following factors important in the review of sunitinib, which are 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 sunitinib. 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.
- The model has not considered whether sunitinib 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 sunitinib with placebo not an intravenous drug comparator.

The **pCODR Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for sunitinib, and which are relevant to the economic analysis: differences between sunitinib and everolimus with respect to costs and treatment outcomes and information on impact of sequential use of sunitinib and everolimus, potential impact of dose reductions of sunitinib, and the impact of oral administration of sunitinib, which could save chemotherapy unit resources and patient travel time to treatment centers. A full summary of Provincial Advisory Group input is provided in the pCODR Clinical Guidance Report.

- The Economic Guidance Panel noted that everolimus did not have a Health Canada indication for pancreatic NETs at the time of the pCODR submission and, therefore, was not considered in the submitted economic evaluation.
- Oral administration of sunitinib could not be considered in the submitted economic evaluation since the submitted analysis compares sunitinib with placebo and not an intravenous comparator.
- Sunitinib dose reductions were not explicitly considered in the submitted model. However, the Economic Guidance Panel noted that based on a one-way sensitivity

analysis, reducing only the sunitinib dose (and corresponding costs) would reduce the incremental cost-effectiveness ratio (ICER) for sunitinib plus best supportive care versus placebo plus best supportive care. Clinical data on the effectiveness of sunitinib at lower doses were not available to permit further analyses by the Economic Guidance Panel.

At the list price, sunitinib costs $126.30 per 25 mg capsule and $63.15 per 12.5 mg capsule. At the recommended dose of 37.5 mg per day, the average cost per day in a 28-day course of sunitinib is $189.46 and the average cost per 28 day course is $5,304.79.

1.2 Summary of Results

The Economic Guidance Panel's best estimate of the incremental cost-effectiveness ratio is between $204,559 and $268,055 per quality-adjusted life year (QALY), or between $120,052 and $156,539 per life year (LY) when sunitinib 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 Pfizer Canada Inc.

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 sunitinib is between $45,598 and $46,601.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 sunitinib is between 0.17 QALYs (8.8 weeks) and 0.23 QALYs (12.0 weeks) or between 0.29 (15.1 weeks) and 0.38 (19.8 weeks) life years. Key clinical effects included progression-free survival and overall survival estimates from Study A61811111 (Raymond et al., 2011), a randomized controlled trial comparing sunitinib with placebo. The biggest influence on both QALYs and life years was the estimate of survival following tumour progression.

In the manufacturer's submitted analysis, it was assumed that a patient's risk of death was the same both before and after tumor progression and that the benefits of sunitinib in improving survivial would continue after tumour progression when patients would no longer be taking sunitinib. The range of best estimates is based on Economic Guidance Panel reanalyses that assumed a patient's risk of death before tumour progression and the risk of death after tumour progression to be different. The EGP assumed the same mortality rate for patients after tumor progression regardless of initial therapy. Survival was assumed to be the same as in the manufacturer's base case model but for placebo only. We examined the impact of different assumptions related to increased mortality after tumour progression – i.e., the use of the odds ratio on the time dependent mortality rates. The assumption that mortality would increase after tumor progression was supported by the pCODR Gastrointestinal Clinical Guidance Panel.

- The upper estimate of the range assumed that the mortality after tumour progression is the same as mortality before tumour progression in patients who received placebo

(i.e. odds ratio = 1). In this analysis the mean survival after tumour progression is approximately equal to 13 months. The extra costs associated with sunitinib were $45,598 and the extra QALYs associated with sunitinib were 0.17, leading to an estimated ICER of $268,055.

- The lower estimate of the range was based on assuming increased mortality post progression based on the input of the Clinical Guidance Panel. The lower estimate of the range assumed that the odds of dying after progression is ten-fold greater than the odds of dying before progression in patients who received placebo (i.e. odds ratio = 10). In this analysis the mean survival after tumour progression is approximately equal to 2.5 months. The extra costs associated with sunitinib were $46,101 and the extra QALYs associated with sunitinib were 0.23, leading to an estimated ICER of $204,559.

The Economic Guidance Panel's estimates differed from the submitted estimates. This is primarily because of two factors within the submitted economic model. First, survival and progression are modelled independently and it is assumed that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression. Secondly, that the decreased rate of mortality on sunitinib which is found in the pre progression stage will continue after tumour progression even though patient's would no longer be taking sunitinib. Therefore, in the Economic Guidance Panel reanalyses, when the risk of death before tumour progression and after tumour progression were assumed to be different, extra QALY gains for sunitinib are lower and lead to a decrease in the extra healthcare-associated costs for sunitinib. This occurs because a significant proportion of life expectancy gain (>80%) is derived from extrapolated data not actual data.

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

- The extra cost (ΔC) of sunitinib is $55,806. Incremental costs for sunitinib are based on a model where survival and progression are modelled independently and the assumption that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.
- The extra clinical effect (ΔE) of sunitinib is 0.70 QALYs or 1.18 life years gained. These were largely driven by the assumptions that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $79,765 per QALY or $47,262 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 before tumour progression and the patient's risk of dying after tumour progression are equivalent. Because of the majority of time in the clinical

trial in the sunitinib arm was before tumor progression, the survival curve in the submitted model is heavily weighted towards assuming the same survival benefit after tumor progression for sunitinib before tumour progression. By assuming that sunitinib continued to improve survival relative to placebo even after patients had progressed and were no longer using sunitinib/placebo (i.e. by assuming that sunitinib has a long carry-over beneficial effect on survival beyond tumor progression), the beneficial effects of sunitinib when compared with placebo was inflated. This inflation is further amplified when extrapolating beyond the trial period to a 10 year time horizon so that only 20% of the benefits suggested by the manufacturer's model occurred within the trial period (i.e. approximately 80% of the benefits suggested by the manufacturer's model occur in a time period beyond trial period where significant uncertainty exists whether those 80% of the benefits are real as there is no trial data to support it and when the majority of patients will have experienced tumour progression and will no longer be using sunitinib). These assumptions have the effect of increasing QALY gains and lowering the ICER of sunitinib dramatically. The assumption that sunitinib continued to improve survival relative to placebo even after patients had progressed was felt to be clinically not supported by the existing literature based on input from the Clinical Guidance Panel.

The Economic Guidance Panel estimate is based on a reanalysis which assumed that the risk of death before tumour progression and the risk of death after tumour progression to be different, partially addressing the aforementioned limitations and reducing the estimated gains in clinical effects for sunitinib plus best supportive care versus placebo plus best supportive care. After adjusting the model so that sunitinib did not have any carry-over beneficial effect, reanalyses consistently showed that the ICER estimate to be much higher (approximately $200,000/QALY) than submitter's estimate of $80,000 per QALY despite a wide range of sensitivity analysis on the risk of death after tumor progression. That means that once the model was adjusted to make the clinically more appropriate assumption that there is no carry-over beneficial effect of sunitinib after progression the ICER estimate will stay consistently higher than reported by the submitter's based on the current price of sunitinib and a time horizon of 10 years. Again, if the focus is on the benefits within the trial period, where there is less uncertainty, then the ICER will potentially increase to beyond $300,000 per QALY gained. As a result, it appears the main driver of the ICER for the economic analysis is the price of sunitinib. At a price of approximately $50,000 per year (~$5,000 per 28 day course of therapy), it is difficult to yield an ICER less than $100,000 per QALY unless there is strong clinical evidence demonstrating pronounced sustained improvements in clinical outcomes and QALY gains over time.

The submitter expressed concerns about that the approach for EGP reanalyses. The Economic Guidance Panel acknowledges the inherent limitations of using estimates based on assumptions versus actual data. However, the data to conduct the analysis was requested by the Economic Guidance Panel but was not provided by the manufacturer due to concerns that because of cross-over and confounding between treatment arms in the trial, post-progression differences cannot be compared and would provide not provide robust estimates. In the absence of this data, the Economic Guidance Panel relied on the reanalyses where the pCODR Clinical Guidance Panel was used to inform assumptions and clinical estimates, and conducted reanalyses where it is assumed that a patient's risk of dying before tumour progression and the patient's risk of dying after tumour progression differ between one and ten-fold greater odds of dying before progression in patients who received placebo. Ideally, the submitter would have provided an economic model that

does not assume carry-over effect of sunitinib on survival post progression and does not assume the risk of dying while patients have at least stable disease to be the same as the risk of dying after patients have progressed. Further, this model should distinguish the benefits of sunitinib within the time horizon of trial from the extrapolated benefits of sunitinib in the time horizon beyond the trial period. Results from Economic Guidance Panel reanalyses suggest that cost per QALY estimates for sunitinib from such a model would be much higher than the submitted estimate of $80,000 per QALY.

The submitter also indicated that the submitted probabilistic sensitivity analyses should have been used to address uncertainty as opposed Economic Guidance Panel reanalyses. However, the Economic Guidance Panel noted that the submitted probabilistic sensitivity analyses do not address the aforementioned limitations as probabilistic sensitivity analyses only characterise parameter uncertainty within the submitted model structure and do not address structural uncertainty. The manufacturer's probabilistic sensitivity analyses still model survival and progression independently and assume the same survival benefit after tumor progression for sunitinib before tumour progression.

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 sunitinib 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 sunitinib. 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 Markov model based analysis in which patients transitioned between three health states, pre-tumour progression, post-tumour progression and death. Transition rates between these health states were determined by progression-free survival and overall survival estimates from Study A6181111 (Raymond 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 before tumour progression and the patient's risk of dying after tumour progression are equivalent. As a result, a significant proportion of life expectancy gain (>80%) in their 10-year model is derived from extrapolated data not actual data, biasing results in favour of sunitinib by overestimating increases in QALY gains.

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?

In the submitted economic model, because survival and progression are modelled independently, it is assumed that a patient's risk of dying before tumour progression is equal to the patient's risk of dying after tumour progression, however, the pCODR Gastrointestinal 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 sunitinib even though treatment with sunitinib 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, Study A61811111 (Raymond et al., 2011) is short (<114 weeks) in comparison with the 10 year time horizon of the model. 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. This information was requested by the Economic Guidance Panel but was not provided by the manufacturer due to concerns that because of cross-over and confounding between treatment arms in the trial, post-progression differences cannot be compared and would provide not provide robust estimates. While the Economic Guidance Panel recognized the limitations of these data, this information, particularly disaggregated data accounting for cross-over, could have reduced uncertainty in economic analysis and could have narrowed the range of possible effect estimates. The submitted probabilistic sensitivity analyses do not address this issue as it only characterises parameter uncertainty within the submitted model structure and does not address structural uncertainty – the manufacturer's sensitivity analyses still model survival and progression independently and assume the same survival benefit after tumor progression for sunitinib before tumour progression. In the absence of this data, the Economic Guidance Panel relied on the pCODR Clinical Guidance Panel to inform assumptions and clinical estimates, and conducted reanalyses where it is assumed that a patient's risk of dying before tumour progression and the patient's risk of dying after tumour progression differ. The probability of tumour progression was generated from the survival curves submitted by the manufacturer. The odds of dying after progression were varied between one and ten-fold greater odds of dying before progression in patients who received placebo, based on input provided by the Clinical Guidance Panel.

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 which estimates of the increased costs to the Ontario Drug Benefit Program for the three years subsequent to the listing of sunitinib for pancreatic NETs. The key variables included in the manufacturer's budget impact analysis are: total population in Ontario in 2011, prevalence of pancreatic NETs, proportion of cases that are unresectable or metastatic with well-differentiated disease, treatment cost, proportion of population covered by Ontario Drug Benefit Program, and the market share for those who are covered. The factors which most heavily influenced the budget impact analysis are the proportion of pancreatic NETs patients eligible for public coverage and the proportion of these patients who would use sunitinib if available rather than best supportive care.

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 and the proportion of these patients who would take sunitinib if available rather than best supportive care.

1.5 Future Research

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

An economic model which models the movement of patients from pre-tumour progression to post-tumour progression to death would have enabled more accurate estimation of cost-effectiveness estimates. To populate this model, an analysis of overall survival where patients who progress are censored would be required and may be available using trial data from Study A61811111. An analysis of survival following tumour progression would be necessary to populate the new model and was not available for this review. While recognizing limitations in the trial data related to patient cross-over and censoring, this uncertainty around model inputs in the improved model could be addressed using standard health economic modeling methodologies such as deterministic or probabilistic sensitivity analysis.

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

An economic analysis addressing the limitations described above should be conducted. This analysis would provide more accurate estimates of the cost effectiveness of sunitinib compared with placebo. If everolimus becomes a standard treatment option for patients with pancreatic NETs, an assessment of effectiveness and cost-effectiveness of treatment sequences including everolimus in the treatment of unresectable locally advanced or metastatic would also provide a more accurate reflection of real-world cost-effectiveness and may improve estimates of budget impact.

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 sunitinib (Sutent) for pancreatic NETs. A full assessment of the clinical evidence of sunitinib (Sutent) for pancreatic NETs 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*. Additionally, as per *pCODR Procedures*, any information provided in the feedback on the pERC Initial Recommendation is also managed according to the *pCODR Disclosure of Information Guidelines.* However, in order to demonstrate how the feedback was considered by pERC, pCODR does not guarantee that any information considered Non-Disclosable by the stakeholder providing the feedback is not disclosed in the Final Recommendation or the Final Clinical or Economic Guidance Reports.

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 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

McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D instrument: the potential to estimate QALYs without generic preference data. Value Health. Jan 2009;12(1):167-171

Ontario Drug Benefit e-formulary. Ontario Drug Benefit Formulary/Comparative Drug Index: https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp

Ontario Case Costing Initiative: Costing Analysis Tool: http://www.occp.com/

Ontario Schedule of Benefits for Physician Services under the Health Insurance Act: July 1, 2011: http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/physserv_mn.html

Ontario Health Insurance (OHIP) Schedule of Benefits and Fees: Schedule of Benefits for Laboratory Services: http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/lab_mn.html

Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364: 501-13.