pCODR EXPERT REVIEW COMMITTEE (pERC)
FINAL RECOMMENDATION

The CADTH 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 reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

pERC Final Recommendation
This pCODR Expert Review Committee (pERC) Final Recommendation is based on a reconsideration of the Initial Recommendation and feedback from eligible stakeholders. This pERC Final Recommendation supersedes the pERC Initial Recommendation.

Drug:
Irinotecan Liposome (Onivyde)

Submitted Reimbursement Request:
For the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treated with gemcitabine-based therapy

Submitted By: Shire Canada	**Manufactured By:** Shire Canada
NOC Date: August 9, 2017	**Submission Date:** April 27, 2017
Initial Recommendation: November 2, 2017	**Final Recommendation:** January 5, 2018

Drug Costs

Approximate per Patient Drug Costs, per Month (28 days) Submitted list price of $1,000.00 per 43 mg vial/10 mL * Note: Costs are calculated based on an average weight of 70 kg and body surface area of 1.7m².	Irinotecan liposome in combination with 5-FU and LV costs: • $6,819.94 per 28-day course

pERC RECOMMENDATION

pERC recommends the reimbursement of irinotecan liposome in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients with locally advanced, unresectable or metastatic adenocarcinoma of the pancreas who have progressed on gemcitabine-based therapy conditional on the cost-effectiveness being improved to an acceptable level. Reimbursement should be for patients with good performance status. Treatment should continue until disease progression or unacceptable toxicity.

The Committee made this Recommendation because it was satisfied that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone based on a modest improvement in overall survival and progression-free survival. pERC noted that the combination therapy is associated with increased, but manageable, toxicities.

pERC agreed that irinotecan liposome in combination with 5-FU/LV aligns with patient values, as there is a need for effective treatment options that prolong survival.

The Committee concluded that, at the submitted price, irinotecan liposome in combination with 5-FU/LV could not be considered cost-effective compared with 5-FU/LV alone.

POTENTIAL NEXT STEPS FOR STAKEHOLDERS

Pricing Arrangements to Improve Cost-Effectiveness
Given that pERC was satisfied that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV in patients who have progressed on gemcitabine-based therapy, jurisdictions may want to consider pricing arrangements and/or cost structures that would improve cost-effectiveness to an acceptable level.

Insufficient Evidence to Support the Use of Irinotecan Liposome in Patients Who Progress After Treatment with Irinotecan-Containing Regimens
There is currently insufficient evidence to support the use of irinotecan liposome in combination with 5-FU/LV in patients who progress after being previously treated with irinotecan-containing regimens (ex. FOLFIRINOX). pERC also noted that there is insufficient evidence to support the substitution of irinotecan liposome in other irinotecan-containing combination therapies.

Time-Limited Need for Irinotecan Liposome for Patients in Third-Line Treatment and Beyond
At the time of implementing a reimbursement recommendation for irinotecan liposome in combination with 5-FU/LV for patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy, jurisdictions may consider addressing the short-term, time-limited need for patients who are currently receiving gemcitabine-based therapy for second-line therapy, based on the clinical discretion of the treating physician.

Clear Labelling of Dose and Packaging to Minimize the Potential for Confusion and Error With Irinotecan Free Base
pERC noted that the Health Canada product monograph indicates that the dose of irinotecan liposome is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI-1 trial indicates that the dose of irinotecan liposome is 80 mg/m^2, which is equivalent to 70 mg/m^2 of irinotecan free base. pERC noted that upon implementation of irinotecan liposome, the dose must be clearly labelled, and packaging should clearly differentiate it from irinotecan free base in order to minimize confusion between the two products.

SUMMARY OF pERC DELIBERATIONS

Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016. However, it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. Patients often experience a rapid decline in health and die soon after diagnosis. The majority of patients present with either metastatic or locally advanced, unresectable disease. The mainstay of treatment for such patients is palliative chemotherapy. Although the palliative treatment of advanced pancreatic cancer has significantly improved in the past several years, with median survival exceeding eight months, long-term survival is not common for most advanced pancreatic cancer patients, with fewer than 20% remaining alive at 18 months. In the first-line setting, for patients fit enough to receive systemic therapy, treatment options include FOLFIRINOX, gemcitabine with nab-paclitaxel, and gemcitabine alone. The Clinical Guidance Panel (CGP) noted that progress in second-line therapy for advanced pancreatic cancer has been modest, with few randomized controlled trials (RCTs). In the second-line setting, treatment options include oxaliplatin with 5-FU (OFF), 5-FU alone, or capecitabine. Registered clinicians noted that there are no high-level data to support the usage of any one regimen over another; however, the choice of second-line therapy is affected by the first-line treatment regimen. Registered clinicians and the CGP indicated an unmet need for second-line treatment options for patients with metastatic pancreatic cancer who have progressed on first-line gemcitabine-based chemotherapy, as there is currently no standard of care for that group of patients. Therefore, pERC agreed that there is a need for more effective and tolerable therapies in the post-progression setting, for which there are limited therapeutic options to prolong survival.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:

CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of one RCT, NAPOLI-1, that compared irinotecan liposome monotherapy with 5-FU/LV or irinotecan liposome plus 5-FU/LV with 5-FU/LV alone. The Committee primarily focused its deliberations on the comparison between the combination of irinotecan liposome and 5-FU/LV compared with 5-FU/LV alone. pERC noted that the NAPOLI-1 trial demonstrated a statistically significant improvement in overall survival (OS) in favour of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone. pERC considered that in a patient population that experiences a rapid decline in health post-progression, and for whom few treatment options are available, a modest OS improvement of 1.9 months was considered to be clinically meaningful. The Committee also noted that there was a similar trend favouring the combination therapy in all key secondary outcomes including progression-free survival (PFS).

pERC discussed whether the results of the NAPOLI-1 trial in patients with metastatic adenocarcinoma of the pancreas could be generalized to the locally advanced disease population. pERC noted that in clinical practice, both patient populations receive similar systemic therapies, and that transition from locally advanced unresectable disease to metastatic disease often occurs rapidly. Therefore, pERC agreed with the CGP that treatment availability should be extended to patients with locally advanced unresectable disease. pERC also discussed the fact that the majority of patients enrolled in the NAPOLI-1 trial had a good performance status, and that in clinical practice, pancreatic cancer patients are more likely to have a worse performance status at this stage of their disease. Registered clinicians also noted that patients often have poor performance status in the post-progression setting, and that many would not be well enough to receive second-line therapy. Therefore, pERC agreed that the use of irinotecan liposome in combination with 5-FU/LV in the post-progression setting should be restricted to patients with good performance status based on the discretion of the treating oncologist.

pERC deliberated on the toxicity profile of the combination of irinotecan liposome and 5-FU/LV, and noted there were more frequent grade 3 or higher treatment-emergent adverse events (TEAEs) compared with 5-FU/LV alone. The most common adverse events (AEs) reported among patients receiving the combination therapy included diarrhea, vomiting, nausea, decreased appetite, and fatigue. pERC noted that febrile neutropenia was more frequent among patients treated with irinotecan liposome combination therapy. Furthermore, the Committee noted that patients could be treated with growth factor support in the NAPOLI-1 trial. pERC discussed the fact that the use of growth factor support is typically low in the

palliative setting, and that growth factor support was used in 17% of patients in the NAPOLI trial, which the Committee noted is much higher than what is used in the Canadian setting. pERC also discussed that the rates of neutropenia and febrile neutropenia may be much higher in clinical practice if growth factor support is not used during treatment with combination therapy. pERC also considered that registered clinicians providing input noted that irinotecan liposome is a new delivery method for an old drug, so clinicians have experience with managing the side effects associated with irinotecan free base. Overall, pERC agreed that the toxicities with the combination therapy are expected and manageable in the context of the disease and drug.

pERC discussed the available quality-of-life (QoL) data from the NAPOLI-1 trial and noted that no significant improvement or deterioration was observed between the irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. However, pERC noted that the QoL data should be interpreted with caution, as there was a low compliance rate and a high amount of missing data due to the discontinuation of treatment because of disease progression, AEs, or death. Overall, pERC concluded that the impact of the combination therapy on QoL is uncertain.

pERC considered the comparison with 5-FU/LV in the NAPOLI-1 trial to be reasonable in this setting, but also considered the results of a network meta-analysis (NMA) provided by the submitter that compared irinotecan liposome in combination with 5-FU/LV with other relevant comparators in Canada, including 5-FU/LV, OFF, mFOLFOX, mFOLFIRI, and best supportive care. pERC discussed the critical appraisal of the NMA and noted that, in agreement with the Methods Team and CGP, the substantial heterogeneity between the included studies made the results highly unreliable and uncertain. Therefore, the comparative efficacy of irinotecan liposome plus 5-FU/LV with other anticancer agents is unknown. pERC also noted that there was no comparison between irinotecan liposome and irinotecan free base; therefore, the comparative efficacy is unknown.

Upon reconsideration of the pERC Initial Recommendation, pERC noted feedback from the Provincial Advisory Group (PAG) stating that it is unknown whether the benefit seen with the irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. PAG noted that jurisdictions have made generic oxaliplatin and irinotecan free base in combination with 5-FU/LV, capecitabine, and fluoropyrimidine available as treatment options, recognizing that there is a lack of high-level evidence for a standard of care in patients previously treated with gemcitabine-based therapies. pERC reiterated that despite available treatment options in the second-line setting, there is no standard of care or high-level data to support the usage of any one regimen over another. The Committee also reiterated the fact that 5-FU/LV was considered to be a reasonable comparator in this setting by the CGP and registered clinicians. pERC reiterated its conclusion that irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone in patients who have progressed on gemcitabine-based therapies demonstrated a statistically significant and clinically meaningful improvement in outcomes important to decision-making, including OS and PFS. The Committee also noted that the use of irinotecan liposome in combination with 5-FU/LV will be limited to a small group of patients with an acceptable performance status who can receive second-line therapy in the post-progression setting.

In addition, although pERC recognized and discussed the concerns raised by PAG, they also reflected on the impact this kind of feedback may have had on patients' timely access to treatments. The Committee noted that there were no data available to inform the comparison of irinotecan free base to irinotecan liposome at the time of deliberations on the pERC Initial Recommendation. pERC acknowledged the importance of balancing the obligation of providing due process for substantive concerns raised by stakeholders with the goal of providing timely access to treatment for patients.

Overall, pERC concluded that there is a net clinical benefit of irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone based on the modest improvement in OS and PFS as well as the need for more effective treatments options for patients with metastatic pancreatic cancer who have progressed on gemcitabine-based therapy.

pERC deliberated on joint input from two patient advocacy groups. Patient input indicated that patients value new effective treatment options that improve QoL and prolong survival. The Committee noted that patients strongly valued a modest improvement in OS for this patient population with rapid decline in health post-progression, for which few treatment options are available. pERC also noted that patient input indicated that patients strongly valued the option of trying new therapies but also valued balancing the benefits and risks of a drug therapy with the overall impact on QoL. pERC noted that patients indicated they would be willing to try new therapies; however, the Committee also acknowledged

comments that patients and their families want to have honest discussions with their oncologists to assess the risks and benefits associated with treatment so that they can make informed and personalized decisions about treatment. pERC noted that, although the results from the NAPOLI trial did not demonstrate an improvement in QoL, it appeared that no appreciable detriment in QoL was observed. However, the Committee noted that there was low compliance and a large amount of missing data, which increases the uncertainty in the results. pERC also noted that the toxicity profile of irinotecan liposome in combination with 5-FU/LV was considered manageable by most patients. Overall, pERC concluded that the therapeutic intent of irinotecan liposome as an effective treatment option that prolongs survival aligns with patient values. However, the Committee was limited by the available QoL data from the NAPOLI trial and was uncertain on how treatment with irinotecan liposome in combination with 5-FU/LV truly impacts QoL.

pERC deliberated on the cost-effectiveness of irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. The Committee noted that the pCODR Economic Guidance Panel's (EGP's) estimates were higher than the manufacturer's estimates. This was primarily due to differences in the estimate of drug wastage, the source of drug costs, the use of time-to-treatment failure as a proxy for treatment duration, and utility values derived from the literature. pERC considered that the use of time-to-treatment failure as a proxy for treatment duration does not account for patients who may have discontinued treatment with irinotecan liposome plus 5-FU/LV prior to progression due to AEs, then re-initiated therapy prior to progressing. Furthermore, since the intent of treatment with irinotecan liposome plus 5-FU/LV is to continue until progression, pERC agreed that the use of PFS as a proxy for treatment duration was more reasonable. The Committee also discussed the fact that the cost of the use of growth factor support that may be required to treat toxicities such as febrile neutropenia while on the combination therapy was not accounted for in the model; therefore, pERC agreed that the costs of managing such toxicities are likely underestimated in the pharmacoeconomic model. Furthermore, pERC noted that the cost of irinotecan liposome is four times that of irinotecan free base; therefore the Committee agreed that a substantial reduction in the drug price of irinotecan liposome would be required. pERC concluded that at the submitted price, the combination therapy could not be considered cost-effective. pERC also agreed with the EGP's assessment regarding the considerable uncertainty in the efficacy estimates from the provided NMA between relevant comparators, including mFOLFOX and OFF and irinotecan liposome plus 5-FU/LV.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted input from PAG that it is unknown whether the benefit observed with irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. In the absence of a comparison with irinotecan free base, the true cost-effectiveness and value of funding irinotecan liposome is difficult to determine. pERC reiterated that there are currently no available data on the comparison between irinotecan liposome and irinotecan free base, and, therefore, the Committee noted that the comparative effectiveness and the relative cost-effectiveness are unknown.

pERC discussed the feasibility of implementing a reimbursement recommendation for irinotecan liposome plus 5-FU/LV. pERC noted that irinotecan liposome is provided in a single 50 mg vial. In most instances, vial sharing will not be feasible, given the small number of patients with pancreatic cancer receiving second-line treatment; therefore, the Committee agreed that there will be significant wastage. As an additional systemic therapy to chemotherapy, pERC noted the PAG's concern that there will be increased chair time for treatment administration to patients. Furthermore, pERC discussed PAG's concern regarding the different dosing in the Health Canada product monograph compared with the NAPOLI-1 trial publication. pERC noted that the product monograph dose is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI-1 trial indicates that irinotecan liposome 80 mg/m^2 is equivalent to 70 mg/m^2 of irinotecan free base. pERC cautioned that the dose must be clearly labelled, and the packaging should clearly differentiate it from irinotecan free base to minimize confusion between the two products.

pERC also discussed the place of irinotecan liposome plus 5-FU/LV in therapy and noted that there is limited evidence evaluating the effectiveness of irinotecan liposome in combination with 5-FU/LV in patients who have progressed after being previously treated with irinotecan-containing regimens (e.g., FOLFIRINOX). pERC noted that both the CGP and registered clinicians indicated that they do not support the use of irinotecan liposome after previous treatment with irinotecan-containing regimens like FOLFIRINOX. Therefore, pERC concluded that irinotecan liposome plus 5-FU/LV should not be considered for patients who have progressed after previous irinotecan-based therapy. Additionally, pERC noted the potential need for the short-term, time-limited need for the combination therapy for patients who are

currently receiving gemcitabine-based therapy as second-line therapy, based on the clinical discretion of the treating physician.

Finally, pERC discussed the budget impact and noted that the factor that most influenced the budget-impact analysis (BIA) is the cost of oxaliplatin in the comparator regimen (e.g., mFOLFOX, OFF). pERC noted that using the generic price of oxaliplatin (approximately $0.70 per mg) in the comparator regimen instead of the brand name price of oxaliplatin increases the budget impact substantially as a lower price of the comparator increases the incremental difference. Other factors that influence the BIA include market share assumptions, time on treatment, and dose intensity. pERC noted that wastage was not considered in the BIA, but that the inclusion of wastage would increase the budget-impact estimate substantially.

EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- a pCODR systematic review
- other literature in the Clinical Guidance Report that provided clinical context
- an evaluation of the manufacturer's economic model and budget-impact analysis (BIA)
- guidance from pCODR clinical and economic review panels
- input from a joint submission from Pancreatic Cancer Canada (PCC) and the Canadian Organization for Rare Disorders (CORD)
- input from registered clinicians
- input from pCODR's Provincial Advisory Group (PAG).

Feedback on the pERC Initial Recommendation was also provided by:

- one registered clinician group
- the PAG.

The pERC Initial Recommendation was to recommend reimbursement of irinotecan liposome (Onivyde) for the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-fluorouracil (5-FU) and leucovorin (LV) in adult patients who have been previously treated with gemcitabine-based therapy. Feedback on the pERC Initial Recommendation indicated that the registered clinicians agreed with the Initial Recommendation and PAG disagreed with the Initial Recommendation. The submitter and the patient advocacy group did not provide feedback on the pERC Initial Recommendation.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of irinotecan liposome (Onivyde) for the treatment of metastatic adenocarcinoma of the pancreas in combination with 5-FU/LV in adult patients who have been previously treated with gemcitabine-based therapy.

Studies included: One randomized controlled trial

The pCODR systematic review included one open-label randomized controlled trial (RCT), NAPOLI-1. The NAPOLI-1 trial publication refers to irinotecan liposome as nanoliposomal irinotecan. Patients were initially randomized (1:1) to receive either irinotecan liposome monotherapy (120 mg/m^2 every three weeks) or 5-FU/LV (2,000 mg/m^2 and 200 mg/m^2 every week for the first four weeks of a six-week cycle) (Protocol version 1). However, after a protocol amendment, a third arm was added to the trial: irinotecan liposome (80 mg/m^2) plus 5-FU/LV (2,400 mg/m^2 and 400 mg/m^2) every two weeks (Protocol version 2). Henceforth, patients were randomized on a 1:1:1 ratio to receive irinotecan liposome monotherapy (n = 151), 5-FU/LV (n = 119), or irinotecan liposome plus 5-FU/LV (n = 117), which was stratified by baseline albumin, Karnofsky performance status (KPS), and ethnic origin. The focus of pERC's deliberations was on irinotecan liposome plus 5-FU/LV compared with 5-FU/LV alone. Patients continued to be treated until disease progression (radiological or clinical deterioration), intolerable toxic effects, or other withdrawal criteria.

The pCODR review also provided contextual information on a critical appraisal of a network meta-analysis (NMA) of irinotecan liposome versus other comparators, such as 5-FU/LV plus oxaliplatin, a modified FOLFIRI regimen, 5-FU/LV plus non-liposomal irinotecan, and best supportive care. pERC noted that there was no comparison made between irinotecan free base and irinotecan liposome.

Patient populations: Karnofsky performance status of greater than 70; majority of patients had received one previous line of metastatic treatment

Baseline characteristics were generally well balanced between the treatment arms. Patients were eligible to participate in the NAPOLI-1 trial if they had histologically or cytologically confirmed adenocarcinoma of the exocrine pancreas; metastatic disease; documented disease progression after prior gemcitabine-based therapy; KPS ≥ 70; and adequate bone marrow, hepatic, and renal function. Previous treatment with irinotecan was allowed.

Overall, the median age of all patients was 63 years (range: 31 to 87); the majority of patients were male (56.8%), white (60.7%), and had a KPS score of 90 (40.5%) or 80 (35.7%). In addition, patients were more likely to have a tumour in the head of the pancreas (57.3%) and have two measurable metastatic sites (44.1%). Additionally, 44.6% of patients had previously received gemcitabine alone and 55.4% had received gemcitabine in combination with another anticancer therapy. 56% of patients had received one previous line of metastatic treatment and 32% had previously received two or more lines of metastatic treatment. Twelve per cent of patients had received gemcitabine-based therapy in the adjuvant, neoadjuvant, or locally advanced setting, but had not had previous treatment for metastatic disease.

pERC discussed whether the results of the NAPOLI-1 trial in patients with metastatic adenocarcinoma of the pancreas could be generalized to the locally advanced unresectable disease population. pERC noted that in clinical practice, both patient populations receive similar systemic therapies, and that the transition from locally advanced unresectable disease to metastatic disease often occurs rapidly. Therefore, pERC agreed with the Clinical Guidance Panel (CGP) that treatment availability should be extended to include patients with locally advanced unresectable disease. pERC also discussed the fact that the majority of enrolled patients had a KPS of 80 or higher, and that in clinical practice, pancreatic cancer patients are more likely to have a worse performance status at this stage of their disease. Therefore, pERC agreed that the use of liposomal irinotecan liposome should be limited to patients with good performance status.

Key efficacy results: Statistically significant difference in overall survival and progression-free survival in favour of Irinotecan liposome plus 5-FU/LV compared with 5-FU/LV

pERC deliberated on overall survival (OS), the primary outcome, as well as progression-free survival (PFS), a key secondary outcome. pERC noted that there was a statistically significant improvement in OS in favour of the irinotecan liposome combination arm (6.1 months [95% CI, 4.76 to 8.87]) compared with 5-FU/LV (4.2 months [95% CI, 3.3 to 5.3]). Irinotecan liposome plus 5-FU/LV therapy was associated with a significantly prolonged OS compared with 5-FU/LV therapy (HR 0.67; 95% CI, 0.49 to 0.92; $P = 0.012$). pERC discussed the magnitude of clinical benefit and noted that it was clinically meaningful in patients who experience rapid decline following progression on gemcitabine-based therapy.

The median PFS for the combination group was 3.1 months (95% CI, 2.7 to 4.2) and 1.5 months (95% CI, 1.4 to 1.8) in the 5-FU/LV group. The combination therapy was associated with a prolonged PFS compared with the 5-FU/LV (HR 0.56; 95% CI, 0.41 to 0.75; $P = 0.0001$). At the final analysis of the NAPOLI trial conducted on November 16, 2015, PFS was prolonged with irinotecan liposome combination therapy compared with 5-FU/LV therapy (3.09 months [95% CI, 2.69 to 4.17] versus 1.46 months [95% CI, 1.41 to 1.84]; HR 0.57; 95% CI, 0.43 to 0.76; $P < 0.001$). pERC agreed with the CGP that, in a patient population with limited treatment options who otherwise face a rapid decline following progression, the consistency of the observed effects across major primary and secondary end points represented clinically meaningful outcomes for patients.

pERC noted that mFOLFOX and oxaliplatin with 5-FU (OFF) were considered relevant comparators in Canada in a NMA provided by the submitter. pERC discussed the critical appraisal of the NMA and noted that, in agreement with the Methods Team and CGP, the substantial heterogeneity between the included trials made the results highly unreliable and uncertain.

Upon reconsideration of the pERC Initial Recommendation, pERC discussed feedback from PAG stating that it is unknown whether the benefit seen with the irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. PAG noted that jurisdictions have made generic oxaliplatin and irinotecan in combination with 5-FU/LV, capecitabine, and fluoropyrimidine therapy available as treatment options, recognizing that there is a lack of high-level evidence for a standard of care in patients previously treated with gemcitabine-based therapies. pERC reiterated that despite available treatment options in the second-line setting, there is no standard of care or high-level data to support the usage of any one regimen over another. While oxaliplatin may be available in some jurisdictions, there is evidence from a phase III RCT that demonstrated no survival benefit with the addition of oxaliplatin. The Committee reiterated the fact that 5-FU/LV was considered to be a reasonable comparator in this setting by the CGP and registered clinicians. pERC also noted that while irinotecan free base may be available in some jurisdictions, there is currently no evidence to support the use of irinotecan free base in combination with 5-FU/LV in the post-progression setting. Furthermore, irinotecan free base was not considered a comparator in this setting by the CGP and registered clinicians. pERC reiterated its conclusion that irinotecan liposome in combination with 5-FU/LV compared with 5-FU/LV alone in patients who have progressed on gemcitabine-based therapies demonstrated a statistically

significant and clinically meaningful improvement in outcomes important to decision-making, including OS and PFS.

Quality of life: Low compliance rates, high attrition rates; no appreciable improvements or deterioration between the irinotecan liposome plus 5-FU/LV arm compared with the 5-FU/LV arm

Patient-reported quality of life (QoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30). Patient-related outcomes were measured at baseline and then every six weeks until disease discontinuation. At week 6 and week 12, there were no appreciable changes in the proportion of patients who demonstrated improvements or deterioration between the irinotecan liposome plus 5-FU/LV arm and the 5-FU/LV arm. pERC noted that this is most likely due to a high degree of missing data, due in turn to high attrition rates.

Safety: Increased toxicity with irinotecan liposome plus 5-FU/LV compared with 5-FU/LV

pERC discussed the toxicity profile of irinotecan liposome in combination with 5-FU/LV. Patients who received treatment with irinotecan liposome, regardless of arm, had more grade 3 or higher treatment-emergent adverse events (TEAEs) than those treated with 5-FU/LV. pERC noted that 92% of patients in the combination therapy group and 87% in the monotherapy group had an adverse event (AE) related to the study drug compared with 69% in the 5-FU/LV group. The most common TEAEs for patients were diarrhea (combination: 59%; control: 26%); nausea (combination: 51%; control: 34%); and vomiting (combination: 52%; control: 26%). Febrile neutropenia was reported in 3% and 4% of patients in the irinotecan liposome combination and monotherapy arms respectively. Furthermore, 17% and 12% in the irinotecan liposome combination and monotherapy arms, respectively, received growth factor support, a practice not common with palliative chemotherapy treatments in Canada.

More patients in the combination arm (70.9%) had an AE that required at least one dose modification as compared with the control groups (35.8%). This was similar for patients who had at least one TEAE that resulted in a dose delay (combination: 61.5%; control: 32.1%).

Sixteen deaths resulted from an AE, five of which were treatment-related, based on the opinion of the investigator. One treatment-related grade 5 AE death occurred in the combination arm (septic shock [N = 1]).

Registered clinician input: Unmet need post-progression on gemcitabine-based therapy

pERC noted that the clinicians providing input indicated that there is no standard of care in second-line treatments of metastatic pancreatic cancer for patients previously treated with gemcitabine-based therapies; therefore, there is an unmet need for this patient population. The clinicians noted that in some provinces, oxaliplatin with 5-FU, 5-FU alone, or capecitabine are options, but that there are no high-level data to support the usage. However, they also noted that patients often have poor performance status in this setting, and many do not have a sufficient performance status to receive second-line therapy. Clinicians reported that approximately one-quarter to one-third of all patients who received gemcitabine (with or without nab-paclitaxel) would be fit enough for treatment with irinotecan liposome plus 5-FU/LV. The clinicians providing input identified that irinotecan liposome should be used according to the NAPOLI trial: second-line with 5-FU/LV (dose as described in trial) after first-line gemcitabine (with or without nab-paclitaxel) in patients with good performance status.

Input from clinicians in Ontario noted that more patients may be treated with gemcitabine/nab-paclitaxel in first-line therapy if irinotecan liposome with 5-FU/LV is approved for second-line therapy. As the sequence of first-line LV, 5FU, irinotecan and oxaliplatin in combination (FOLFIRINOX) followed by gemcitabine plus nab-paclitaxel second-line therapy is not funded in Ontario, there is already a high rate of first-line gemcitabine/nab-paclitaxel usage. Over time, second-line irinotecan liposome will have little impact on first-line gemcitabine/nab-paclitaxel usage.

Need: More effective treatment options required that improve survival and offer more favourable toxicity profiles

Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016 and an equal distribution between men and women. However, it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. The majority of patients present with either metastatic or locally advanced, unresectable disease. The mainstay of treatment for such patients is palliative chemotherapy. Although

the palliative treatment of advanced pancreatic cancer has significantly improved in the past several years, with median survival now exceeding eight months, long-term survival remains elusive for most pancreatic cancer patients, with fewer than 20% being alive at 18 months. Clinicians now have a choice between FOLFIRINOX, gemcitabine with nab-paclitaxel, and gemcitabine alone for the first-line treatment of locally advanced and metastatic pancreatic cancer patients who are well enough for systemic therapy. To date, no drug or drug combination has been approved for previously treated patients post-progression, and there is currently no standard-of-care therapy in this setting. pERC noted that this post-progression setting represents an unmet need in the management of advanced pancreatic cancer.

PATIENT-BASED VALUES

Experiences of patients with adenocarcinoma of the pancreas: High symptom burden and poor quality of life

Patient input noted that pancreatic cancer is a rare type of cancer with a very low prevalence. However, pERC noted that it is not considered a rare disease, as it is the fourth-leading cause of cancer death, with 4,700 deaths in 2016. Patient input noted that patients are often diagnosed at a very late stage; thus, their disease may not be amenable to treatment. Respondents reported a high degree of distress due to cancer symptoms, including nausea, vomiting, and pain. The majority of respondents indicated that a diagnosis of pancreatic cancer was devastating and has significantly impacted their QoL.

PCC and CORD indicated that treatment options are limited for metastatic pancreatic patients, and that the current drug therapies for managing cancer symptoms and progression are ineffective. Side effects related to all types of therapies were considered manageable, and side effects were tolerable by patients.

Patient values regarding treatment: Improved quality of life, more effective options, and better balance between the benefits and risks of drug therapy

PCC and CORD indicated that the majority of respondents were not aware of the new therapy, irinotecan liposome. Both patients and caregivers agreed that patients should be given the option to try the new therapy for the potential to prolong life. Patient input indicated that patients value new effective treatment options that improve QoL and prolong survival. The Committee noted that patients strongly valued a modest improvement in OS for this patient population with rapid decline in health post-progression, for which few treatment options are available. pERC also noted that patient input indicated that patients strongly valued the option of trying new therapies but also valued balancing the benefits and risks of a drug therapy with the overall impact on QoL pERC noted that patients indicated they would be willing to try new therapies; however, the Committee also noted comments that patients and their families want to have an honest discussion with their oncologists to assess the risks and benefits associated with treatment so they can make informed and personalized decisions about treatment. pERC noted that the results from the NAPOLI trial did not demonstrate an improvement in QoL; however, it appeared that no appreciable detriment was observed. This may be attributable to low compliance and a large amount of missing data, which increases the uncertainty in these QoL results.

Eight respondents who had direct experience with irinotecan liposome provided input. All noted that irinotecan liposome had positive effects for reducing pain and fatigue. Most respondents felt that the side effects were manageable. Overall, pERC concluded that the therapeutic intent of irinotecan liposome as an effective treatment option that prolongs survival aligns with patient values. However, the Committee was limited by the QoL data from the NAPOLI trial, and was uncertain about how treatment with irinotecan liposome in combination with 5-FU/LV impacts QoL.

ECONOMIC EVALUATION

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

The pCODR Economic Guidance Panel (EGP) assessed the submitter's cost-effectiveness and cost-utility analysis of irinotecan liposome in combination with 5-FU/LV for patients with metastatic pancreatic cancer who have been previously treated with gemcitabine-based therapy as compared with 5-FU/LV alone (NAPOLI-1, direct comparison), or mFOLFOX or OFF (NMA, indirect treatment comparison).

Basis of the economic model: No extrapolation of efficacy outcomes

The pharmacoeconomic model was comprised of four health states: pre-progression on treatment, pre-progression off treatment, post-progression, and death. The pre-progression off treatment state is meant to account for patients who discontinue treatment for reasons other than progression.

Costs considered in the analysis included treatment costs, administration costs, and AE costs.

The clinical effect considered in the analysis was based on OS, PFS, time-to-treatment failure, the incidence of AEs, and utilities. No extrapolation of outcomes was needed, as these estimates were based entirely on full data from the trial. By the end of three years of total follow-up, all trial patients were dead.

Drug costs: High cost of irinotecan liposome

The list price of irinotecan liposome is $1,000.00 per 43 mg 10 mL vial. The cost of the combination of irinotecan liposome plus 5-FU/LV is $243.57 per day, or $6,819.94 per 28-day course, assuming an average body weight of 70 kg.

The costs of relevant comparators, assuming an average body weight of 70 kg, are as follows:

- The cost of the FOLFIRI regimen is $89.68 per day, or $2,511.18 per 28-day course.
- The cost of the OFF regimen is $40.92 per day, or $1,145.99 per 28-day course.
- The cost of the mFOLFOX6 regimen is $53.47 per day, or $1,497.29 per 28-day course.
- The cost of the 5-FU/LV regimen is $35.87 per day, or $1,004.49 per 28-day course.

Cost-effectiveness estimates: Not cost-effective at the submitted price

pERC deliberated upon the cost-effectiveness of irinotecan liposome in combination with 5-FU/LV with other possible therapies. pERC noted that the pCODR EGP's best estimates (lower bound: $326,774 per quality-adjusted life-year [QALY] to upper bound: $335,528 per QALY) were much higher than the submitter's estimate ($182,719 per QALY). pERC noted that this was primarily due to differences in the estimate of drug wastage, the source of drug costs, the use of time-to-treatment failure as a proxy for treatment duration, and utility values derived from the literature. The EGP conducted reanalyses to adjust for these limitations in the submitted model, including:

- Using PFS as a proxy for treatment duration, as the intent of treatment is to treat until progression; no vial sharing of irinotecan liposome to account for wastage
- Including disutilities, as patients on the combination therapy are likely to experience AEs due to increased toxicity
- Using Canadian utilities to reflect Canadian utility values
- Removing post-progression treatment, as the CGP identified that currently in Ontario, no subsequent treatments are funded for another line of therapy, and it is likely that patients who progress further would not be eligible to receive any further treatment
- Sourcing drug costs from Quintile IMS for standard pricing
- Discounting both costs and effects by 1.5% to align with current CADTH guidelines.

The Committee discussed that the cost of growth factor support, which may be required to treat toxicities such as febrile neutropenia while on the combination therapy, was not included in the submitted model. Therefore, the costs of managing such toxicities are likely underestimated in the submitted economic model. Furthermore, pERC noted that the cost of irinotecan liposome is four times greater than that of irinotecan free base; the Committee agreed that a substantial reduction in the drug price of irinotecan liposome would be required to improve the cost-effectiveness to an acceptable level. Therefore, pERC noted that at the submitted price, the combination therapy could not be considered cost-effective. pERC also agreed with the EGP's assessment regarding the uncertainty of estimates provided using the NMA between relevant comparators, including mFOLFOX, OFF, and irinotecan liposome plus 5-FU/LV.

Upon reconsideration of the pERC Initial Recommendation, the Committee noted input from PAG that it is unknown whether the benefit observed with irinotecan liposome combination is due to the formulation or due to the active irinotecan molecule. In the absence of a comparison with irinotecan free base, the true cost-effectiveness and value of funding irinotecan liposome is difficult to determine. pERC reiterated the

fact that there are currently no available data on the comparison between irinotecan liposome and irinotecan free base, and, therefore, the Committee noted that the comparative effectiveness and the cost-effectiveness are unknown.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Second-line therapy post-progression on gemcitabine therapy; no use for patients who have progressed on irinotecan-containing regimens

pERC discussed the feasibility of implementing a reimbursement recommendation for irinotecan liposome in combination with 5-FU/LV. pERC noted that irinotecan liposome is provided in a single 50 mg vial. In most instances, vial sharing will not be feasible given the small number of patients with pancreatic cancer receiving second-line treatment; therefore, there will be significant wastage. As an additional systematic therapy to chemotherapy, pERC noted PAG's concern that there will be increased chair time for treatment administration to patients. Furthermore, pERC discussed PAG's concern regarding the different dosing in the Health Canada product monograph compared with the NAPOLI-1 trial publication. pERC noted that the product monograph dose is 70 mg/m^2 based on irinotecan free base, and that the NAPOLI trial indicates that irinotecan liposome 80 mg/m^2 is equivalent to 70 mg/m^2 of irinotecan free base. pERC cautioned that the dose must be clearly labelled, and the packaging should clearly differentiate it from irinotecan free base to minimize confusion between the two products.

pERC also discussed the place of irinotecan liposome plus 5-FU/LV in therapy, and noted that there is limited evidence evaluating the effectiveness of irinotecan liposome in combination with 5-FU/LV in patients who have progressed after being previously treated with irinotecan-containing regimens (e.g., FOLFIRNOX). pERC noted that both the CGP and registered clinicians indicated that they do not support the use of irinotecan liposome after previous treatment with irinotecan-containing regimens like FOLFIRINOX. Therefore, pERC concluded that irinotecan liposome plus 5-FU/LV should not be considered for patients who have progressed after previous irinotecan-based therapy. Additionally, pERC discussed the potential for the short-term, time-limited need for the combination therapy for patients currently receiving gemcitabine-based therapy as second-line therapy, based on the clinical discretion of the treating physician.

Finally, pERC discussed the budget impact, and noted that the factor that most influences the BIA is the cost of oxaliplatin in the comparator regimens (ex. mFOLFOX, OFF). Using the generic price of oxaliplatin (approximately $0.70 per mg) instead of the brand name price of oxaliplatin increases the budget impact substantially, as a lower price of the comparator regimen increases the incremental difference. Other factors that influence the BIA include market share assumptions, time on treatment, and dose intensity. The key limitations of the BIA model include the lack of consideration of wastage (vial sharing) of irinotecan liposome. The EGP was not able to modify or explore these parameters, but the inclusion of wastage would increase the BIA.

DRUG AND CONDITION INFORMATION

Drug Information	• Irinotecan liposome (Onivyde) is administered by intravenous infusion 70 mg/m^2 over 90 minutes, followed by leucovorin (LV) 400 mg/m^2 IV over 30 minutes, followed by 5-fluorouracil (5-FU) 2,400 mg/m^2 IV over 46 hours, every two weeks. • One vial contains 43 mg of irinotecan free base, which is equivalent to 50 mg irinotecan liposome.
Cancer Treated	• Locally advanced unresectable or metastatic adenocarcinoma of the pancreas with previous treatment with gemcitabine-based therapy.
Burden of Illness	• Pancreatic cancer is the 10th most common cancer in Canada, with 5,200 new cases in 2016 and equal distribution among men and women. • It is fourth-leading cause of cancer death, with 4,700 deaths in 2016.
Current Standard Treatment	• FOLFIRI • OFF • mFOLFOX • 5-FU/LV
Limitations of Current Therapy	• No standard of care in this patient population • Current available treatments do not have high-level data to support usage.

ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC *Deliberative Framework*. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice Chair)
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Mike Doyle, Health Economist
Dr. Craig Earle, Oncologist
Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Cameron Lane, Patient Member Alternate
Valerie McDonald, Patient Member
Carole McMahon, Patient Member
Dr. Marianne Taylor, Oncologist

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

- Dr. Kelvin Chan and Lauren Flay Charbonneau, who were not present for the meeting
- Cameron Lane, who did not vote due to his role as a Patient Member Alternate.

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

- Dr. Avram Denburg and Dr. Craig Earle, who were not present for the meeting
- Lauren Flay Charbonneau, who did not vote due to a conflict of interest
- Cameron Lane, who did not vote due to his role as a patient member alternate.

Avoidance of conflicts of interest

All members of the pCODR pERC 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 irinotecan liposome for metastatic pancreatic cancer, through their declarations, no members had a real, potential, or perceived conflict. Based on the application of the *pCODR Conflict of Interest Guidelines*, no members were excluded from voting. For the Final Recommendation, one member had a real, potential, or perceived conflict, and based on application of the *pCODR Conflict of Interest Guidelines*, one member was excluded from voting.

Information sources used

pERC 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 its 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.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to pERC for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. There was no non-disclosable information in this Recommendation document.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers 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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