PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review Submitter or Manufacturer Feedback on a pCODR Expert Review Committee Initial Recommendation

# Sunitinib (Sutent) for pancreatic neuroendocrine tumours

**May 3, 2012**

# 3 Feedback on pERC Initial Recommendation

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| Name of the Drug and Indication(s) | **Sutent** in patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuronendocrine tumours, whose disease is progressive. |
| Role in Review (Submitter and/or Manufacturer): | Submitter and manufacturer |
| Organization Providing Feedback | Pfizer Canada Inc. |

## 3.1 Comments on the Initial Recommendation

a) Please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees or disagrees with the initial recommendation:

_____ agrees ___X__ agrees in part _____ disagree

Please explain why the Submitter (or the Manufacturer of the drug under review, if not the Submitter) agrees, agrees in part or disagrees with the initial recommendation.

We acknowledge the validity of the assumption by the Economic Guidance Panel (EGP) and supported by the Gastrointestinal Clinical Guidance panel that the patient's risk of dying pre progression is different compared to that of post progression. However, we point out that the original model is based on a functional form for disease progression that accounts for overall risks of mortality regardless of the pre or post progression status of the disease course. In other words, patient mortality outcomes predicted by the model is likely to be overestimated given that the mortality rate is based on the amalgamation of events that occurred during both pre and post-progression stages.

The original model submitted, did not incorporate an explicit difference in a patient's risk of dying in pre-progression health state compared to the post progression state because the OS curve was modelled using trial based survival data that did not differentiate the risk between the 2 health states. Instead, the model uses a pooled rate of mortality for both pre- and post-progression populations, which can be explicitly taken from the overall survival data. It is important to recognize that this pooled rate of mortality is not constant over time. In the original model, the overall survival curve was fitted with a Weibull function whose shape parameter is greater than 1, which means that the risk of mortality in the overall patient population steadily increases over time. This conservative approach is supported by the EGP's comparison of cost-effectiveness using the Weibull function (time-dependent risks) versus an exponential function (constant risks). The increasing risk of mortality over time is consistent with a population that gradually shifts to the post-progression state and an assumption of higher mortality in that state relative to pre-progression. We believe that the EGP's comment around the submitted model not being a "standard Markov model" is related to these time-varying risks and the use of a pooled mortality risk. We would propose that Pfizer's submitted modified Markov approach is more appropriate to accurately capture the trial data available.

In order to model mortality separately among patients pre- and post-progression, it would be necessary to quantify the difference between these rates, but adequate data to do so was not available. We understand that the range in the odds ratios of dying alluded to by the EGP being between 1 and 10

when comparing the placebo arm to the Sutent arm was arbitrarily defined. We note that a fixed odds ratio also does not enable any variation in the risk of mortality over time, though an increasing risk of mortality within a single health state should be appropriate. This is supported by the increasing risk of progression over time in the model (and the trial data), which can only occur from the pre-progression health state.

However, the main point of contention with the Initial Economic Guidance Report is due to the impossibility in replicating the revised ICUR estimates with the information provided to us. Based on the data and comments included on the Initial Economic Guidance Report dated 16th of February, we tried to replicate the analyses to obtain the same range of ICURs proposed by EGP (cost/QALYs between $204,559 for odds ratio=10 and $268,055 for odds ratio=1).We were not able to replicate the EGP calculated ICURs ranges based on the content of the Initial Economic Guidance Report.

One reason may be that EGP has modified the overall survival component of the sunitinib treatment arm such that the post-progression survival (in both arms) reflected the pre-progression mortality in the placebo arm. However, this implicit aim was not fully disclosed.

To better understand the EGP analyses, we tested a limit in which post-progression survival was set to zero in both arms. Thus the ICUR for this approach reflects only benefits prior to progression and this is the most conservative assumption in term of OS gain:

- The ICUR we found was $177,013/QALY – higher than the original model, but still lower than either of the re-analyses by pCODR. This strongly implies that the EGP re-analyses may have altered the pre-progression period.
- In addition, the incremental cost of sunitinib in this scenario was $51,462, which is greater than EGP found in either of their evaluations. Again, this may suggests a reduction in progression-free survival with sunitinib relative to the original model.

An alternative approach we tested was to replicate the EGP analyses by computing the transitions to post-progression and death states for sunitinib. In this approach, the transition rate from progression-free to post-progression is computed based on the original Weibull fit to the PFS curves and the transitions from progression-free and post-progression to death are individually computed from the original OS Weibull for placebo with an explicit assumption that the odds ratio for mortality between the pre- and post-progression states was 10. This approach yields the closest fit of any approach we tested to the EGP results f with ICUR of $236,346/QALY.

There are two challenges to this method. First, it penalizes sunitinib during the PFS period; this is evident as the PFS curve lies systematically below the Kaplan-Meier PFS curve. The deviation appears small in the graph, but as a consequence the QALY benefit estimated is below that of an analysis of PFS only (i.e. where post-progression survival is set to 0). Second, the overall survival of sunitinib deviates markedly from the Kaplan-Meier data within the first year and has underestimated OS at 2 years by between 14% (40% vs. 54% vs. the Kaplan Meier data) and 20% (40% vs. 60% in the Weibull fit to the Kaplan-Meier). In other words, the method we suspect were used by the EGP projects PFS and OS curves that are below the observed ones from the clinical trial.

**Therefore, we question whether the Gastrointestinal Clinical Guidance panel, the clinician community and other methodologists would agree to assumptions leading to ICURs beyond**

**$200,000/QALY seeing that these assumptions drive survival extrapolations away from observed (real) trial data**

Although EGP proposed a valid argument with regards to differences in post progression probabilities, we believe that the only appropriate way to explore the range of pre- vs. post-progression mortality risks is through a probabilistic sensitivity analysis (PSA). The EGP noted this as an important approach as well in their summary, though they did not consider the PSA results submitted. The PSA we performed on the original submission found that the ICUR is below $75,000/QALY in 24% of cases and is under $150,000/QALY in greater than 70% of cases. This PSA explored the range of plausible progression-free and overall survival parameters based on the confidence intervals obtained when fitting the individual patient survival data from the trial. This allows for a wide range of implicit pre- and post-progression mortality risks, but constrains them to be consistent with the trial data. Actually, with the PSA performed, the ICUR is above $200,000/QALY in only 16% of cases. Thus, we believe that the ICURs suggested by the EGP in their re-analyses are of low probability.

In conclusion Pfizer has confidence that the base case economic model submitted to pCODR provides a robust and reliable estimate of the true economic value for Sutent in pNET (unresectable locally advanced or metastatic, well-differentiated pancreatic neuronendocrine tumours, whose disease is progressive). Sutent's cost utility ratio is below $80,000 per QALY based on sound and reasonable modeling. We trust that the EGP will consider the points made above to re-calibrate its estimates of the economic value of Sutent in order to allow the pERC committee to take a balanced position that recognises the strength of the estimates of cost utility provided by Pfizer.

Although we disagree with the EGP's conclusion that: "the limitations with respect to model structure and survival data requires reanalysis with much higher estimates of cost-effectiveness ratios", Pfizer agrees in part with the recommendation based on the two following statements around the clinical benefit and the budget impact:

- … Because it was satisfied that there is an overall clinical benefit of sunitinib based on the magnitude of the observed PFS difference between sunitinib and placebo.
- …pERC considered that because the number of patients living with pancreatic neuroendocrine tumours at any one time 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.

b) Notwithstanding the feedback provided in part a) above, please indicate if the Submitter (or the Manufacturer of the drug under review, if not the Submitter) would support this initial recommendation proceeding to final pERC recommendation ("early conversion"), which would occur within 2(two) business days of the end of the consultation period.

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| _____ Support conversion to final recommendation. | ___X__ Do not support conversion to final recommendation. |
| Recommendation does not require reconsideration by pERC | Recommendation should be reconsidered by pERC |

c) Please provide feedback on the initial recommendation. Is the initial recommendation or are the components of the recommendation (e.g., clinical and economic evidence) clearly worded? Is the intent clear? Are the reasons clear?

| Page Number | Section Title | Paragraph, Line Number | Comments and Suggested Changes to Improve Clarity |
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# About Completing This Template

pCODR invites the Submitter, or the Manufacturer of the drug under review if they were not the Submitter, to provide feedback and comments on the initial recommendation made by pERC. (See www.pcodr.ca for information regarding review status and feedback deadlines.)

As part of the pCODR review process, the pCODR Expert Review Committee makes an initial recommendation based on its review of the clinical, economic and patient evidence for a drug. (See www.pcodr.ca for a description of the pCODR process.) The initial recommendation is then posted for feedback and comments from various stakeholders. The pCODR Expert Review Committee welcomes comments and feedback that will help the members understand why the Submitter (or the Manufacturer of the drug under review, if not the Submitter), agrees or disagrees with the initial recommendation. In addition, the members of pERC would like to know if there is any lack of clarity in the document and if so, what could be done to improve the clarity of the information in the initial recommendation. Other comments are welcome as well.

All stakeholders have 10 (ten) business days within which to provide their feedback on the initial recommendation and rationale. If all invited stakeholders agree with the recommended clinical population described in the initial recommendation, it will proceed to a final pERC recommendation by 2 (two) business days after the end of the consultation (feedback) period. This is called an "early conversion" of an initial recommendation to a final recommendation.

If any one of the invited stakeholders does not support the initial recommendation proceeding to final pERC recommendation, pERC will review all feedback and comments received at the next possible pERC meeting. Based on the feedback received, pERC will consider revising the recommendation document as appropriate. It should be noted that the initial recommendation and rationale for it may or may not change following consultation with stakeholders.

The final pERC recommendation will be made available to the participating provincial and territorial ministries of health and cancer agencies for their use in guiding their funding decisions and will also be made publicly available once it has been finalized.

# Instructions for Providing Feedback

a) Only the group making the pCODR Submission, or the Manufacturer of the drug under review can provide feedback on the initial recommendation.

b) Feedback or comments must be based on the evidence that was considered by pERC in making the initial recommendation. No new evidence will be considered at this part of the review process, however, it may be eligible for a Resubmission.

c) The template for providing *Submitter or Manufacturer Feedback on pERC Initial Recommendation* can be downloaded from the pCODR website. (See www.pcodr.ca for a description of the pCODR process and supporting materials and templates.)

d) At this time, the template must be completed in English. The Submitter (or the Manufacturer of the drug under review, if not the Submitter) should complete those sections of the template where they have substantive comments and should not feel obligated to complete every section, if that section does not apply. Similarly, the Submitter (or the Manufacturer of the drug under review, if not the Submitter) should not feel restricted by the space allotted on the form and can expand the tables in the template as required.

e) Feedback on the pERC Initial Recommendation should not exceed three (3) pages in length, using a minimum 11 point font on 8 ½″ by 11″ paper. If comments submitted exceed three pages, only the first three pages of feedback will be forwarded to the pERC.

f) Feedback should be presented clearly and succinctly in point form, whenever possible. The issue(s) should be clearly stated and specific reference must be made to the section of the recommendation document under discussion (i.e., page number, section title, and paragraph). Opinions from experts and testimonials should not be provided. Comments should be restricted to the content of the initial recommendation.

g) References to support comments may be provided separately; however, these cannot be related to new evidence. New evidence is not considered at this part of the review process, however, it may be eligible for a Resubmission. If you are unclear as to whether the information you are considering to provide is eligible for a Resubmission, please contact the pCODR Secretariat.

h) The comments must be submitted via a Microsoft Word (not PDF) document to the pCODR Secretariat by the posted deadline date.

i) If you have any questions about the feedback process, please e-mail submissions@pcodr.ca.

*Note: Submitted feedback may be used in documents available to the public. The confidentiality of any submitted information cannot be protected.*