PAN-CANADIAN ONCOLOGY DRUG REVIEW

# pan-Canadian Oncology Drug Review
# Final Economic Guidance Report

# Nab-paclitaxel (Abraxane) for Pancreatic Cancer

**September 23, 2014**

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# FUNDING

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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.

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# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Background

The main economic analysis **submitted to pCODR by Celgene Inc.** compared nab-paclitaxel plus gemcitabine to gemcitabine alone as a first-line treatment for patients with metastatic cancer of the pancreas. Nab-paclitaxel is administered intravenously and gemcitabine is administered intravenously.

**According to the pCODR Clinical Guidance Panel (CGP)**, this comparison is appropriate. The submitter also provided a complementary analysis comparing nab-paclitaxel plus gemcitabine to FOLFIRINOX, which was also deemed relevant as a complementary analysis given the current use of FOLFIRINOX in some patients with metastatic cancer of the pancreas.

**Patient advocacy group input** considered the following factors important in the review of nab-paclitaxel, which are most relevant to the economic analysis: pain, decreased appetite, and nausea or vomiting. The least tolerable side-effect of nab-paclitaxel was neuropathies. The economic model considered these either as adverse events or within the scope of quality of life. A full summary of the patient advocacy group input is provided in the pCODR Clinical Guidance Report.

The **Provincial Advisory Group (PAG)** considered that the following factors would be important to consider if implementing a funding recommendation for nab-paclitaxel, and which are relevant to the economic analysis:

- Drug wastage: as there is only one vial size, PAG has significant concerns for incremental costs due to drug wastage; and
- Time to prepare the infusion: more pharmacy preparation time is required to reconstitute and prepare the infusion as nab-paclitaxel takes a long time to go into solution.

Both of these concerns were taken into consideration when developing the EGP's best estimate. A full summary of the PAG input is provided in the pCODR Clinical Guidance Report.

At the list price nab-paclitaxel costs $971.00 per 100mg vial. At the recommended dose of 125 mg/$m^2$ qw 3/4 weeks, nab-paclitaxel costs $221.0759 per day and $ 6190.1250 per 28-day course. At the submitted confidential price nab-paclitaxel costs $[redacted] per 100mg vial. At the recommended dose of 125mg/$m^2$ qw 3/4 weeks, and using the confidential price, nab-paclitaxel costs $[redacted] per day and $[redacted] per 28-day course. *(Non-Disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by the manufacturer that it can be publicly disclosed.)*

Gemcitabine costs $ 0.062 per mg. At the recommended dose of 1000 mg/m2 (3/4 weeks), gemcitabine costs $11.2929 per day and $316.2000 per 28 day course. FOLFIRINOX costs 10.2 $/mg (Oxaliplatin), 0.5 $/mg (Leucovorin), 0.0033 $/mg (Irinotecan) and 0.0033 $/mg (Fluorouracil). At the recommended dose of 85mg/$m^2$ Day 1 every 14 days (Oxaliplatin), 400 mg/$m^2$ Day 1 every 14 days (Leucovorin), 180 mg/$m^2$ Day 1 every 14 days (Irinotecan), 400 mg/$m^2$ Day 1 every 14 days (Fluorouracil) and 2400 mg/$m^2$ Day 1 CIV over 46 hours, every 14 days (Fluorouracil), FOLFIRINOX costs $119.6557 per day and $3350.3600 per 28 day course.


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## 1.2 Summary of Results

**The EGP's best estimate of the incremental cost-effectiveness ratio (ΔC / ΔE) is between $182,714 and $192,995 when nab-paclitaxel plus gemcitabine is compared with gemcitabine. The most significant cost drivers of the model are the inclusion of patient-level data for dose intensity/doses missed, time on treatment pre-progression, health state utilities and wastage.**

The incremental cost-effectiveness ratio was based on an estimate of the extra cost (ΔC) and the extra clinical effect (ΔE). The Economic Guidance Panel's best estimate assumed the price of nab-paclitaxel to be the confidential price submitted to pCODR. The EGP's best estimate of:

- the extra cost of nab-paclitaxel plus gemcitabine is approximately $22,900, mostly due to the inclusion of wastage.
- the extra clinical effect of nab-paclitaxel plus gemcitabine is between 0.119 and 0.125 (ΔE), mostly due to the time horizon and different utility estimates post-progression.

**The EGP based these estimates on the model submitted by Celgene Inc. and reanalyses conducted by the EGP.** The reanalysis conducted by the EGP using the submitted model showed that when:

- wastage is included (no vials shared), the extra cost of nab-paclitaxel plus gemcitabine is $22,534 ($\Delta C_1$), which increases the estimated incremental cost-effectiveness ratio ($174,996). The EGP included wastage in the economic model as vial wastage was a concern raised by the PAG, and it is unlikely that more than one patient will be treated at the same time at the same center, leading to the potential of having unused vials.
- pharmacy costs for preparation is included, the extra cost of nab-paclitaxel plus gemcitabine is $20,523 ($\Delta C_2$), which increases the estimated incremental cost-effectiveness ratio ($159,377). The EGP included pharmacy costs for preparation in the economic model as this was also a concern raised by the PAG, given the time to prepare nab-paclitaxel.
- changing the second line treatment to 80% supportive care, 15% capecitabine and 5% FOLFOX (from the base case analysis of 90% supportive care, 0% capecitabine and 10% FOLFOX), the extra cost of nab-paclitaxel plus gemcitabine is $19,911 ($\Delta C_3$), which decreases the estimated incremental cost-effectiveness ratio ($154,568). This change was based on feedback from the Clinical Guidance Panel.
- the time horizon was made to be 3 years (form the base case analysis of 5 years), the extra clinical effect of nab-paclitaxel plus gemcitabine is 0.125 ($\Delta E_1$), which increases the estimated incremental cost-effectiveness ratio ($159,667). Based on feedback from the Clinical Guidance Panel, and compared to other published economic models for pancreatic cancer, a 3-year time horizon is appropriate.
- the three parameters are changed—pharmacy preparation costs are included, second-line treatment as per the CGP feedback, and a time horizon of 3 years is used—the extra cost of nab-paclitaxel plus gemcitabine is $21,027 and the extra clinical effect is 0.125, which increases the estimated incremental cost-effectiveness ratio ($167,904).
- all four parameters outline above are changed based on the EGP's best estimate – vial wastage is included, pharmacy preparation costs are included, second-line treatment as per the CPG feedback and a time horizon of 3 years is used—the extra cost of nab-


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paclitaxel plus gemcitabine is $$22,900.00 and the extra clinical effect is 0.125, which increases the incremental cost-effectiveness ratio ($182,714).

- Using an averaged value of three studies that report a utility for pancreatic cancer for both pre-/post-progression states, as well as changing all four parameters outlined above (vial wastage is included, pharmacy preparation costs are included, second-line treatment as per the CPG feedback and a time horizon of 3 years is used), the extra cost of nab-paclitaxel plus gemcitabine is $22,900.00 and the extra clinical effect is 0.119, which increases the incremental cost-effectiveness ratio ($192,995)
- Though not included in the best estimate, it should be noted that should the price of the drug increase by approximately 15%, the ICER, independently of any other changes would increase from the baseline of $155,549 to $174,359, which approaches the impact of vial wastage as a cost driver

**The EGPs estimates differed from the submitted estimates.**

According to the economic analysis that was submitted by Celgene Inc., when nab-paclitaxel plus gemcitabine is compared with gemcitabine (using quality-adjusted life years):

- the extra cost of nab-paclitaxel plus gemcitabine is $20,030 (ΔC). Costs considered in the analysis included treatment costs, administration costs, second line treatment costs and costs of adverse events.
- the extra clinical effect of nab-paclitaxel plus gemcitabine is 0.129 quality-adjusted life years or 0.190 life years (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, time on treatment, the incidence of adverse events and utilities.

So, the Submitter estimated that the incremental cost-effectiveness ratio (ΔC / ΔE) was $155,549 per QALY or $105,423 per LY. The manufacturer's estimates were based on a confidential price of nab-paclitaxel submitter to pCODR.

According to the economic analysis that was submitted by Celgene Inc. when nab-paclitaxel plus gemcitabine is compared with FOLFIRINOX, via a naïve indirect comparison:

- the cost savings associated with nab-paclitaxel plus gemcitabine is $34,086 (ΔC). Costs considered in the analysis included treatment costs, administration costs, second-line treatment costs and costs of adverse events. Note that this represents less cost when comparing nab-paclitaxel plus gemcitabine to FOLFIRINOX.
- the extra clinical effect of nab-paclitaxel plus gemcitabine is 0.126 quality-adjusted years gained (ΔE). The clinical effect considered in the analysis was based on overall survival, progression-free survival, time on treatment, the incidence of adverse events and utilities. Note that this represents increased effectiveness with FOLFIRINOX compared to nab-paclitaxel.

As there are no head to head comparison trials of these two regimens, an indirect comparison was done. This indirect comparison, however, was a naïve (unadjusted) indirect comparison, as it does not take into account within trial comparisons and therefore is not adjusted for the results of the common control group.[15] Further, in this particular case, there is only one randomized controlled trial to inform each arm of the indirect comparison, limiting the generalizability of the results and increasing any potential risk of bias. The EGP considered the submitted estimates to be highly uncertain and unreliable given the lack of a robust indirect comparison. Therefore, any estimates


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that the EGP produced would also be extremely uncertain, so they did not conduct further analyses.

## 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 EGP estimates in cost for nab-paclitaxel plus gemcitabine were higher because the EGP considered wastage and pharmacy costs in their best case estimate. These two inclusions were based on feedback from the PAG. It is unlikely that vials would be shared by two patients being treated at the same time at the same center. Nab-paclitaxel was identified by the PAG as having a more intense preparation than other solutions, and thus pharmacy preparation costs should be included. When changing the time horizon from 5 years to 3 years, based on both CGP feedback and other published economic models in this area, the estimate of effectiveness decreased, and the incremental costs decreased slightly. A time horizon of 3 years is more realistic in this set of patients.

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

In addition to increased survival and quality of life, which are highly valued by patients and are important considerations, other important factors identified by patients were included, namely the reduction of side-effects. The economic model did include adverse events, based on the randomized trial done.

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

Yes, the model captured relevant health states and was informed by the best data available. The EGP was able to modify the majority of the estimates and assumptions. However, given that the manufacturer submitted a partitioned-survival based analysis in which patients transition between one of three health states, and transition rates are determined by progression-free survival and overall survival estimates from the clinical trial, it is difficult to modify and examine the impact of varying these survival estimates. Further, in a partition model, survival and progression are modelled independently, and that a patient's risk of dying is a function of time. As the time horizon is shorter in this economic model and therefore does not contribute a big impact, post-progression survival, which is often an issue with partition survival analyses, was not significant in this economic analysis.

Further, the manufacturer included a time-on-treatment arm in order to reflect that a patient may discontinue treatment prior to progression. This treatment arm did not have a significant impact on results and the clinical guidance panel agreed that the inclusion of this data is not unreasonable.

Though several clarifications were required from the manufacturer on the economic model, all questions and concerns were eventually adequately addressed.


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**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?**

The submitter assumed that vial wastage would not be an issue. The submitter also assumed that pharmacy costs did not need to be included. A further structural assumption the submitter made was the inclusion of a time on treatment estimate in the model (that patients may not stay on their designated treatment pre-progression). The inclusion of this estimate was examined in complementary analyses, and was found to have a significant impact on costs, however, the assumption that not all patients stay on treatment pre-progression is more reflective of a real world setting. The submitter also assumed that a 5 year time horizon would be appropriate for this group of patients, and with guidance from the CGP, the economic model reduced the time horizon to 3 years. Finally, the utilities used in the economic model, which were a cost driver, were not collected from the clinical trial, which the economic analyses is based on, but were collected from the literature for pancreatic cancer.

**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?**

Yes, the estimates for clinical effects and costs were reasonable, based on the availability of data. The data was based on a single phase III clinical trial. The CGP was consulted to provide feedback on all assumptions and estimates included in the economic model. The EGP modified some of the inputs in their best case estimate, including wastage, pharmacy costs, time horizon and second line treatment options.

## 1.4 Summary of Budget Impact Analysis Assessment

**What factors most strongly influence the budget impact analysis estimates?**

In the BIA submitted, in the first line setting, it is assumed that half of the patients currently on gemcitabine alone would be treated with nab-paclitaxel plus gemcitabine, with the goal of having two thirds of patients being treatment with nab-paclitaxel plus gemcitabine after three years. The percentage of patients treated with FOLFIRINOX decreases slightly over the three years.

If the price of the drug were to increase, or the number of patients treated were to increase, the increased incremental costs could be substantial. The choice of second-line treatment and the inclusion of wastage has minimal impact on the BIA results.

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

The submitter addressed a key limitation, wastage, through a sensitivity analysis. Though the submitter's estimates in market share projections were validated independently by the Clinical Guidance Panel, it is uncertain if people on FOLFIRINOX may drift towards nab-paclitaxel in the future. This uncertainty is due to a lack of evidence in clinical practice on the use of nab-paclitaxel vs FOLFIRINOX and the reliance on assumptions of the relative use of these regimens. In the future, a diagram depicting the various scenarios would have been helpful.


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## 1.5 Future Research

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

A true Markov model that is transparent and easy to manipulate would improve on the current designed model. A Markov model explicitly accounts for the timing of events. More effort could be made to collect utilities, resource use and frequency of important diagnostic and laboratory test alongside the clinical trials in order to better inform the economic models.

**Is there economic research that could be conducted in the future that would provide valuable information related to nab-paclitaxel for metastatic pancreatic cancer?**

As identified above, a study that collects both utilities and costs alongside the randomized controlled trial. A randomized controlled trial that examines nab-paclitaxel plus gemcitabine compared to FOLFIRINOX may be useful as well. All efforts should be made to collect utilities and all costs alongside randomized controlled trials determining the effectiveness of therapies.


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# 2 DETAILED TECHNICAL REPORT

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# 3 ABOUT THIS DOCUMENT

This Final 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 nab-paclitaxel (Abraxane) for metastatic adenocarcinoma of the pancreas. A full assessment of the clinical evidence of nab-paclitaxel (Abraxane) for metastatic adenocarcinoma of the pancreas 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*. The manufacturer, as the primary data owner, did not agree to the disclosure of some economic information, therefore, this information was redacted from this publicly available Guidance Report.

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

The Economic Guidance Panel is comprised of economists selected from a pool of panel members established by the pCODR Secretariat. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package and the Economic Guidance Panel Terms of Reference, which are available on the pCODR website (www.pcodr.ca). Final selection of the pool of Economic Guidance Panel members was made by the pERC Chair in consultation with the pCODR Executive Director. The Economic Guidance Panel is editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.


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