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PAN-CANADIAN  
ONCOLOGY DRUG REVIEW

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

**Irinotecan liposome (Onivyde) for Metastatic  
Pancreatic Cancer**

January 5, 2018

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## **FUNDING**

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# TABLE OF CONTENTS

DISCLAIMER .....	ii
FUNDING .....	ii
INQUIRIES .....	iii
TABLE OF CONTENTS.....	iv
1 ECONOMIC GUIDANCE IN BRIEF.....	1
1.1 Submitted Economic Evaluation .....	1
1.2 Clinical Considerations .....	4
1.3 Submitted and EGP Reanalysis Estimates .....	5
1.4 Detailed Highlights of the EGP Reanalysis .....	6
1.5 Evaluation of Submitted Budget Impact Analysis.....	7
1.6 Conclusions .....	8
2 DETAILED TECHNICAL REPORT .....	9
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 <i>pCODR Disclosure of Information Guidelines</i> , this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations.	
3 ABOUT THIS DOCUMENT .....	10
REFERENCES .....	11

# 1 ECONOMIC GUIDANCE IN BRIEF

## 1.1 Submitted Economic Evaluation

The economic analysis submitted to pCODR by Shire Canada compared irinotecan liposome (Onivyde) in combination with 5-fluorouracil (5-FU) and Leucovorin (LV) to 5-FU/LV and modified FOLFOX6 (mFOLFOX6), i.e. the addition of oxaliplatin to 5-FU and LV using Canadian dosing norms for patients with metastatic pancreatic ductal adenocarcinoma after disease progression with a gemcitabine-containing treatment.

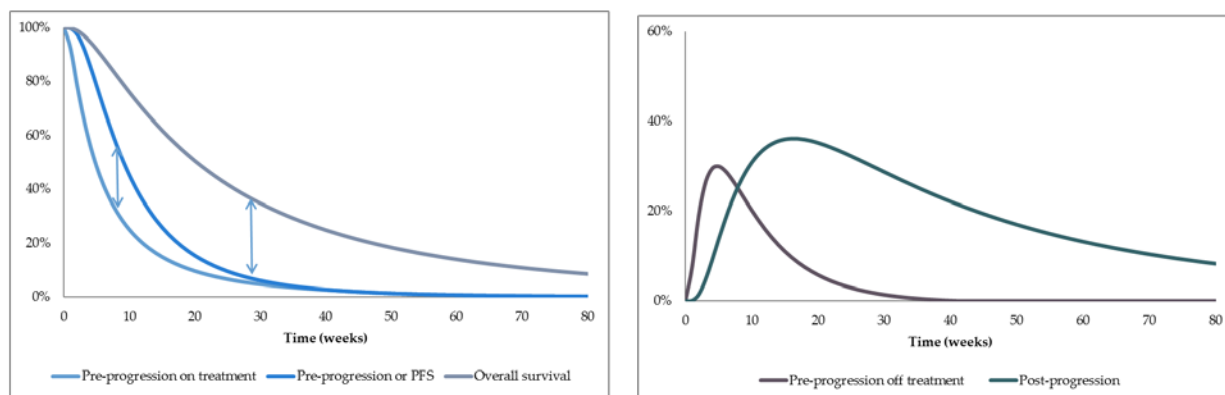
Table 1. Summary of submitted Economic Model

Funding Request/Patient Population Modelled	Aligns with clinical trial: metastatic pancreatic adenocarcinoma patients previously treatment with gemcitabine-based therapy, including gemcitabine monotherapy, gemcitabine and capecitabine (GEMCAP), nab paclitaxel+GEM as a first or second-line therapy
Type of Analysis	CUA
Type of Model	Partitioned-survival
Comparator	5-FU/LV mFOLFOX6 OFF
Year of costs	2016
Time Horizon	3 years
Perspective	Government (health ministry)
Cost of Irinotecan liposome injection plus 5-FU/LV	<p>Irinotecan liposome costs \$1000.00 per 43 mg per 10 mL vial At the recommended dose of 70 mg/m<sup>2</sup> IV over 90 minutes every 2 weeks irinotecan liposome costs</p> <ul style="list-style-type: none"> <li>• \$197.67 per day</li> <li>• \$5,534.88 per 28 day course</li> </ul> <p>5-FU costs \$2.03 per 50 mg/mL vial At the recommended dose of 2400 mg/m<sup>2</sup> IV over 46 hrs every 2 weeks, 5-FU costs</p> <ul style="list-style-type: none"> <li>• \$11.87 per day</li> <li>• \$332.53 per 28 day course</li> </ul> <p>LV costs \$7.00 per 10 mg/mL vial At the recommended dose of 400 mg/m<sup>2</sup> IV over 30 min every 2 weeks LV costs</p> <ul style="list-style-type: none"> <li>• \$34.01 per day</li> <li>• \$952.51 per 28 day course</li> </ul> <p>Total Regimen (Irinotecan liposome + 5-FU/LV) costs:</p> <ul style="list-style-type: none"> <li>• \$243.57.18 per day</li> <li>• \$6,819.94 per 28 day course</li> </ul>
Cost of mFOLFIRI	Irinotecan costs \$107.00 per 20 mg/mL

	<p>At the recommended dose of 70mg/m<sup>2</sup> IV on days 1 &amp; 3, every 2 weeks, irinotecan costs</p> <ul style="list-style-type: none"> <li>• \$45.48 per day</li> <li>• \$1273.30 per 28 day course</li> </ul> <p>5-FU costs \$2.03 per 50 mg/mL vial At the recommended dose of 400mg/m<sup>2</sup> bolus, then 1,200mg/m<sup>2</sup> /day X 2 days (total 2,000mg/m<sup>2</sup>), as a 46-48 hr continuous infusion, every 2 weeks, 5-FU costs</p> <ul style="list-style-type: none"> <li>• \$10.08 per day</li> <li>• \$282.37 per 28 days</li> </ul> <p>LV costs \$7.00 per 10 mg/mL vial At the recommended dose of 400mg/m<sup>2</sup> IV every 2 weeks, LV costs</p> <ul style="list-style-type: none"> <li>• \$34.02 per day</li> <li>• \$952.52 per 28 days</li> </ul> <p>Total regimen costs:</p> <ul style="list-style-type: none"> <li>• \$89.68 per day</li> <li>• \$2511.18 Per 28 day course</li> </ul>
Cost of OFF	<p>Oxaliplatin costs \$3.63 per 5mg/mL vial At the recommended dose of 85 mg/m<sup>2</sup> IV day 1, every 2 weeks, oxaliplatin costs</p> <ul style="list-style-type: none"> <li>• \$7.58 per day</li> <li>• \$212.24 per 28 day course</li> </ul> <p>5-FU costs \$2.03 per 50 mg/mL vial At the recommended dose of 2,000mg/m<sup>2</sup> IV over 24 hours on Days 1,8, 15, 22 of 6 week cycle, 5-FU costs</p> <ul style="list-style-type: none"> <li>• \$13.20 per day</li> <li>• \$369.49 per 28 days</li> </ul> <p>LV costs \$7.00 per 10 mg/mL vial At the recommended dose of 400 mg/m<sup>2</sup> IV day 1, every 2 weeks, LV costs</p> <ul style="list-style-type: none"> <li>• \$34.02 per day</li> <li>• \$952.52 per 28 days</li> </ul> <p>Total regimen costs:</p> <ul style="list-style-type: none"> <li>• \$40.92 per day</li> <li>• \$1145.99 per 28 day course</li> </ul>
Cost of mFOLFOX6	<p>Oxaliplatin costs \$3.63 per 5mg/mL vial At the recommended dose of 85 mg/m<sup>2</sup> IV day 1, every 2 weeks, oxaliplatin costs</p> <ul style="list-style-type: none"> <li>• \$7.58 per day</li> <li>• \$212.24 per 28 day course</li> </ul> <p>5-FU costs \$2.03 per 50 mg/mL vial</p>

	<p>At the recommended dose of 2400 mg/m<sup>2</sup> IV over 46 hours, every 2 weeks, 5-FU costs</p> <ul style="list-style-type: none"> <li>• \$11.88 per day</li> <li>• \$34.02 per 28 day course</li> </ul> <p>LV costs \$7.00 per 10 mg/mL vial At the recommended dose of 400 mg/m<sup>2</sup> IV day 1, every 2 weeks, LV costs</p> <ul style="list-style-type: none"> <li>• \$34.02 per day</li> <li>• \$952.52 per 28 day course</li> </ul> <p>Total regimen costs:</p> <ul style="list-style-type: none"> <li>• \$53.47 per day</li> <li>• \$1497.29 per 28 day course</li> </ul>
Cost of 5-FU/LV <sup>a</sup>	<p>5-FU costs \$2.03 per 50 mg/mL vial At the recommended dose of 2400 mg/m<sup>2</sup> IV over 46 hours, every 2 weeks, 5-FU costs</p> <ul style="list-style-type: none"> <li>• 5-FU costs \$11.88 per day</li> <li>• \$332.54 per 28 days</li> </ul> <p>LV costs \$7.00 per 10 mg/mL vial At the recommended dose of 400 mg/m<sup>2</sup> IV over 30 minutes every over 46 hours every 2 weeks, LV costs</p> <ul style="list-style-type: none"> <li>• \$34.02 per day</li> <li>• \$952.52 per 28 day course</li> </ul> <p>Total regimen costs:</p> <ul style="list-style-type: none"> <li>• \$ 35.87 per day</li> <li>• \$ 1004.49 per 28 day course</li> </ul>
Model Structure	<p><i>Model comprises 4 health states: pre-progression on treatment, pre-progression off treatment, post-progression and death. Pre-progression off treatment state is to account for patients who discontinue treatment for reasons other than progression. Figure 1 highlights the curves used to determine the health states.</i></p>
Key Data Sources	<ul style="list-style-type: none"> <li>- <i>NAPOLI-1 clinical trial for the comparison to 5-FU/LV</i></li> <li>- <i>Network meta-analysis for the comparison to mFOLFOX6</i></li> </ul>
<p><b>Note:</b> * Drug costs for all comparators in this table are based on costing information under license from IMS Health Canada Inc. concerning the following information service(s): DeltaPA and may be different from those used by the submitter in the economic model. The analyses, conclusions, opinions and statements expressed are those of the Canadian Agency for Drugs and Technologies in Health and not those of IMS Health Canada Inc. Quintile IMS DeltaPA- accessed on August 21, 2017. All calculations are based on = 70kg and BSA = 1.7m<sup>2</sup>.</p> <p><sup>a</sup> The dose of 5-FU/LV in the NAPOLI trial was 5-FU 2000 mg/m<sup>2</sup> and LV 200 mg/m<sup>2</sup> every weeks for the first 4 weeks of a 6 week cycle. The dose and schedule of 5-FU/LV listed in Table 1 is more typical of Canadian practice.</p>	

Figure 1. Illustration depicting the health states as taken from pCODR submission



## 1.2 Clinical Considerations

According to the pCODR Clinical Guidance Panel (CGP), the comparators chosen for the economic analysis are appropriate, as there is no one standard of care across Canada. The CGP identified relevant comparators including but not limited to 5-FU/LV, OFF, mFOLFOX, and FOLFIRI. Relevant issues identified included:

- NAPOLI-1 assessed the effect of irinotecan liposome, alone and in combination with 5-FU and LV, compared with 5-FU and LV.
- There is a net clinical benefit to irinotecan liposome when given in combination with 5-FU/LV compared to 5-FU/LV in patients who have been previously treated with gemcitabine-based therapy.
- Primary and secondary endpoints all favored the irinotecan liposome + 5-FU/LV arm.
- Toxicity including gastrointestinal toxicity and neutropenia were significantly higher in the irinotecan liposome+5-FU/LV arm.
- 17% of patients in the irinotecan liposome combination arm in the NAPOLI-1 trial received growth factor support. The cost of growth-colony stimulating factors (GSF) was not considered in the PE model. Non-febrile neutropenia is not typically treated with (GSF) in the non-curative treatment setting in most of Canada.
- There is no widely acceptable standard of care in this patient population in Canada. Although the drugs used in the comparator arm are available across the country, the specific dose of 5-FU/LV is not commonly used. The dose and schedule used in the combination arm is more typical of Canadian practice. Despite this difference, the CGP considers the outcomes between the two different schedules of 5-FU/LV to be clinically comparable.
- The submitter provided a network meta-analysis (NMA) that compared irinotecan liposome plus 5-FU/LV to 5-FU/LV, OFF, mFOLFOX, mFOLFIRI3 and BSC in patients with metastatic pancreatic cancer. The results of the NMA indicated that treatment with mFOLFOX was associated with a statistically significant detrimental effect on progression-free survival (HR: 1.95, 95% CI: 1.02 to 3.67) and on overall survival (HR: 2.35, 95% CI: 1.20 to 4.46) as compared to irinotecan liposome plus 5-FU/LV. Similar results were also reported for 5-FU/LV as compared to irinotecan liposome plus 5-FU/LV (PFS [HR: 2.07, 95% CI: 1.48 to 2.91] and overall survival [HR: 1.45, 95% CI: 1.03 to 2.08]). However, the overall conclusions of the NMA are limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. The estimates of mFOLFOX should also be interpreted with caution given the additional heterogeneity that was introduced into the NMA by pooling mFOLFOX and mFOLFOX6. Given these limitations, the comparative efficacy of irinotecan liposome plus 5-FU/LV to other anticancer agents is uncertain. Refer



to Section 1.2 and Section 7 of the Clinical Guidance Report for more details. As a result, the EGP did not undertake re-analysis estimates for the comparisons against OFF and mFOLFOX.

#### Summary of registered clinician input relevant to the economic analysis

Registered clinicians considered the need for a second-line treatment option for patients with metastatic pancreatic cancer who have been treated with gemcitabine based chemotherapy in the first line and there is overall survival benefit with irinotecan liposome plus 5-FU/LV is compared to 5-FU/LV.

#### Summary of patient input relevant to the economic analysis

Patients who experienced irinotecan liposome considered the manageable side effects, the option of an additional treatment and prolonged survival as important factors. All were considered in the economic analysis.

#### Summary of Provincial Advisory Group (PAG) input relevant to the economic analysis

PAG considered the following factors important to consider if implementing a funding recommendation for irinotecan liposome which are relevant to the economic analysis:

#### Barriers

- Lack of direct comparison data with FOLFIRI and mFOLFOX or OFF.
- High cost of irinotecan liposome. PAG noted that regular irinotecan is available as generic products and is relatively low cost. PAG identified that the modest incremental benefit of liposomal irinotecan may not justify its higher price.
- Concern regarding drug wastage due to availability of only one vial size.
- Treatment of adverse events associated with irinotecan liposome but not seen with regular irinotecan
- Additional chair time of 90 minute infusion when compared to 5-FU/LV but is similar to the infusion time of regular irinotecan.

### 1.3 Submitted and EGP Reanalysis Estimates

Table 2. Submitted and EGP reanalysis estimates

Estimates (range/point)	Submitted	EGP Reanalysis Lower Bound	EGP Reanalysis Upper Bound
$\Delta E$ (LY)	0.154	0.154	0.154
Progression-free	N/A	N/A	N/A
Post-progression	N/A	N/A	N/A
$\Delta E$ (QALY)	0.131	0.152	0.133
Progression-free	0.152	0.153	0.135
Post-progression	-0.021	-0.022	-0.002
$\Delta C$ (\$)	\$23,871	\$43,039	\$44,496
ICER estimate (\$/QALY)	\$182,719	\$326,774	\$335,528

The main assumptions and limitations with the submitted economic evaluation were:

- Treatment duration was not incorporated directly into the model, and was therefore not modifiable. Time to treatment failure was used as a proxy for treatment duration. In this particular case, this may be a reasonable assumption as 40% of patients in each treatment

arm discontinued prior to progression. However, if a patient is taken off the drug, and then resumes, time to treatment failure does not reflect that. The CGP confirmed that the intent of irinotecan liposome is to continue treatment until progression.

- Though utilities were collected in the clinical trial, the economic model is not informed by these. The submitter chose to use an average of published values in the literature. Not all sources included in the average were deemed relevant by the CGP. Further, utilities are modeled by health state and not by treatment arm. The CGP identified that side effects are higher with irinotecan liposome, and therefore may have a negative impact on the quality of life of these patients.
- The submitter provided a network meta-analysis (NMA) in order to consider alternative comparators such as mFOLFOX and OFF, which are considered relevant in the Canadian setting. However, the uncertainty in the NMA is very high. There was high heterogeneity in both the studies included and patient characteristics in the NMA.

#### 1.4 Detailed Highlights of the EGP Reanalysis

The EGP made the following changes to the submitted economic model:

- Discount rate of 1.5% (base case: 5%). In order to align with recent CADTH guidelines, a discount rate of 1.5% was applied to both costs and effects.
- Source of drug cost taken from Quintile IMS (base case: previous pCODR submissions). Given that pricing is not standardized across previous pCODR submission, using Quintile IMS as the source for drug costs (other than irinotecan liposome) was preferred.
- Treatment duration as progression-free survival (PFS) (not as time to treatment failure): the intent of this treatment is to treat until progression. Time to treatment failure does not account for patients who may have discontinued prior to progression, and then re-initiated therapy prior to progressing.
- No vial sharing of irinotecan liposome (base case: vial sharing). Wastage was not accounted for in the submitted base case. This drug is not common enough to consider vial sharing in smaller centres. Including wastage was explored as an upper bound to the EGP reanalysis.
- Inclusion of disutilities (base case: disutilities excluded). As the CGP identified that irinotecan liposome patients may face more adverse events due to increased toxicity, disutilities were included in the EGP reanalysis.
- Use of Canadian utilities from Lien et al. (base case: average from various sources). In order to inform the utility values in the model, the EGP explored using one study (Lien et al), in Canada, to inform the EGP reanalysis upper bound as this study used the Canadian EQ-5D value set. The study by Lien et al. has demonstrated that Canadian utility values differ from other jurisdictions.
- No post-progression treatment (base case: values from PANCREOX trial). The EGP sought guidance from the CGP, who identified that currently in Ontario, no subsequent treatments are funded for another line of therapy. Further, this patient population is extremely frail and most likely would not be eligible to receive any further treatment.

Table 3. EGP Reanalysis Estimates, main analysis irinotecan liposome +5-FU/LV vs 5-FU/LV

	$\Delta C$	$\Delta E$ QALYs	ICUR (QALY)	
Baseline	\$23,871	0.131	\$182,719	-----
<b>EGP's Reanalysis for the Best Case Estimate - Lower Bound</b>				
Description of Reanalysis	$\Delta C$	$\Delta E$ QALYs	ICUR (QALY)	$\Delta$ from baseline submitted ICER
<i>Discount rate - 1.5%</i>	\$23,950	0.132	\$181,844	-\$875
<i>Source of drug cost - Quintile IMS</i>	\$25,600	0.131	\$196,041	\$13,322
<i>Treatment duration as PFS</i>	\$33,997	0.131	\$260,231	\$77,512
<i>Vial sharing - none</i>	\$28,038	0.131	\$214,614	\$31,895
Best case estimate - lower bound	\$43,039	0.132	\$326,774	\$144,055
<b>EGP's Reanalysis for the Best Case Estimate - Upper Bound</b>				
<i>Disutilities - included</i>	\$23,871	0.121	\$196,980	\$14,261
<i>Utilities - Lien et al.</i>	\$23,871	0.140	\$170,064	-\$12,115
<i>Post-progression treatment proportion - none</i>	\$25,004	0.131	\$191,394	\$8,675
Best case estimate - upper bound	\$44,496	0.133	\$335,528	\$152,809

Table 4. Detailed Description of EGP Reanalysis on the unit cost of irinotecan liposome +5-FU/LV vs 5-FU/LV (NAPOLI-1 trial)

	Base Case Value	Sensitivity Analysis Value	$\Delta$ costs	$\Delta$ effects	Result (\$/QALY)	$\Delta$ from baseline ICER
Cost irinotecan liposome	\$20 / mg	\$15 / mg	\$19,063	0.131	\$145,916	-\$36,803
Cost irinotecan liposome	\$20 / mg	\$10 / mg	\$14,266	0.131	\$109,198	-\$73,521
Cost irinotecan liposome	\$20 / mg	\$5 / mg	\$9,480	0.131	\$72,564	-\$110,155

### 1.5 Evaluation of Submitted Budget Impact Analysis

The factor that most influences the budget impact analysis is the cost of oxaliplatin. Based on the EGP re-analysis, using the generic price of approximately \$0.70 per mg, increases the budget impact. Other factors that influence the budget impact analysis include are the market share assumptions, time on treatment, and dose intensity.

Key limitations of the BIA model include the lack of consideration of wastage (vial sharing) of irinotecan liposome. These parameters were not able to be modified and explored by the EGP,

though the inclusion of wastage would increase the budget impact analysis. Further, if the cost of oxaliplatin were to reflect generic pricing, the resulting budget impact would be much greater.

## 1.6 Conclusions

The EGP's best estimate of  $\Delta C$  and  $\Delta E$  for irinotecan liposome+5-FU/LV when compared to 5-FU/LV is:

- Between \$326,774/QALY and \$335,528/QALY
- The extra cost of irinotecan liposome+5-FU/LV is between \$43,039 and \$44,496. *The factors that most influence  $\Delta C$  that are relevant to the main analysis are the curve to inform treatment duration (time to treatment failure versus progression-free survival), the source of drug costs, and the post-progression treatments.*
- The extra clinical effect of irinotecan liposome+5-FU/LV is between 0.132 and 0.133 ( $\Delta E$ ). *The factors that most influence  $\Delta E$  are the time horizon and utilities.*

Overall conclusions of the submitted model:

- *This model addresses many concerns regarding the extrapolation of data by utilizing only trial data. No extrapolation of outcomes was needed as all trial patients were dead by the end of three years of total follow-up. However, some concerns remain around treatment duration and the utilities used to inform the model.*
- *The network meta-analysis conducted to inform alternate comparators (mFOLFOX and OFF) was of insufficient quality to produce re-analysis estimates.*

## 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 Irinotecan liposome (Onivyde) for metastatic pancreatic cancer. A full assessment of the clinical evidence of Irinotecan liposome (Onivyde) for metastatic pancreatic cancer 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.cadth.ca/pcodr](http://www.cadth.ca/pcodr)).

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*. There was no non-disclosable information in the Economic Guidance Report provided to pERC for their deliberations.

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.cadth.ca/pcodr](http://www.cadth.ca/pcodr)). 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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