pCODR EXPERT REVIEW COMMITTEE (pERC) FINAL RECOMMENDATION

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
This Final Recommendation was based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug: Sunitinib malate (Sutent) **Funding Request:** Patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours, whose disease is progressive.	
Submitted By: Pfizer Canada Inc.	**Manufactured By:** Pfizer Canada Inc.
NOC Date: June 30, 2011	**Submission Date:** November 7, 2011
Initial Recommendation: March 2, 2012	**Final Recommendation:** May 3, 2012

RECOMMENDATION	The pCODR Expert Review Committee recommends funding sunitinib malate (Sutent) conditional on the cost-effectiveness of sunitinib being improved to an acceptable level to jurisdictions. Funding should be for the treatment of patients with progressive, unresectable, well-differentiated, locally advanced or metastatic pancreatic neuroendocrine tumours, with Eastern Cooperative Oncology Group (ECOG) status of 0 or 1, until disease progression. The Committee made this recommendation because it was satisfied that there is an overall clinical benefit of sunitinib based on the magnitude of the observed hazard ratio for risk of death and the observed progression-free survival difference between sunitinib and placebo, while noting that sunitinib could not be considered cost-effective at the submitted price and the Economic Guidance Panel's estimates of the range of incremental cost effectiveness ratios.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Pricing Arrangements to Improve Cost-Effectiveness** Given pERC was satisfied that there is a net clinical benefit with sunitinib, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of sunitinib to an acceptable level. pERC acknowledged that affordability is a separate but related consideration which jurisdictions also address prior to implementing any funding recommendation. **Collecting Evidence to Inform Effectiveness and Cost-Effectiveness** Jurisdictions that have evidence-gathering systems in place may want to consider collecting additional effectiveness data on sunitinib use for pancreatic neuroendocrine tumours. These data could contribute to providing clarity on the magnitude of benefit observed with sunitinib and better inform real-world cost-effectiveness estimates of sunitinib in the treatment of pancreatic neuroendocrine tumours.

SUMMARY OF pERC DELIBERATIONS

pERC noted there is currently no standard treatment for pancreatic neuroendocrine tumours (pNETs) and that effective treatment options for patients with pNETs are limited. Therefore, the Committee recognized that there is a need for effective therapies in this treatment setting. The one randomized controlled trial comparing sunitinib with placebo, which was included in the pCODR systematic review (Study A6181111, Raymond 2011) was, therefore, considered appropriate.

pERC's *Deliberative Framework* for drug funding recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC discussed the results of Study A6181111 and noted that the trial was stopped upon recommendation from a data safety and monitoring committee due to a greater number of deaths and serious adverse events in the placebo group, as well as a difference in progression-free survival favouring the sunitinib group. Given that the trial was stopped due to the decision of a data safety and monitoring committee, pERC agreed that the early stopping of the trial was appropriate and in patients' best interests, but they also agreed that this likely resulted in an overestimation of the benefit of sunitinib when compared with placebo. It was noted that interpretation of the overall survival results from the trial was challenging because of the early stopping of the trial and the large proportion of patients crossing over from the placebo group to the sunitinib group. pERC further deliberated upon the magnitude of the observed hazard ratio for death and the magnitude of the observed hazard ratio for progression-free survival. The Committee considered that, despite uncertainty in the exact estimates for the risk of death and progression-free survival, the observed magnitude of these effects was clinically meaningful and large enough that the Committee was satisfied that sunitinib is an effective treatment. pERC also noted the stabilization of disease is important to patients and that progression-free survival is one measure of disease stabilization, based on input from one patient advocacy group. pERC also considered that there are no current trials in progress evaluating the effectiveness of sunitinib in pancreatic neuroendocrine tumours to address any remaining uncertainty and that there are unlikely to be further trials specifically addressing this question in the small population of patients with pancreatic neuroendocrine tumours.

pERC discussed the safety of sunitinib in the context of the grade three and grade four serious adverse events observed in Study A6181111 as well as the most commonly observed adverse events. The Committee considered that both the pCODR Clinical Guidance Panel and input from one patient advocacy group supported that these potential side effects were manageable for clinicians and patients.

The incidence of pancreatic neuroendocrine tumours was discussed and it was noted that, although they are uncommon, they would not be considered rare under various existing definitions of rare disease. pERC further discussed that there is considerable uncertainty in the prevalence estimates for pancreatic neuroendocrine tumours, i.e. the number of patients living with the disease at any one time. This is because these tumours have a variable natural history, wherein survival for patients with pancreatic neuroendocrine tumours ranges from a few months to twenty years or more. Therefore, pERC considered that estimates of prevalence and how long a patient would be receiving sunitinib would significantly influence estimates of budget impact and should be considered by provinces. pERC noted that because the number of patients living with pancreatic neuroendocrine tumours is generally low, there would likely be a limited impact on provincial budgets, which could ease the feasibility of implementing a funding recommendation for sunitinib.

Finally, pERC reviewed the results of the manufacturer's submitted economic evaluation and discussed the estimates of cost-effectiveness provided by the pCODR Economic Guidance Panel. It was noted that these estimates were substantially higher than the estimates provided by the manufacturer. The Committee agreed, however, that the assumption underlying the Economic Guidance Panel's estimates, i.e. that the risk of death before tumour progression differs from the risk of death after tumour progression, was more realistic and had more clinical validity than the manufacturer's assumption that the risks are similar.

Upon reconsideration of the pERC Initial Recommendation, the Committee discussed feedback from the manufacturer but noted that this did not change pERC's assessment of the cost-effectiveness of sunitinib given the fundamental limitations in the structure of the submitted economic model and the invalid clinical assumptions made by the manufacturer. The majority of the Committee considered that sunitinib was not cost-effective based on the incremental cost-effectiveness ratios that were presented although the uncertainty associated with these estimates was acknowledged. Upon reconsideration pERC further discussed that additional clinical data would have been of value in order to better inform the magnitude of sunitinib's benefit and the precision of cost-effectiveness estimates.

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 panel ,
- input from one patient advocacy group (Carcinoid-NeuroEndocrine Tumour Society Canada),
- input from pCODR's Provincial Advisory Group,
- feedback on the pERC Initial Recommendation from
    - pCODR's Provincial Advisory Group,
    - the Submitter (Pfizer Canada Inc.)

The pERC Initial Recommendation was to consider funding sunitinib malate for the treatment of patients with progressive, unresectable, well-differentiated, locally advanced or metastatic pancreatic neuroendocrine tumours, with ECOG status of 0 or 1, until disease progression, if the cost-effectiveness of the drug were improved to an acceptable level to the funding jurisdiction. Feedback on the pERC Initial Recommendation indicated that pCODR's Provincial Advisory Group agreed with the recommendation and Pfizer Canada Inc. agreed with the recommendation in part.

OVERALL CLINICAL BENEFIT

pCODR review scope

The pCODR review evaluated the use of sunitinib compared with standard treatments or placebo in patients with progressive, unresectable locally advanced or metastatic well-differentiated pancreatic neuroendocrine tumours.

Studies included: Early termination of trial

The pCODR systematic review included one double-blind, randomized controlled trial (Study A6181111, Raymond 2011) comparing sunitinib with placebo in 171 patients with pathologically confirmed, well-differentiated, advanced or metastatic pancreatic neuroendocrine tumours, who were not eligible for surgery. Based on an assessment by the trial's data and safety monitoring committee, it was discontinued early and prior to the planned interim analysis. pERC noted the trial was terminated early due to a greater number of deaths and serious adverse events in the placebo group and because there was a difference in progression-free survival in favour of the treatment group. Based on the above, pERC considered the decision to terminate the trial early both appropriate and ethical.

Patient populations: Trial population and population targeted for treatment similar

Study A6181111 (Raymond 2011) included patients with pathologically confirmed, well-differentiated advanced or metastatic pancreatic endocrine tumours who were not eligible for surgery. As well, patients were required to have documented disease progression within the previous 12 months as assessed by RECIST criteria, one or more measurable target lesions and an Eastern Cooperative Oncology Group (ECOG) score of 0 or 1. pERC considered that the population evaluated in the trial was generally the same as the population targeted for treatment, although, it was noted that only 65% of patients had received prior chemotherapy.

Key efficacy results: Clinically effective but size of effect uncertain

Efficacy outcomes deliberated upon by pERC included overall survival, the risk of death and progression-free survival. Progression-free survival was the primary endpoint of the trial and at the time of early termination of the trial, patients treated with sunitinib had an improvement in median progression-free survival compared with placebo [11.4 months for sunitinib versus 5.5 months for placebo; hazard ratio = 0.42; 95% CI: 0.26 to 0.66]. pERC noted a post-hoc analysis of the data indicated the test statistic did not cross the efficacy boundary; however, pERC considered the magnitude of this observed difference to be clinically meaningful. An analysis of overall survival was also performed at the time of the early termination of the trial. The median overall survival time could not be estimated due to data censoring, however, the hazard ratio for death was 0.41 (95% CI: 0.19 to 0.89) for sunitinib compared with placebo. pERC considered that the early termination of the trial likely resulted in an overestimation of the benefits of progression-free survival and risk of death although the observed differences were large enough that the Committee was satisfied that sunitinib is clinically effective.

Quality of life: Similar between sunitinib and placebo

With the exception of more diarrhea and insomnia with sunitinib, there were no differences in quality of life and patient reported outcomes between patients treated with sunitinib and placebo in Study A6181111 (Raymond 2011), as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core. The Committee noted these differences but generally considered that these data supported that quality of life did not differ considerably between pancreatic neuroendocrine tumour patients receiving sunitinib and those receiving placebo. pERC also noted that quality of life was valued by patients as outlined in the patient advocacy group input received from the Carcinoid-NeuroEndocrine Tumour Society Canada.

Safety: Potential side effects manageable for patients and clinicians

In Study A6181111 (Raymond 2011), the proportion of patients experiencing a serious adverse event was lower for the sunitinib group compared with the placebo group (27% versus 42%). The most frequently reported serious adverse events with sunitinib were disease progression, cardiac failure, abdominal pain, nausea, vomiting, and renal failure. Grade three and grade four adverse events occurred more frequently in the sunitinib group compared with placebo (49% versus 44%) and included a greater incidence of neutropenia, hypertension, leukopenia and hand-foot syndrome. pERC discussed these potential side effects and noted that they were consistent with sunitinib use in patients with metastatic renal cell carcinoma and gastrointestinal stromal tumours. It was also noted that no additional toxicities or safety concerns have been observed in two extension studies with sunitinib in patients with pancreatic neuroendocrine tumours. pERC concluded that experienced clinicians can likely manage these adverse effects and that patients seem to be willing to tolerate side effects based on input from the patient advocacy group Carcinoid-NeuroEndocrine Tumour Society Canada.

Limitations: Overestimation of effectiveness due to early termination of trial

The main limitation deliberated upon by pERC was that due to the early termination of Study A6181111 (Raymond 2011), the magnitude of the observed difference in effectiveness between sunitinib and placebo is likely an overestimate. pERC discussed that the estimates were based on only a small number of patients and that it was challenging to determine actual treatment duration based on a trial that is terminated early. Furthermore, the low event rate and the high number of censored events make the interpretation of overall survival challenging. pERC discussed these limitations associated with the early termination of the trial but noted that the magnitude of the benefit was large enough that pERC was satisfied that sunitinib is clinically effective in treating pancreatic neuroendocrine tumours. pERC also noted that, although there remains uncertainty in the exact magnitude of effect of sunitinib, there are no ongoing trials or trials planned for the near future that are likely to address this question.

Need: Limited Treatment Options Available

pERC discussed that there is no single standard of care for patients with pancreatic neuroendocrine tumours. Although options such as surgery, nuclear medicine and chemotherapy exist, there are numerous limitations associated with these current therapies such as eligibility and accessibility. pERC also considered that while these treatment options may have an impact on survival, controlled trials evaluating impact on survival have not been conducted.

PATIENT-BASED VALUES

Values of patients with pancreatic neuroendocrine tumours: Disease stabilization and improved quality of life

Patient advocacy group input indicated that, as there is currently no cure for pancreatic neuroendocrine tumours, stabilization of tumours and preventing the further spread of the cancer to other areas of the body is very important to patients with pancreatic neuroendocrine tumours. This would also mean more manageable disease symptoms for patients. pERC considered that patients receiving sunitinib in Study A6181111 (Raymond 2011) had a clinically meaningful improvement in progression-free survival compared with patients receiving placebo.

Input also indicated that patients are looking for a therapy that will help to improve their quality of life and enable them to continue to work and maintain a normal life. Quality of life data and patient-reported outcomes were considered by pERC and only minor differences in diarrhea and insomnia were noted. Quality of life estimates were also incorporated into the economic evaluation and the Committee considered quality-adjusted life year estimates when deliberating upon cost-effectiveness.

The impact of pancreatic neuroendocrine tumours on caregiver burden is also an important consideration for patients as described in patient advocacy group input; pERC noted that data exploring the impact of sunitinib treatment on caregiver burden was not available from Study A6181111 (Raymond 2011).

Patient values on treatment: Willing to tolerate side effects

Patient advocacy group input noted that although there are side effects associated with sunitinib therapy, patients are willing to tolerate certain side effects if this means stabilization or regression of the pancreatic neuroendocrine tumours. pERC considered the potential side effects associated with sunitinib based on adverse events observed in Study A6181111 (Raymond 2011) and noted that these appeared manageable. pERC also discussed that patient advocacy group input had noted that an oral drug such as sunitinib may be more convenient than going to the hospital for chemotherapy treatments.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis

pCODR assessed an economic model looking at the cost-effectiveness and cost-utility of sunitinib plus best supportive care compared to placebo plus best supportive care for patients with progressive, unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumors. pERC considered this was an appropriate comparison as there is no single standard therapy for these patients.

Basis of the economic model: Clinical and economic inputs

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 end-of-life care. Costs associated with management of serious adverse events were also considered.

Key clinical effects included progression-free survival and overall survival estimates from Study A6181111 (Raymond et al., 2011), a randomized controlled trial comparing sunitinib with placebo. The biggest influence on both QALYs and life years in the submitted evaluation was the estimate of survival following tumour progression. Because the Study A6181111 was terminated early a significant proportion of life expectancy gain (>80%) in the model is derived from extrapolated data not actual trial data.

Drug costs: Treatment duration and resulting drug costs uncertain

Sunitinib costs $126.30 per 25 mg capsule and $63.15 per 12.5 mg capsule at the list price. At the recommended dose of 37.5 mg per day for the treatment of pancreatic neuroendocrine tumours, 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. pERC considered the cost of sunitinib therapy would depend upon duration of therapy. Because Study A6181111 (Raymond et al., 2011) was terminated early, pERC noted that the trial would not be able to provide a good estimate of the true duration of sunitinib therapy for patients with

pancreatic neuroendocrine tumours and due to the variable natural history of disease, this could differ considerably across patients.

Cost-effectiveness estimates: Invalid model structure and clinical assumptions made by manufacturer

pERC noted that the Economic Guidance Panel's estimate of the range of incremental cost-effectiveness ratio is between $204,559 and $268,055 per quality-adjusted life year (QALY) when sunitinib plus best supportive care is compared to placebo plus best supportive care. pERC did not consider these estimates to be cost-effective, even after considering feedback from the manufacturer on the pERC Initial Recommendation.

pERC discussed that the main reason these estimates were greater than the estimates submitted by the manufacturer was because the Economic Guidance Panel conducted analyses that assumed a patient's risk of death before tumour progression and the risk of death after tumour progression to be different. This led to lower QALY gains for sunitinib and a decrease in the extra healthcare-associated costs for sunitinib. pERC deliberated upon the appropriateness of this assumption and agreed that the Economic Guidance Panel estimates were more realistic than those provided by the manufacturer. pERC further noted that this assumption had been validated by the pCODR Gastrointestinal Clinical Guidance Panel and was considered clinically appropriate. pERC agreed that if a patient's disease has progressed, the risk of dying would increase and not be the same as if the disease were stable.

When reconsidering the Economic Guidance Panel's cost-effectiveness estimates, pERC recognized that there was uncertainty associated with the Panel's estimates given the inherent limitations in the model structure and that further clinical data was not available to the Panel to address these limitations. Therefore, pERC considered that the approach taken by the Economic Guidance Panel was reasonable under these circumstances. pERC discussed feedback from the manufacturer indicating that probabilistic sensitivity analyses that were submitted with the economic evaluation would address some of the uncertainty in the cost-effectiveness estimates. However, pERC agreed with the Economic Guidance Panel that probabilistic sensitivity analyses that are based on a flawed model structure would have limited validity. pERC considered that additional clinical data could have improved the precision of the Economic Guidance Panel's estimates and helped pERC better understand the magnitude of benefit as it relates to cost-effectiveness. However, pERC noted that the price of sunitinib is approximately $50,000 per year and that drug price is the main driver of the incremental cost of sunitinib compared with best supportive care. pERC recognized that at a price of approximately $50,000 per year, it would be difficult to obtain an ICER of less than $100,000 per QALY without strong clinical evidence demonstrating pronounced and sustained improvements over time in clinical outcomes. Therefore, pERC noted that there could be value to further clinical trial data as it matures in order to better understand the magnitude of benefit as it relates to cost-effectiveness, even if the data were confounded by cross-over.

pERC also considered feedback from the manufacturer indicating they could not replicate the Economic Guidance Panel's estimates. pERC noted that, while the exact estimates were not obtained, the manufacturer's attempt to reanalyze the data produced estimates that were similar to the Economic Guidance Panel's estimates. pERC further noted that, in response to the manufacturer's feedback, the Economic Guidance Panel had provided more clarity and transparency in their report to allow for better replication of their reanalyses.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: prevalence estimates, treatment duration and everolimus

pERC considered potential factors influencing the budget impact and noted that duration of sunitinib treatment and the number of patients with pancreatic neuroendocrine tumours at any one time would be important factors for provinces to consider when evaluating estimates of budget impact. pERC considered that because the number of patients living with pancreatic neuroendocrine tumours is generally low, there would likely be a limited impact on provincial budgets, which could ease the feasibility of implementing a funding recommendation for sunitinib.

Upon reconsideration, pERC also considered feedback provided by pCODR's Provincial Advisory Group indicating that cost-effectiveness and affordability are two separate matters for jurisdictions. As such, pERC recognized that even if jurisdictions are able to improve the cost-effectiveness of sunitinib to an acceptable level, sunitinib may still be unaffordable, depending on its budget impact at the local level.

pCODR's Provincial Advisory Group input indicated that differences between sunitinib and everolimus for pancreatic neuroendocrine tumours would be a key consideration. pERC noted that there are no randomized clinical trials directly comparing sunitinib and everolimus or sequential therapy with these two drugs. It was also considered that at the time of the pCODR submission everolimus did not have a Health Canada indication for treatment of patients with pancreatic neuroendocrine tumours but that an evaluation incorporating both sunitinib and everolimus may be of benefit to provinces, in the future.

DRUG AND CONDITION INFORMATION

Drug Information	• Multi-target tyrosine kinase inhibitor • 12.5 mg, 25 mg and 50 mg tablets reviewed by pCODR • Recommended dosage of 37.5 mg administered orally once daily
Cancer Treated	• Advanced or metastatic well-differentiated pancreatic neuroendocrine tumours
Burden of Illness	• 1% to 4% of pancreatic neoplasms. Incidence approximately 0.2 per 100,000 but also appears to be increasing. The majority of patients (> 80%) present with metastatic or locally advanced disease.
Current Standard Treatment	• No standard treatment. Treatment approach is multi-disciplinary and options may include surgery, Peptide Receptor Radionucleotide Therapy and systemic chemotherapy
Limitations of Current Therapy	• Surgery is only curative for patients presenting with early stage disease • Peptide Receptor Radionucleotide Therapy is not easily accessible to all patients • Systemic chemotherapy has associated toxicities and rigorous clinical trials supporting a benefit not conducted

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

All members participated in deliberations and voting on the pERC Initial Recommendation except:

- Dr. Maureen Trudeau and Dr. Bill Evans who were not present for the meeting
- Jo Nanson who did not vote as the patient member alternate acted in her place at this meeting

All members participated in deliberations and voting on the pERC Final Recommendation except:

- Carole McMahon who did not vote as the patient member alternate.

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 sunitinib for pancreatic neuroendocrine tumours, through their declarations, nine members had a real, potential or perceived conflict. 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.

The pERC Final Recommendation may also be informed by feedback on the pERC Initial Recommendation from pCODR's Provincial Advisory Group, patient advocacy groups that provided input at the beginning of the review and the Submitter and/or the manufacturer of the drug under review if they were not the Submitter. Feedback that was considered is posted on the pCODR website.

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*.

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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