Canada's Drug and Health Technology Agency

DRAFT Reimbursement Recommendation

Nab-paclitaxel

Reimbursement request: In combination with gemcitabine for the adjuvant treatment of pancreatic cancer

Draft 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, multicenter, 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.

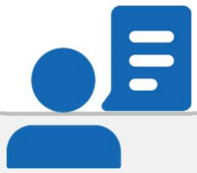
Therapeutic Landscape

What Is Pancreatic Cancer?

In Canada, pancreatic cancer is expected to be the 3rd leading cause of death in 2024, with an estimated 7,100 Canadians diagnosed with pancreatic cancer in 2024. Pancreatic cancer commonly starts in cells of the pancreatic duct, called pancreatic ductal cell adenocarcinoma (PDAC), with the recommended curative therapy being surgical resection followed by adjuvant chemotherapy. Of various adjuvant chemotherapies, the preferred regimen includes modified FOLFIRINOX (mFOLFIRINOX), and gemcitabine plus capecitabine combination therapy, and gemcitabine monotherapy are other possible options.

Why Did CDA-AMC Conduct This Review?

In the adjuvant setting, there is currently an unmet need for patients with pancreatic cancer, particularly those intolerant to 5-fluorouracil, those with dihydropyrimidine dehydrogenase deficiency, or those with contraindications to mFOLFIRINOX treatment. Given the emergence of new evidence for the use of nab-paclitaxel in combination with gemcitabine for adjuvant treatment, publicly funded drug plans requested a reimbursement review and recommendation after receiving requests from clinicians. Nab-paclitaxel is later in the drug development lifecycle making this treatment eligible for review at FMEC.



Person With Lived Experience

A person with lived experience presented to the committee on his journey being diagnosed with stage 2 Pancreatic adenocarcinoma in June 2023 at 69 years old. He underwent Whipple surgery and subsequent chemotherapy with the FOLFIRINOX regime. 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. As they remain hopeful for the future, they highlighted the importance of strong support systems throughout treatment and shared their mottos of "Adapt or die"; and "Go forth boldly".

Input from Community Partners

What Did We Hear From Patients?

Input was jointly submitted by two patient groups (Canadian Cancer Society and Craig's Cause Pancreatic Cancer), featuring the perspectives from two 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 one 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 (DPD) deficiency, and 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 Stakeholder Input section of the report.

Deliberation

The Formulary Management Expert Committee (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 (Figure 1):

- 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/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 & 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.

Figure 1: Deliberative Framework

Alt Text: The committee deliberated on 6 domains: clinical value, unmet clinical need, comparable efficacy, patient values, health system & social considerations, and economic implications.

Decision Summary

Table 1: Why Did FMEC Make This Recommendation?

Domains	Reason
Patient Values: 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 clinicial 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 was 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 (DFS). • FMEC discussed that the overall benefit remains unclear. Overall survival in the APACT trial was a secondary endpoint, and the authors did not control for type 1 error. Nevertheless, combination treatment might offer improved survival benefits compared to gemcitabine monotherapy.

Domains	Reason
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 endpoint on blinded review of improved DFS. • 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 while 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/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 nor gemcitabine with capecitabine (e.g., those with DPD deficiency, or DPYD polymorphisms) would benefit from additional treatment options in the adjuvant setting.
Health System & Social Considerations: whether there are health system or social	• FMEC discussed that the combination regimen with nab-paclitaxel and gemcitabine does require longer chair time

Domains	Reason
considerations for the drug under review.	for infusion when compared to gemcitabine monotherapy and may result in more admissions for febrile neutropenia.
Economic Implications: what are the 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 which may be higher for nab-paclitaxel and gemcitabine related to toxicity (e.g., costs of hospital admission to manage febrile neutropenia).

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-gemcitabine should be reimbursed in the adjuvant setting in patients who meet all of the following criteria: 1) Resected pancreatic ductal adenocarcinoma (PDAC) with R0/R1 and N0/N1 2) Unable to receive other treatment options including mFOLFIRINOX 3) With good performance status	Treatment with adjuvant nab-paclitaxel-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 would include those with DPD deficiencies, DPYD polymorphisms, or comorbidities.
Discontinuation		
Treatment should be continued until: 1. Evidence of progression of disease; or 2. Patient intolerance; or 3. Withdrawal of consent. Nab-paclitaxel-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.	
Prescribing		
Nab-paclitaxel-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	

Reimbursement condition	Reason	Implementation guidance
	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.	

Feedback on Draft Recommendation

<to be updated after the stakeholder feedback period.>

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 two 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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