Canada's Drug and
Health Technology Agency

CADTH Reimbursement Recommendation

Nab-Paclitaxel

Reimbursement request: In combination with gemcitabine for the adjuvant treatment of pancreatic cancer
Final recommendation: Reimburse with conditions

Summary of Recommendation

The Formulary Management Expert Committee (FMEC) recommends that nab-paclitaxel in combination with gemcitabine be reimbursed with conditions listed in Table 2 for the adjuvant treatment of adult patients with resected pancreatic ductal adenocarcinoma. Reimbursement should be restricted to patients with good performance status but who are unable to receive other standard adjuvant treatment options, including mFOLFIRINOX.

Pancreatic cancer is a severe condition with unmet clinical needs, and nab-paclitaxel in combination with gemcitabine may be used in specific patients who cannot receive other treatments in the adjuvant setting. FMEC reviewed a phase III, multicentre, open-label, randomized controlled trial (the APACT trial) and concluded that nab-paclitaxel in combination with gemcitabine shows at least comparable efficacy to gemcitabine monotherapy, although the added clinical benefit of the dual therapy is unclear. FMEC noted the substantial uncertainty surrounding disease-free survival and overall survival outcomes, yet this dual treatment may offer a survival advantage compared to gemcitabine monotherapy.

FMEC also highlighted that nab-paclitaxel in combination with gemcitabine is associated with additional toxicities and higher discontinuation rates due to adverse events compared to gemcitabine monotherapy.

The expected cost of nab-paclitaxel in combination with gemcitabine is higher than that of gemcitabine monotherapy based on publicly available prices.

Therapeutic Landscape

What Is Pancreatic Cancer?

Pancreatic cancer commonly starts in cells of the pancreatic duct. The recommended curative therapy for pancreatic ductal cell adenocarcinoma is surgical resection followed by adjuvant chemotherapy, with mFOLFIRINOX, gemcitabine plus capecitabine combination therapy, and gemcitabine monotherapy being the preferred regimens.

Why Did We Conduct This Review?

There is currently an unmet need for pancreatic cancer patients, particularly those intolerant to 5-fluorouracil, with dihydropyrimidine dehydrogenase deficiency, or contraindications to mFOLFIRINOX treatment. Publicly funded drug plans requested a reimbursement review based on the emergence of new evidence.

Person With Lived Experience

A person with lived experience presented to the committee on his journey being diagnosed with stage II pancreatic adenocarcinoma in June 2023 at age 69 years. He underwent Whipple surgery and subsequent chemotherapy with the FOLFIRINOX regimen. Supported by his wife as his caregiver, he navigated treatment challenges, including fatigue, loss of appetite, and neuropathy. They explained that the treatment outcomes they most valued were longevity and quality of life as well as demonstrably efficacious treatment. Furthermore, their insights into treatment decision-making helped inform the committee's understanding of how patients choose which treatments are acceptable given the trade-offs with side effects and potential outcomes. They emphasized the importance of accessible, effective care and having choice in treatment location that best suits the patient's needs. They remain hopeful for the future and highlighted the importance of strong support systems throughout treatment, sharing their mottoes of "adapt or die" and "go forth boldly."

Input From Community Partners

What Did We Hear From Patients?

Input was jointly submitted by 2 patient groups (Canadian Cancer Society and Craig's Cause Pancreatic Cancer), featuring the perspectives from 2 patients in total. The patients described pain from cancer, debilitating lethargy, concerns about delays in diagnosis, and some of the limitations of current treatments, including neuropathy.

What Did We Hear From Clinicians?

Input was provided by 1 clinician group who shared that there are currently no effective adjuvant treatment options for patients with pancreatic cancer. Treatment options are limited for patients who are intolerant of 5-fluorouracil, those with dihydropyrimidine dehydrogenase deficiency, and those for whom mFOLFIRINOX is contraindicated.

What Did We Hear From the Pharmaceutical Industry?

No input was provided from the pharmaceutical industry.

What Did We Hear From Public Drug Programs?

Public drug programs inquired about considerations for initiation of therapy, relevant comparators, and treatment implementation. Questions were asked regarding comparability to other treatment options, patient eligibility, re-treatment eligibility, and downstream treatment options for patients who receive nab-paclitaxel in combination with gemcitabine in the adjuvant setting.

Refer to the Input section of the report.

Deliberation

FMEC agreed that pancreatic cancer has high mortality with high unmet needs. With a 4 to 3 vote, FMEC concluded that nab-paclitaxel in combination with gemcitabine was considered at least comparable to gemcitabine monotherapy in adjuvant pancreatic cancer, although the added clinical benefit of the combination therapy is unclear. FMEC concluded that the combination treatment was associated with potential additional harms and incremental costs. However, for patients unable to be treated with other recommended options in the adjuvant setting (e.g., FOLFIRINOX or gemcitabine plus capecitabine), nab-paclitaxel in combination with gemcitabine might offer improvement in outcomes versus gemcitabine monotherapy.

FMEC deliberated on the following 6 domains as illustrated in the Deliberative Framework:

- Clinical value — Whether the drug under review provides clinical value.
- Unmet clinical need — Whether there is an unmet clinical need that available treatment(s) is or are not currently addressing.
- Comparable efficacy — Whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.
- Patient perspective — Whether the drug under review addresses patients' specific unmet needs and values.
- Health system and social considerations — Whether there are health system or social considerations (e.g., administration, testing, equity, access, ethical) for the drug under review.
- Economic implications — Economic implications of reimbursing the drug under review based on public list prices.

Decision Summary

Table 1: Why Did FMEC Make This Recommendation?

Domains	Reason
Patient perspective: Whether the drug under review addresses patients' specific unmet needs and values.	• FMEC recognized that pancreatic cancer is a therapeutic area where there should be greater allowance for uncertainty with clinical evidence given that it is a severe disease with poor prognosis and significant unmet needs. • FMEC highlighted that the unmet need is greatest in those who cannot be treated with mFOLFIRINOX. • FMEC discussed that patient groups and the person with lived experience emphasized that longevity and quality of life are important outcomes. FMEC highlighted that no quality-of-life data were available and there were greater toxicities with nab-paclitaxel in combination with gemcitabine than gemcitabine monotherapy.
Clinical value: Whether the drug under review provides clinical value.	• FMEC noted the uncertainty regarding the clinical benefit of nab-paclitaxel and gemcitabine. The study did not meet the primary end point for independently assessed disease-free survival. • FMEC discussed that the overall benefit remains unclear. Overall survival in the APACT trial was a secondary end point, and the authors did not control for type I error. Nevertheless, combination treatment might offer improved survival benefits compared to gemcitabine monotherapy.
Comparable efficacy: Whether the drug under review shows at least similar efficacy to other available treatment(s) for the condition.	• FMEC discussed that the comparative efficacy between the combination nab-paclitaxel with gemcitabine therapy to gemcitabine monotherapy is uncertain, citing that the APACT trial did not meet its primary end point on blinded review of improved disease-free survival. • Despite the limitations in the evidence, FMEC concluded that the efficacy of nab-paclitaxel in combination with gemcitabine is at least comparable to gemcitabine. Overall survival may also be improved with combination therapy compared to gemcitabine monotherapy. • FMEC noted that there was no identified evidence comparing nab-paclitaxel and gemcitabine to either mFOLFIRINOX or gemcitabine combined with capecitabine. However, both clinical experts reported that this latter drug combination is not well tolerated and is rarely used in patients who cannot receive mFOLFIRINOX. • FMEC members highlighted that although there may be comparable efficacy between nab-paclitaxel in combination with gemcitabine and gemcitabine monotherapy, there is also increased toxicity and higher discontinuation rates related to adverse events with nab-paclitaxel in combination with gemcitabine compared to gemcitabine monotherapy. However, the clinical experts reported that adverse events from the combination therapy are manageable and improve once treatment is completed.
Unmet clinical need: Whether there is an unmet clinical need that available treatment(s) is or are not currently addressing.	• FMEC discussed that given the high mortality rate with pancreatic cancer, there is an unmet need for additional and better treatment options. • In addition, patients who are not candidates for mFOLFIRINOX or gemcitabine with capecitabine (e.g., those with DPD deficiency, or *DPYD* polymorphisms) would benefit from additional treatment options in the adjuvant setting.

Domains	Reason
Health system and social considerations: Whether there are health system or social considerations for the drug under review.	• FMEC discussed that the combination regimen with nab-paclitaxel and gemcitabine does require longer time and resources for pharmacy and nursing for infusion compared to gemcitabine monotherapy and may result in more admissions for febrile neutropenia.
Economic implications: Economic implications of reimbursing the drug under review based on public list price?	• FMEC discussed that the acquisition costs per patient per 28-day cycle are higher for nab-paclitaxel and gemcitabine compared to other options. • FMEC highlighted that there are also system costs that may be higher for nab-paclitaxel and gemcitabine related to toxicity (e.g., costs of hospital admission to manage febrile neutropenia).

FMEC = Formulary Management Expert Committee; mFOLFIRINOX = modified leucovorin calcium (folinic acid)–fluorouracil–irinotecan hydrochloride–oxaliplatin.

Full Recommendation

With a unanimous 6 to 0 vote, FMEC recommends the following conditions (Table 2) for the reimbursement of nab-paclitaxel in combination with gemcitabine for the adjuvant treatment of adult patients with resected pancreatic ductal adenocarcinoma.

Table 2: Conditions, Reasons, and Guidance

Reimbursement condition	Reason	Implementation guidance
Initiation		
Nab-paclitaxel with gemcitabine should be reimbursed in the adjuvant setting in patients who meet all the following criteria: 1. have resected pancreatic ductal adenocarcinoma with R0 or R1 and N0 or N1 2. are unable to receive other treatment options including mFOLFIRINOX 3. have good performance status.	Treatment with adjuvant nab-paclitaxel with gemcitabine should be reimbursed for patients whose disease characteristics are consistent with patients included in the APACT clinical trial.	According to the clinical experts, mFOLFIRINOX remains the preferred adjuvant chemotherapy regimen. Patients unable to receive other treatment options include those with DPD deficiencies, *DPYD* polymorphisms, or comorbidities.
Discontinuation		
Treatment should be continued until 1 of the following: • evidence of progression of disease • patient intolerance • withdrawal of consent. Nab-paclitaxel with gemcitabine should be continued until a maximum of 6 cycles.	The APACT clinical trial investigated the use of nab-paclitaxel-gemcitabine up to a maximum of 6 cycles.	—

Reimbursement condition	Reason	Implementation guidance
Prescribing		
Nab-paclitaxel with gemcitabine must be initiated by a clinician with expertise in the treatment of pancreatic cancer.	Patients with pancreatic cancer are expected to be under the care of an experienced clinical team to address the complexity of treatment, maximize potential benefits, and mitigate adverse events.	—
Pricing		
A price reduction may be required.	Based on publicly available prices, nab-paclitaxel in combination with gemcitabine is more costly than all other relevant comparators. Due to an absence of clinical evidence in the reimbursed population, the cost-effectiveness of nab-paclitaxel in combination with gemcitabine relative to gemcitabine monotherapy is unknown. Given that nab-paclitaxel in combination with gemcitabine is associated with incremental costs and unknown clinical benefit relative to alternative treatment options, a price reduction may be required.	—

mFOLFIRINOX = modified leucovorin calcium (folinic acid)–fluorouracil–irinotecan hydrochloride–oxaliplatin.

Feedback on Draft Recommendation

We received feedback on the draft recommendations from drug plans and no reconsideration was requested. Based on feedback from the drug plans, an editorial revision was made under Patient Perspective.

FMEC Information

Members of the committee: Dr. Emily Reynen (Chair), Dr. Alun Edwards, Ms. Valerie McDonald, Dr. Jim Silvius, Dr. Marianne Taylor, Dr. Maureen Trudeau, Dr. Dominika Wranik, as well as 2 medical oncologists from Alberta and Ontario.

Meeting date: July 4, 2024

Conflicts of interest: None

Special thanks: Canada's Drug Agency extends our special thanks to the individuals who presented directly to FMEC on behalf of people with lived experience and to the patient organizations representing the community of those living with Pancreatic Cancer, notably Pancreatic Cancer Canada, which includes Christina Halladay, Keith McAllister, Doris Heinrichs, and Amy Fishleigh.

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